National Institute for Health and Clinical Excellence

Ovarian Cancer
Guideline Consultation Comments Table
24 Sept – 19th November 2010

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
PR	NETSCC, Health Technology Assessment	5.19	Full			**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The calculation of negative predictive values is not consistent within the report – some points suggest a formula of TN / [FN + TN] (values approach 1, e.g. Tables 2.1 and 2.2), others suggest FN / [FN + TN] (values approach 0, e.g. text on p42). TN / [FN + TN] is more conventional.	We have changed the NPVs to make them consistent (values approaching 1).
SH	Royal Pharmaceutical Society of Great Britain	10.00	General			The RPS welcomes these guidelines	Thank you
SH	NHS Direct	15.00	Full			No comments, NHS Direct welcome the guidance.	Thank you
SH	UK Clinical Pharmacy Association	17.00				Thank you for the opportunity to respond to the NICE draft ovarian cancer guideline. However, at this time UKCPA does not have any further comments to submit on this guideline.	Thank you
SH	NHS Improvement	22.05					
SH	British Nuclear Medicine Society	32.00				The BNMS has no comments to make on the Ovarian Cancer draft guideline consultation.	Thank you
SH	British Gynaecological Cancer Society 2	34.05					
SH	British Gynaecological Cancer Society 2	34.25					
SH	Royal College of General Practitioners Wales	6.04	Full	General		This is a helpful guideline for GP.	Thank you
SH	Royal College of	14.00		Gener		Thank you for inviting the RCOG to comment on this	Thank you

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	Obstetricians and Gynaecologists			al		Guideline.	
SH	NHS Improvement	22.00	Full	general		A meeting was held on 15 October 2010 to present the guidance in the draft document to members of the and Gynae NSSG Leads. The Gynaecological Oncology Guidelines Group works on behalf of both organisations developing clinical guidelines, and served as a conduit for collating responses to the NICE draft guidelines. The 15 October meeting was advertised via the BGCS and the NSSG Leads' Group to members. Gynaecological Oncology, Medical oncology, Radiology, Clinical Nurse Specialists, Ovarian Charities, Patient Groups, Network Leads, Unit Leads and MDT Coordinators were represented. Delegates from England, Wales and N Ireland attended. The guidance was presented measure by measure as written in the document. Delegates then voted on the guidance and discussed their views. Minutes of the meeting were circulated to members of the BGCS. All Network Leads were asked to circulate the minutes to their MDTs and Network members. Histopathology was not represented at the meeting but a response from this group has been coordinated by email. The comments below are the views expressed at the meeting in the context of a broader consultation with BGCS members and following review of the consultation document at the NSSG Leads meeting at University College Hospital London on Friday November 12 2010.	Thank you for your comments. We have responded to individual comments below.
SH	NHS Improvement	22.32	Full	General		There is a strong consensus within the membership of the NSSG leads group that the guidelines require extensive revision, especially with regards to surgical practice. The recommendations are contrary to established high quality practice in leading international and UK gynaecological cancer centres, and if adopted without extensive revision would fundamentally harm the development and delivery of world class care for ovarian cancer patients in the UK. Sincerely, Mr Andy Nordin	Thank you for your comments. We have responded to individual comments below.

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						Clinical Advisor, NHS Improvement-Cancer Chair, Gynae NSSG Leads Group	
SH	Department of Health	23.00	Full	General		We understand that there are significant concerns about this draft guidance in the Gynaecology Oncology community. We would encourage you to consider their comments carefully when drafting your final clinical guideline on ovarian cancer.	We have considered these comments
SH	Central South Coast Cancer Network	24.00	Full	General		**On behalf of the Central South Coast Cancer Network Gynae-Oncology Site Specific Group we have several concerns which are also reflected in the BCGS review.** **Comments from the following individuals have been received and are included below:** Robert Bates MD FRCOG Consultant Gynaecologist & Cancer Lead Clinician Basingstoke and North Hampshire NHS Foundation Trust (Chair of CSCCN Gynae-Oncology NSSG) Simon Crawford Consultant Gynaecological Oncologist Southampton University Hospitals NHS Trust Southampton SO16 023-8079-4698 simon.crawford@suht.swest.nhs.uk Adrian Green FRCOG Consultant Gynaecologist and Lead Clinician for Gynaecological Cancer St Mary's Hospital, Newport, Isle of Wight Mr Doug. McKenna, Consultant Gynaecologist and Lead Clinician for Gynaecological Cancer Salisbury NHS Foundation Trust, Salisbury, Wiltshire Dirk Brinkmann Consultant Gynaecologist and Lead Clinician for	Thank you for your comments. We have responded to individual comments below.

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						Gynaecological Cancer Portsmouth Hospitals NHS Trust	
SH	Central South Coast Cancer Network	24.04	Full	General		On the whole I agree with the recommendations of the BGCS. Many of the NICE recommendations appear a bit dated and retrograde.	Thank you for your comments
SH	North East London Cancer Network	29.04		GENERAL		The time period for stakeholders' review should be extended to allow significant rewriting of the recommendations with input from experts (no expert opinion has been sought by this GDG).	The timescales for stakeholder consultation are set by NICE and the GDG are not able to control these. Invited experts can be called upon If the GDG does not have sufficient knowledge or expertise to make recommendations in a particular area. This was not required for this guideline
SH	NCRI/RCP/RCR/ACP/JCCO	30.02	Full	General		There is no mention of borderline disease management (not excluded from analysis)	Whilst borderline ovarian cancer is technically within the scope of the guideline, stakeholders did not highlight that this was a priority issue for investigation in the guideline during consultation. Therefore borderline disease was not included as a topic.
SH	Ovarian Cancer Action	31.00	Full	General		We welcome the inclusion of guidance on the symptoms that may be associated with a potential diagnosis of ovarian cancer, when they are persistent, frequent or new onset, based on the Department of Health Key Messages for Ovarian Cancer agreed by the Department of Health, ovarian cancer specialists and ovarian cancer organisations in 2008.	Thank you
SH	Target Ovarian Cancer	33.00	Full	general		Target Ovarian Cancer welcomes this clinical guidance as a particularly important step forward in terms of helping GPs understand which women should be investigated for ovarian cancer, and in terms of giving women important information on when they should seek medical help for what are often seemingly unimportant symptoms. Almost all women with ovarian cancer see this as the main priority in terms of improving the outlook for women in the future (Target Ovarian Cancer Pathfinder Study 2009).	Thank you

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						There is much progress to be made in this area. The recent NCIN data briefing on routes to diagnosis showed that the most common route for women with ovarian cancer was as an emergency presentation (29% - NCIN report on routes to diagnosis, November 2010)) This is despite the fact that around 90% of women with ovarian cancer experience symptoms and have visited their GP about them (Sources Target Ovarian Cancer Pathfinder Study and Hamilton et al, both 2009). Ovarian Cancer is a challenging disease to diagnose, and GPs in particular must be given support to update their knowledge, and have access to urgent diagnostic tools that will ensure women get referred in a timely manner. The Target Ovarian Cancer Pathfinder Study (2009) which was overseen by a panel of multidisciplinary experts http://www.targetovarian.org.uk/page.asp?section=119&sectionTitle=The+Target+Ovarian+Cancer+Pathfinder+Study+Advisory+Panel showed that a third of women with ovarian cancer who responded waited six months or more after first visiting their GP before getting a correct diagnosis. Late diagnosis is a critical issue in ovarian cancer. We recognise that this clinical guidance is not a comprehensive guide on the recognition and management of ovarian cancer, and therefore inevitably misses some questions which remain unanswered. We welcome the importance placed on evidence, particularly in relation to symptoms, which have in recent years been the subject of debate in the clinical community, and we hope that this guidance will once and for all put an end to the phrase so often used in relation to ovarian cancer ' a silent killer'.	
SH	British Gynaecological Cancer Society 2	34.00	Full	general		A meeting was held on 15 October 2010 to present the guidance in the draft document to members of the BGCS. The meeting was advertised via the BGCS and the NSSG Leads' Group to members. Gynaecological Oncology, Medical oncology,	Thank you for your comments. We have responded to individual comments below.

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						Radiology, Clinical Nurse Specialists, Ovarian Charities, Patient Groups, Network Leads, Unit Leads and MDT Coordinators were represented. Delegates from England, Wales and N Ireland attended. The guidance was presented measure by measure as written in the document. Delegates then voted on the guidance and discussed their views. Minutes of the meeting were circulated to members of the BGCS. All Network Leads were asked to circulate the minutes to their MDTs and Network members. Histopathology was not represented at the meeting but a response from this group has been coordinated by email. The comments below are the views expressed at the meeting in the context of a broader consultation with BGCS members.	
SH	British Gynaecological Cancer Society 2	34.33	Full	General		BRITISH GYNAECOLOGICAL CANCER SOCIETY 12 November 2010 **Re: Ovarian Cancer Guidelines – NICE document – Consultation process 2010** Dear Sir, The above document has undergone discussion with BGCS members in October 2010. There were many concerns voiced and many of the comments will already have been returned to the NICE group. I should emphasise that the BGCS is a multidisciplinary society. The comments are from such a group – not just gynaecological cancer surgeons. The BGCS strongly recommends that the document is	Thank you for your comments. We have responded to individual comments below.

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						reviewed and the comments and proposals made, addressed. Proceeding with the document in its present form would have serious ramifications for the care of women with ovarian cancer, Yours sincerely  Sean Kehoe President of the British Gynaecological Cancer Society	
SH	A Little Wish	35.02	Full	general		Ovary(ies) should not be removed during a hysterotomy or hysterectomy unless cancer has been proven and the patient has given informed consent. Unfortunately this is undertaken too often and the patient is later told by the doctor that the ovary(ies) looked cancerous or that it would reduce the risk of cancer in the future.	We agree that informed consent is very important and that all risks and benefits should be discussed with the patient before any procedure. We feel that this is implicit in our recommendations.
SH	Royal College of Nursing	39.00	General	General		The Royal College of Nursing welcomes this guideline. It is comprehensive.	Thank you
SH	Royal College of Nursing	39.01	Full	General		The guideline is good well written document - which will improve the care for women with ovarian cancer. Many of these practices are already undertaken and it will enable healthcare professionals to follow the same guidelines.	Thank you
PR	NETSCC, Health Technology Assessment	5.01	Full	general	general	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** There is limited detail regarding the statistical methodology.	If statistical analysis was done for a particular topic the details were recorded in the review strategy section for that topic in the evidence review document. If figures from published meta-analysis were used then the details of that meta-analysis were recorded in the evidence tables.
PR	NETSCC, Health Technology Assessment	5.02	Full	general	general	**2.2 Please comment on the health economics and/or statistical issues depending on your area**	If statistical analysis was done for a particular topic the details were recorded in the review strategy

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						of expertise. In some recommendations, the evidence is simply from a review of the literature, whereas in others it is a systematic review. There needs to be a methodology section, to describe the approach to analysis. In particular, for the meta analyses that were undertaken: 1.Were fixed or random effect models used? 2. What statistical program was used for analysis e.g. RevMan? 3.What about heterogeneity tests? 4. What about forest plots?	section for that topic in the evidence review document. If figures from published meta-analysis were used then the details of that meta-analysis were recorded in the evidence tables.
PR	NETSCC, Health Technology Assessment	5.03	Full	general	general	Overall the report is statistically well presented.	Thank you
PR	NETSCC, Health Technology Assessment	5.06	Full	general	general	**3.2 Are any important limitations of the evidence clearly described and discussed?** Following each recommendation there is a section that sets this in context: Linking evidence to recommendations. These are clearly written and summarise the sections well.	Thank you
PR	NETSCC, Health Technology Assessment	5.07	Full	general	general	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** Excellent report. Very readable and clearly presented.	Thank you
PR	NETSCC, Health Technology Assessment	5.08	Full	general	general	The review of the literature fed clearly into the recommendations, but due to the low quality papers in some cases the evidence is weak and further research is required in all aspects of the pre-diagnosis phase and delays (patient, primary care and secondary care),	Thank you
PR	NETSCC, Health Technology Assessment	5.09	Full	general	general	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** The research recommendations are very clear. They do however highlight the weak evidence base for the algorithm on page 19.	Thank you
PR	NETSCC, Health Technology Assessment	5.10	Full	general	general	**Section five – additional comments** **Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish.** Well written report. It highlights the problematic	Thank you

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						nature of diagnosing patients. As quoted a GP will see "one case of ovarian cancer every five years which makes recognition of the symptoms and early diagnosis more difficult".	
PR	NETSCC, Health Technology Assessment	5.11	Full	general	general	There is limited evidence of the natural history of ovarian cancer, so delays the impact of delays in diagnosis are unclear.	We agree, but the assumption that it might underpins many current goverment cancer inititiatives, and delays in diagnosis are thought to be an correctable and contributary factor to relatively poor UK survival rates.
PR	NETSCC, Health Technology Assessment	5.12	Full	general	general	Once diagnosed, the treatment and support needs of patients are discussed, but again hindered by a lack of evidence.	Thank you
PR	NETSCC, Health Technology Assessment	5.23	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Appropriate use is made of the LETR method to contextualize the evidence for recommendations.	Thank you
SH	Ovacome		Full	General	All	Ovacome has participated in the BGCS consultations regarding this guideline and fully endorses its submission.	Thank you
SH	North East London Cancer Network	11.00		General	General	Please find enclosed comments on the recent draft guidance on ovarian cancer. Section 5.1 on management of advanced ovarian cancer does not cover the need for optimal staging or consider the role of frozen section. We suggest the publication of this guideline is delayed to allow a full rewrite of this section.	Thank you for your comments. We have responded to individual comments below. Optimal staging is covered in section 4.1. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic.
SH	National Forum of Gynaecological Oncology Nurses	20.01		General	General	CNS's have a positive impact on cancer services these are: ● Enabling care to be delivered closer to home ● Shaping services uniquely for individual patients with cancer ● Self management of symptoms & side effects of treatment ● Contributing to the quality of care for patients with a	Thank you for this information, we agree.

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						cancer diagnosis ● Increasing in supportive role for people living beyond cancer (cancer survivorship) as more than 2 million people are living with cancer and is quoted to set to rise to 4 million by 2030 ● CNS's work closely with patients and other members of the multidisciplinary team to adapt to patients emerging themes which may led to reducing the need for unplanned care	
SH	National Forum of Gynaecological Oncology Nurses	20.02		general	General	**Recommendations:** - Consider the importance of the role of the Gynaecological Oncology CNS for any women at the point of an ovarian cancer diagnosis	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis, rather than who should deliver this information so we are not able to recommend who should do this.
SH	National Forum of Gynaecological Oncology Nurses	20.03		general	General	- That all women with a newly diagnosed ovarian cancer should have access to a CNS/keyworker and receive an appropriate contact number for them and their team.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.04		general	General	- A Gynae Cancer CNS is competent in assessing a woman's information needs and to be a source of support for a woman, their families and carer's when diagnosed with an ovarian cancer	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.05		general	General	- The CNS's unique role allows a continuous support for women with an ovarian cancer through their disease trajectory this holds a valuable insight in the supportive care needs of women at all points along their pathway.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what

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							information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.06		General	General	- CNS's in Gynaecological Oncology are sensitive to the increased awareness and focus on the needs of women who have completed their treatment for ovarian cancer.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.07		general	General	- We acknowledge that this consultation focuses on a new ovarian cancer diagnosis. A CNS through their expert skills and knowledge can identify key areas as a result of an ovarian cancer that a woman, their family and carer's may wish to discuss at the point of diagnosis. For example innovations in the management of malignant ascites in the out patient setting and the use of long term catheters are of huge benefit to patients.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.08		general	general	- Women who are undergoing or have undergone treatment for an ovarian cancer may required ongoing specialist support which is often provided by CNS's or a CNS can sign post to the appropriate specialist in areas such as: ● Premature menopause ● Psychological support for women, their family and carer's ● Psychosexual support for women and their partners ● Fertility or assisted conception/surrogacy support ● Lymphodema ● Dietetics/ nutrition/ weight loss advice ● Physiotherapy ● Urogynaecological specialist ● Financial advice	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.09		general	general	- All cancer CNS's as part of their mandatory training should have undergone Advanced Communication Skills Training (Cancer Standards Peer Review Measure) It is imperative to highlight the higher level communication skills that a CNS's holds to enable to	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of

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						support women through what is a complex disease trajectory.	diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.10		general	general	Gynaecological Oncology Clinical Nurse Specialists provide support provision through all treatment modalities (surgery and chemotherapy) this may differ in other tumour sites where CNS's provide support for one treatment modality. This is key in supporting women with a newly diagnosed ovarian cancer as a cohort of these women will commence neo adjuvant chemotherapy as first line treatment. The CNS will remain the same through all treatments which builds better trust and support for women with a newly diagnosed ovarian cancer.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.11		general	general	- Clinical Nurse Specialists in Gynaecological Oncology act as a liaison in communicating with all health care professionals across primary, secondary and tertiary care. Women with ovarian cancer spend a very small percentage of their time in an acute hospital setting; hence a CNS's assisting in enhancing collaborative working to ensure optimal care for women with a newly diagnosed ovarian cancer.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.12		general	general	The majority of women diagnosed with ovarian cancer have advanced disease (Stage III and IV) and is widely known that ovarian cancer has both a complex diagnosis with complex treatments. Women may have had a delayed diagnosis therefore it is imperative that women, their families and carers have access to a CNS	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.
SH	National Forum of Gynaecological Oncology Nurses	20.13		general	General	- CNS's often act as a women's advocate and are the patient's voice in the MDT when treatment decisions are made. This ensures a woman's care is planned with a holistic approach.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis. Therefore we are not able to make recommendations outside of this issue.

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SH	National Forum of Gynaecological Oncology Nurses	20.14		general	General	- NICE (2004) Supportive and Palliative Care Guidance recommends that all CNS's are trained with advanced communication skills and training to competently undertake psychological and holistic assessment at the point of a cancer diagnosis.	We agree
SH	National Forum of Gynaecological Oncology Nurses	20.15		general	General	- Clinical Nurse Specialist's in a variety of settings provide a nurse led service for women with ovarian cancer and provide fast track diagnostic clinics to enhance the pathway for women with ovarian cancer.	We agree
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.11	Full	General	General	There is very little in the guideline on the subject of debulking surgery. Why?	We have revised the background in section 5.1 to be more comprehensive. We have also inserted a recommendation which the GDG believe accuratly reflects the extent of the available evidence.
SH	College of Occupational Therapists	27.00	NICE version	General	General	There seems to be no mention anywhere in the document of the Rehab Care Pathways.	This is correct. Rehab care pathways are not in the scope of this guideline and this guideline is not a complete patient pathway – just focuses on key areas of uncertainty.
SH	NCRI/RCP/RCR/ACP/JCCO	30.00	Full/NICE	General	General	The NCRI/RCP/RCR/ACP/JCCO are grateful for the opportunity to comment on the draft guideline. We would like to make the following comments which have been coordinated across the NCRI Gynaecological Clinical Studies Group with feed-in from expert fellows and members of the RCP/RCR/ACP/JCCO.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.01	Full/NICE	General	General	Second line treatment is <u>not</u> in the remit of : **Ovarian cancer: the recognition and initial management of ovarian cancer** Therefore, it is vital that <u>all references to second line treatment</u> should be removed from the draft.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.84	NICE	General	General	The title and the scope of the review excludes relapsed disease as shown on page 14. Any reference to second line treatment should be deleted. It is very complicated and merits a separate guideline by itself. Quality of life assumes progressively greater importance as the survival gain diminishes as in resistant or partially platinum sensitive disease populations	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.

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SH	NCRI/RCP/RCR/ACP/JCCO	30.85	NICE	General	General	Same comment as above	Same response as above
SH	Royal College of Nursing	39.02		General	General	Primary care guidelines are very helpful – which will improve the patient's pathway. We would have liked to have seen some guidelines on Ascites management of women for symptomatic relief as this varies from hospital to hospital and doctor to doctor. Many women have more distress with these symptoms whilst waiting for treatment.	This guideline is not intended to cover all aspects of ovarian cancer. Instead it is supposed to focus on those issues where there is uncertainty or variation in practice. Stakeholders were consulted on the topics included in the scope in line with NICE methodology. We are only able to make recommendations on these topics.
SH	NCRI/RCP/RCR/ACP/JCCO	30.03	Full	3	6	The clinical questions chosen are often not the most important. There needs to be a better way to involve stakeholders so the right questions are chosen.	NICE encourages all relevant stakeholders to participate in a workshop where the draft scope is discussed. The draft scope is then subject to a 4 week period of consultation with stakeholders to obtain their feedback. This feedback is then considered when developing the final scope of the guideline. Consequently the topics included in the ovarian cancer guideline are those considered by the stakeholders to be the most important.
SH	NCRI/RCP/RCR/ACP/JCCO	30.04	Full	3	11	The recommendations, although evidence-based, appear to have a distant and protracted connection, at times. Whilst accepting that the evidence is weak in various sections, it is also clear that a large degree of personal opinion and has influenced the majority of recommendations throughout the document. The opinions and recommendations in the document may not reflect main-stream or expert opinion either in the UK or Internationally	NICE methodology for developing guidelines is that the published literature is systematically searched for papers that are relevant to a particular topic. These papers are then sifted and critically appraised by an independent systematic reviewer. The results of this evidence appraisal are presented to the GDG (14 people in this guideline) who come to a group consensus on what recommendations to make. These recommendations are supported by a LETR paragraph (linking evidence to recommendations) which explains the GDGs decision making process when moving from the evidence to the recommendations. NICE guidelines are predominantly evidence-based and may not necessarily reflect main stream practice or expert opinion.
SH	NCRI/RCP/RCR/ACP/JCCO	30.05	Full	3	19	The GDG membership could have been more diverse. Only two gynaecological oncologists were present on the panel. We would have expected more	When deciding on the constitution of a GDG, several factors are considered. The specialties on the GDG need to be consistent with the topics in

						and for at least one to have RCOG sub-specialty accreditation. The recommendations made in the NICE document do not always reflect practice at Leading Centres in the UK or main-stream practice within the UK or Internationally. We are surprised that only one Pathologist was present on the GDG panel.	the guideline scope. There also needs to be a balance between the number of individuals from the same specialty who are represented on the GDG so that it is not dominated by one group. It is also important that the individuals on the GDG have a reasonable geographic distribution, so that variations in clinical practice across the UK can be better understood. The total number of people on the group also needs to be limited in order that the group can function effectively. To ensure the correct balance of GDG membership has been achieved, the proposed list of specialties is checked and approved by NICE before it is advertised. It is also discussed at the scoping workshop where stakeholders have an opportunity to comment. The list of specialties for the GDG membership of the ovarian cancer guideline specified a gynaecological oncologist from both a cancer centre and a cancer unit. The GDG job description did not specify that these individuals needed to be RCOG accredited. NICE guidelines are predominantly evidence-based and may not neccessarily reflect main stream practice or expert opinion. Stakeholders did not raise any concerns during the scoping workshop or scope consultation on the proposed number of pathologists on the GDG.
SH	Royal College of General Practitioners Wales	6.00	Full	4		Outline of symptomatology is helpful.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.06	Full	4	2	Detection of ovarian cancer in general practice: - age threshold should be defined here eg women over 50.	The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who were younger. Text explaining this decision has

							been added to the LETR paragraph. Current health policy in an effort to improve UK one year survival has established greater awareness of symptoms and earlier diagnosis as a means to achieve an improvement in outcomes. These recommendations support this policy which is underpinned by evidence (page reference to evidence summary). Health services resources will need to respond to patient demand.
						- there is little grade A evidence to support investigation on the basis of symptoms - Implementing this recommendation is likely to lead to vastly increased referrals to ultrasound and 2 week wait systems. This is likely to adversely affect accurate diagnosis and management of women who actually do have cancer.	
SH	Target Ovarian Cancer	33.01	Full	4	2	Given that most GPs will probably only read the key priorities, should the red flag symptoms for urgent referral (pelvic mass and/or abdominal distension on examination) be included here as well? Whilst it is recognised that most cases occur in women over the age of 50, we know from reports from some patients who are under the age of 50 that they were told that they could not possibly have cancer as it does not affect young women. Therefore we would like NICE to reconsider the wording here to be helpful to all age groups.	The GDG voted on which recommendations were included in the list of key priorities. The recommendation you are referring to didn't get voted as a key priority and hence cannot be included in this list. The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who were younger. Text explaining this decision has been added to the LETR paragraph.
SH	Target Ovarian Cancer	33.02	Full	4	10	Given that IBS is the most common misdiagnosis given to women with ovarian cancer (Target Ovarian Cancer Pathfinder Study 2009) we particularly welcome the inclusion of this recommendation.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.07	Full	4	11	Word "new" needs inserting before symptoms	The Goff definition is 'within the last 12 months', which we have now added to the recommendation.
SH	Target Ovarian Cancer	33.02	Full	4	16	Target Ovarian Cancer believes there is potential confusion in the way this guidance is worded. 1) It is not clear whether the guideline refers to pelvic or abdominal, or pelvic and abdominal ultrasound. It should be the latter. 2) Nor does it say whether this should be done IN primary care, or just ACCESSED from primary care. It is important that those carrying out the scans have sufficient training and experience in the procedure and reporting as this can influence outcomes.	We do not think the wording is confusing as it states "ultrasound of abdomen and pelvis" We agree and have amended the background to take this issue into account.
SH	Target Ovarian Cancer	33.03	Full	4	17	We would urge some reference to timescale being	There is no basis on which to inform a timescale for

						included here. Whilst we recognise this is not a 'red flag' situation, we know from the Target Ovarian Cancer Pathfinder Study that currently 53% of UK GPs do not have direct access to urgent transvaginal ultrasound. In Wales this figure rises to 61%. The study also showed that for non urgent scans it takes anywhere between 2 weeks and 2 months for results to come through, after ordering the tests (Abdominal 75%>2 weeks, 35%> 1 month, 2%> 2 months, TVU 71%> 2 weeks, 33%> 1 month, 3%>2 months). This contrasts with CA125% where 84% of results are within 2 weeks from ordering the test. These results reflect overall UK results except where highlighted.	these tests.
SH	Target Ovarian Cancer	33.04	Full	4	18	We welcome the inclusion of this recommendation, but would hope it could be made even stronger. CA125 is not sensitive and specific enough, particularly in early stage disease, leaving a large proportion of those with early stage disease disadvantaged if they are not actively encouraged to return. This point was made by an MP, who is also a GP, at the meeting of the All Party Parliamentary Group on Ovarian Cancer on October 29th 2010. An Ovacome survey some years ago showed that the greatest gap between GP visits occurs between their first and second visit.	We feel that the current wording is specific and instructive. We do not think further changes are necessary
SH	NCRI/RCP/RCR/ACP/JCCO	30.08	Full	4	20	RMI – this is not consistent with green top guidelines issued by the Royal College of Obstetricians and Gynaecologists. In the absence of age criteria this is likely to result in many young women being referred for endometriosis for example and being subjected to anxiety and unnecessary surgery.	In view of the lack of a definitive cut off point for RMI I the GDG are happy to amend our recommendation to be consistent with current RCOG guidelines.
SH	NCRI/RCP/RCR/ACP/JCCO	30.09	Full	4	28	Retroperitoneal lymph node assessment is standard practice in staging early ovarian cancer in many Centres. This is part of "optimal staging" as defined on page 74 of 144 (full guidance) Recommendation risks condoning suboptimal practice	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes.

							Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 4, line 28 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed.
						Frozen section is relevant here but not reviewed	The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic.
						ACTION trial not mentioned. It should be.	The ACTION trial was designed to investigate the use of adjuvant chemotherapy in patients with early stage ovarian cancer. Therefore it was not identified by the literature search for the topic on systematic retroperitoneal lymphadenectomy. In addition, the subgroup analysis in ACTION, of optimal vs sub-optimal surgery was done post hoc and was not powered to assess this comparison. Therefore these results would have been difficult to interpret with certainty.
						The wording requires redrafting to provide clarity.	We have revised the background to clarify why we are looking at this topic and to ensure that all definitions are made explicit.
						The role of lymph node “assessment” or “dissection” should be discussed here	The text you refer to are the key priorities for implementation. The background to lymph node assessment is in chapter 4.
						At a one day meeting on the optimal management of early stage ovarian cancer (Belfast, March 2010) 75% of delegates voted that retroperitoneal node dissection (para-aortic and pelvic) should be performed if frozen section reported malignancy	The guideline has not recommended that optimal surgical staging should not be performed.

						The relevant Cochrane Review (Winter-Roach) states that “there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy”. Not performing this procedure reduces options for patients The last is particularly relevant in women wishing to retain fertility.	
SH	Target Ovarian Cancer	33.05	Full	4	28	There appears to be confusion here, as the title suggests staging but the recommendation (line 30) refers to treatment. It is imperative that there is clarity on this point. There is an apparent contradiction in that systematic retroperitoneal lymphadenectomy is not recommended as standard treatment in those whose ovarian cancer appears confined to the ovaries, but adjuvant chemotherapy is not to be offered to women who have had optimal staging and have low risk disease. Optimal staging includes lymph node assessment and could prevent women undergoing chemotherapy unnecessarily. The problem may lie with the original questions, but the final guidance should be absolutely clear as to what is being suggested. We would like to ask what consideration has been given to the ACTION trial, and to draw the group’s attention to the Rouzier et al publication (BJOG October 2010)	We have deleted “staging” from the title This guidance has defined optimal staging as comprising *“midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)”.* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 4, line 28 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. The ACTION trial was not included in the evidence review for this topic because this was a subgroup

						http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2010.02633.x/abstract.	analysis of optimal vs sub-optimal surgery which was not powered to assess this comparison. Therefore these results were difficult to interpret with certainty. The Rouzier study was not identified by the update search conducted prior to consultation in the guideline. We have looked at the paper but there is considerable overlap with the patient group in Chan and the results do not materially alter the conclusions of the GDG. Therefore we have not included this paper in the evidence review
SH	Target Ovarian Cancer	33.06	Full	4	35	As a patient led organisation, Target Ovarian Cancer welcomes this prioritisation. However we feel its importance could be further strengthened by placing it mid guidance, to reflect the fact that it is at point of diagnosis that this information should be considered. The Target Ovarian Cancer Pathfinder Study showed that approximately a third of women did not have access to emotional support that they needed, and as a whole this group represented 25% of all those diagnosed.	The GDG were unanimous in their support for the flow of the guideline including where the chapters were sited. Therefore we do not think any changes are needed
SH	Target Ovarian Cancer	33.08	Full	6	15	We would support this research recommendation, as for those women whose RMI is less than 200 (and particularly those women who are premenopausal and therefore likely to fall into this group) there may well still be uncertainty and risk that needs to be managed.	Thank you
SH	Target Ovarian Cancer	33.07	Full	6	2	We welcome this research recommendation.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.10	Full	6	28	Case control studies are inappropriate. Randomised trials of MRI vs CT should be performed. In addition diffusion weighted MRI should be included as well.	Whilst an RCT would be preferable, there are questions about the feasibility of conducting a straight randomised trial of CT vs MRI, given the implication on services and availability
SH	NCRI/RCP/RCR/ACP/JCCO	30.11	Full	6	26	There are already significant data that have demonstrated the absence of benefit from retro-peritoneal lymphadenectomy. It would be more useful to develop advanced imaging techniques in parallel with the above research suggestion.	We are confused by this statement as it seems to contradict one of your earlier comments. However we are keeping the research recommendation on systematic retroperitoneal lymphadenectomy because this remains an important question that needs to be addressed. We would agree that developing advanced imaging techniques should be supported however we felt that our current research recommendation on CT vs MRI was a higher priority.

SH	NCRI/RCP/RCR/ACP/JCCO	30.12	Full	6	38	A trial of RPLND is considered unrealistic as very few surgeons can do such an operation up to renal veins. As there is no survival benefit there is little point.	There is considerable debate about this issue. One of the objectives of guideline development is to address areas of uncertainty in terms of management. From the data available, it is not clear whether there is or is not a therapeutic or survival benefit from systematic retroperitoneal lymphadenectomy compared to lymph node sampling. Therefore research is required. Cluster randomisation could overcome your concerns about the number of surgeons currently skilled to undertake this surgery. Surgical consensus in this area is that surgeons do need to be properly skilled in order to demonstrate a survival benefit.
SH	Target Ovarian Cancer	33.09	Full	6	43	It is important that women are able to make informed choices when it comes to treatment options. Therefore it is vital that they are told about the benefits and risks of systematic retroperitoneal lymphadenectomy, versus the potential benefit of avoiding unnecessary chemotherapy. To reiterate, it is not clear in the guidance whether this relates to staging, treatment or both.	Research, by definition, requires patient informed choice as part of the recruitment process and we do not feel that further changes to the text are required.
SH	Target Ovarian Cancer	33.10	Full	7	4	We believe this study should not only look at surgery or no surgery, but also show the extent of surgery for women with advanced ovarian cancer whose tumour cannot be fully excised.	The precise design of the study would need to characterise the nature and extent of the surgery in the surgical arm, but we do not feel it is necessary to specify this in the recommendation
SH	Target Ovarian Cancer	33.11	Full	7	16	We would like to ask that further research be considered for the role of HE4 alone, and in combination with other markers, for detecting and managing ovarian cancer treatment (see our comments relating to page 51.	NICE methodology restricts the number of key priorities for research to five areas. Given that research is currently ongoing on the role of HE4, the GDG did not feel it was a priority to recommend additional research.
PR	NETSCC, Health Technology Assessment	5.14	Full	8--18	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual). I can find no fault with the methods. It is impressive to see how NICE's methods have evolved over the years, to distinguish for example between grades of evidence and priority for implementation.**	Thank you
PR	NETSCC, Health Technology Assessment	5.15	Full	8--18	General	**I can find no fault with the methods. It is impressive to see how NICE's methods have**	Thank you

						evolved over the years, to distinguish for example between grades of evidence and priority for implementation.	
PR	NETSCC, Health Technology Assessment	5.13	Full	10	General	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** The work fulfills the declared intentions.	Thank you
SH	British Gynaecological Cancer Society	8.01	full	11	14-16	This states a contradiction in terms: definition of optimal staging – how is optimal staging possible if lymph nodes are not assessed (see previous recommendations)? In this context, the definition of optimal surgical staging must be clarified	In section 4.1, the guideline has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins.
SH	British Gynaecological Cancer Society	8.02	full	11	23,24	• Recommendation based on just one inadequately powered study (Bell et al) • This illustrates the inconsistent approach throughout the guidance on the level of evidence required for recommendations	This section covers the methodology and it is not clear how these comments relate to this text.
SH	British Gynaecological Cancer Society	8.00	full	11	8-11	I strongly disagree with this statement • Retroperitoneal lymph node assessment is standard practice in staging early ovarian cancer in many Centres. This is part of "optimal staging" as defined on page 74 of 144 (full guidance) • Recommendation condones suboptimal practice • Frozen section relevant here but not reviewed • ACTION trial not mentioned - this also suggests a lack of expertise in selecting relevant literature • Wording confusing	This section covers the methodology and it is not clear how these comments relate to this text. This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic

						• The role of lymph node “assessment” or “dissection” is not discussed • At a one day meeting on the optimal management of early stage ovarian cancer (Belfast, March 2010) 75% of delegates voted that retroperitoneal node dissection (para-aortic and pelvic) should be performed if frozen section reported malignancy • The relevant Cochrane Review (Winter-Roach) states that “there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy”. Not performing this procedure reduces options for patients • The last is particularly relevant in women wishing to retain fertility.	retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 4, line 28 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic. The ACTION trial was designed to investigate the use of adjuvant chemotherapy in patients with early stage ovarian cancer. Therefore it was not identified by the literature search for the topic on systematic retroperitoneal lymphadenectomy. In addition, the subgroup analysis in ACTION, of optimal vs sub-optimal surgery was done post hoc and was not powered to assess this comparison. Therefore these results would have been difficult to interpret with certainty. We have revised the background to clarify why we are looking at this topic and to ensure that all definitions are made explicit. The text you refer to are the key priorities for implementation. The background to lymph node assessment is in chapter 4. The guideline has not recommended that optimal surgical staging should not be performed.
PR	NETSCC, Health Technology Assessment	5.28	Full	19		4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence. Yes, the report is well written. The figures are well drawn (e.g. the Algorithm)	Thank you
SH	Royal College of General	19.05	Full	19		Algorithm should say urgent USS (i.e. within 2 weeks)	Changes have been made to the algorithm to bring

	Practitioners						it in line with changes made to the guideline as a result of consultation.
SH	NCRI/RCP/RCR/ACP/JCCO	30.13	Full	19		There is an excessive focus on gynaecological cancer in view of the symptoms described. If a woman over 50 presents with IBS symptoms or a change in bowel habit she should surely undergo GI investigations. The Ca125 could be raised in the presence of GI pathology. As colorectal cancer is 4-5 times more common than ovarian cancer it is more appropriate to investigate for GI malignancy than to focus on gynaecological cancer. Conversely, there is too much stress on Ca-125. Up to 25% of ovarian cancers will be non-secretory. If too much importance is attributed to Ca-125 then a significant proportion of ovarian cancers will have a delayed diagnosis. The guidance should explain this so that GPs remember that a normal Ca-125 does not negate the possible diagnosis of ovarian cancer. The implementation of Ca-125 in the way that is described here, because of the prevalence of Ca-125, would lead to a widespread use of screening through Ca-125; a strategy that we know leads to excess morbidity and in some cases mortality.	The issue that is being addressed is that only a minority of women with ovarian cancer are referred on the correct pathway initially. The guideline does not state that women with symptoms should be referred on the ovarian cancer pathway, rather it suggests that in this group the possibility of ovarian cancer should be considered in primary care and the appropriate initial tests performed to enable better secondary referral. In the main text of the guideline it is clear in the recommendations presented that patients with persistent symptoms, despite normal investigations should return to their GP for onward investigation. Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. The introduction of CA125 in this symptomatic population (and therefore not screened asymptomatic population) is likely to direct more appropriate patients on the most appropriate pathway, sooner. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available.
SH	NCRI/RCP/RCR/ACP/JCCO	30.14	Full	19		There is sometimes a need to rely on cytology if there is a pelvic mass and a Ca-125: CEA ratio that exceeds 25. It would be useful to include this as a possible but less desirable strategy	A CA125:CEA ratio may be useful but it was not considered as an intervention in our question on tumour markers. Therefore the evidence for this ratio has not been examined and we are not able to make recommendations on its use.
SH	NCRI/RCP/RCR/ACP/JCCO	30.15	Full	19		Our experts are uneasy about omitting chemotherapy in low risk stage I disease (except well diff Ia) until the long term results of ICON1 have been peer reviewed and published. This guidance has implemented the long term results of ICON1 before they have been published.	Changes have been made to the algorithm to bring it in line with amendments made to the recommendations following consultation
SH	NCRI/RCP/RCR/ACP/JCCO	30.16	Full	19		We are not aware of any evidence that suggests that 3 cycles of chemotherapy are acceptable in stage I disease. The only data we have seen on this	Changes have been made to the algorithm to bring it in line with amendments made to the recommendations following consultation

						demonstrated the requirement for 6 cycles. This is particularly relevant to the UK where the quality of surgery and therefore surgical staging is variable. Thus there is a significant risk of administering 3 cycles of platinum based chemotherapy to patients with occult stage III disease.	
SH	NCRI/RCP/RCR/ACP/JCCO	30.17	Full	19		The algorithm describes not to perform systematic retroperitoneal lymphadenectomy (SRL) and leads to a box recommending diagnosis by biopsy. It would be inappropriate to biopsy a tumour which appears confined to the ovary for risk of up-staging. This requires correction. The algorithm also states “for stage IC or above, offer 6 cycles of carboplatin or consider 3 cycles of carboplatin/paclitaxel. Does this refer to stage II, III and IV? If so, it is inappropriate.	Changes have been made to the algorithm to bring it in line with amendments made to the recommendations following consultation
SH	NCRI/RCP/RCR/ACP/JCCO	30.18	Full	19		Flow diagram box indicates the use of 6 cycles carboplatin or 3 cycles carboplatin-paclitaxel for all patients with ovarian cancer stage Ic or above. This contradicts all current evidence and the use of 3 cycles of chemotherapy in such patients would be undertreatment.	Changes have been made to the algorithm to bring it in line with amendments made to the recommendations following consultation
SH	Target Ovarian Cancer	33.12	Full	19	1	This guidance is not comprehensive in terms of the diagnosis and management of ovarian cancer, and therefore we believe that it would be clearer to break up this algorithm to suit its audience: primary care, secondary care. Within that aimed at secondary care, there appears to be confusion, with the diagram not making it explicitly clear what relates to diagnosis, staging or management. It also implies that the suggested dose for those with grade 1c (or higher) should receive that drug regime, which is not what the guidance says on page 74. There is a strong need for this section to be very explicit in what it does and does not cover.	The algorithm indicates on the right hand side, which parts are relevant to primary and secondary care. We do not feel any further changes are needed.
SH	Target Ovarian Cancer	33.13	Full	19	1	Third box of second line of algorithm – ‘reports persistent or frequent’ - see comment 2 above.	See response above
SH	Target Ovarian Cancer	33.14	Full	19	1	No advice given for Risk of RMI<200 (see comment 10 above).	We have made relevant changes to the algorithm and recommendation.
SH	Birmingham cancer network	37.00	Algorithm[3]	19	1	CA125 and ultrasound of pelvis and abdomen should be the first line of investigation in women >50yrs in primary care. We know from population study that	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most

						50% of stage 1 ovarian cancer will have normal CA125. Our aim is to detect early stage ovarian cancer as well. We all know that it will also delay the referral if we leave these women with CA125 <35 and ask them to come back with persistent symptoms. We also do not know what duration we call persistent symptoms. I recommend altering this algorithm. Further clarification is required in the box stating confirm diagnosis using surgical specimen or biopsy not cytology. Image guided biopsy depends on the centre and available expertise and willingness of interventional radiologists. Block analysis of centrifuged cells with immunohistochemistry could ascertain reasonably for a diagnosis. The sentence of laparoscopy for biopsy when not requires rephrasing. For example consider laparoscopy only above diagnostic intervention is not possible. There are risks of laparoscopy as well in advanced ovarian cancer.	appropriate cancer diagnosis pathway. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. We agree and believe that the algorithm, and the recommendations from which it was derived, are clear
SH	Ovacome		Full	19	1	Symptomatic women with CA125 below 35 are asked to return if symptoms persist. We would advocate a stronger statement, with repeat of the CA125 in a defined period of time which reflects research findings suggesting that it is the rate of rise, rather than the number itself which is a better predictive value.(see comment 9 below)	Repetitive testing was not the subject of a literature search or evidence appraisal. We are therefore unable to make recommendations on this
SH	Ovacome		Full	19	1	The algorithm does not specify that the woman should be referred to a specialised centre for Gynae oncology, rather referral to an MDT after further tests – this is contrary to existing best practice. The mode and interpretation of ultrasound is highly operator dependant. Ovacome believes that women should be investigated at centres with specialist skill in this area. Not only is a womens survival is enhanced by specialist care, but a second referral may lead to unnecessary delays in treatments as well as causing undue psychological distress.	The IOG stipulates that the specialist MDT for gynaecological cancer resides in a specialist centre. Therefore the recommendation on patients with an RMI >250, and subsequent recommendations are wholly consistent with the IOG and what you suggest.

SH	Ovacome		Full	19	1	Provision of information at MDT referral – only 1 in 3 screen positive women actual go on to be diagnosed with the disease – We would advocate that initial support be provided by referral to specialised organisations. Written information on issues such as staging/fertility and HRT would be more appropriate at a later stage when CT or further evidence suggests ovarian cancer	We believe that the principle of information provision and support related to ovarian cancer is crucial at every step of the pathway. There may be elements of the information needs that are more relevant at different times, for example fertility and HRT may be an issue at a later stage. However the needs assessment and detailed provision of information should be based on individual patient preferences, following a discussion between the patient and their keyworker.
SH	Ovacome		Full	19	1	Treatment – please see later comments.	Thank you
SH	Royal College of General Practitioners	19.02	NICE guide	19	1-3	The algorithm again appears to suggest that physical exam is not part of the assessment of non-specific symptoms and that such symptoms should trigger bloods and scan. Is this the intended perception? It does not clarify that a negative physical exam still should trigger tests.	The issue of physical exam is covered in the second row, left hand box.
SH	Ovacome		Full	20	19	It is our understanding that this data (stage/grade) is not currently collected for ovarian cancer	The minimum dataset has been agreed as containing all of these things. However collection of this dataset is still very variable.
SH	Target Ovarian Cancer	33.15	Full	20	32	It is expected that the first tranche of data from the International Cancer Benchmarking Partnership will be published in December 2010. This will give updated figures on survival rates (five year, one year, and five conditional on one year) and on international positioning across the partner countries. For further information contact John Butler at the Department of Health (john.butler@dh.gsi.gov.uk).	Thank you for this information. We contacted John Butler, but unfortunately did not receive a reply in time to update this data.
PR	NETSCC, Health Technology Assessment	5.16	Full	20	Gene ral	Epidemiology: the report usefully includes limited or partial datasets where these are the only source of information available, for example Table 1.3 p32. This helps to highlight gaps in knowledge.	Thank you
PR	NETSCC, Health Technology Assessment	5.35	Full	21 . 33 63 . 71 . . 76		Minor grammatical / typographic errors Conflict of number: “These data record the speciality associated with the appointment but does not record the particular investigation” Fig 1.16: Ğ Table 4.1 Column “Quality” – characters not printing in pdf; what is the abbreviation “Ppts” – could just write “Patients”? Table 4.2 Column “Number of patients” includes percentage figures for survival. These are proportions.	We have made these changes.

						The ratio of actual numbers would be preferable, or change the name of the column. "The two objectives of this chapter were:" … the present tense works better in Guidelines	Outcomes were reported variously as absolute numbers, ratios or percentages. One column heading does not suit all
SH	NCRI/RCP/RCR/ACP/JCCO	30.19	Full	26,27		Fig 1.7 shows the age-stand mortality in UK as ranging 7.9 to 13 (2005) whereas Fig 1.10-Globocan (labelling needs correcting - UK) shows it is on average either 5.8 or 6.4.(2008). This appears to show that mortality has fallen significantly between 2005 and 2008. If so, we would be grateful for comment on this. We wonder why the UK network figures, ranging from 7.9 to 13 are so out of date if Globocan has 2008 figures?	The Globocan project gives contemporary estimates of mortality rates and hence doesn't show the true rates. Because Fig 1.7 and Fig 1.10 show different sets of data it would not be appropriate to compare between the two. There is always a delay in the publication of the network data, due to cleaning the data.
SH	Ovacome		Full	29	4	We are advised that there is no robust evidence to support the assertion that poor survival is solely the consequence of advanced stage at diagnosis	We have amended the text to "contributes to ovarian cancer having the lowest"
SH	Birmingham cancer network	37.01	Full	31	7	Suggest describing staging as this has been described on the original FIGO 2009 classification format.	We have inserted a definition of optimal surgical staging for clarity.
SH	Royal College of General Practitioners Wales	6.01	Full	31	7-26	Figure is rather difficult to follow.	This is a standard staging format and we believe is clear as is.
SH	Airedale NHS Foundation Trust	16.00	Full	32	1	There is a 'deprivation gradient' in 1-year survival in ovarian cancer suggesting that there is late access to palliative treatment for less well-off people Cooper et al British Journal of Cancer (2008) 99, S70 – S72.	Thank you for this information which we have incorporated into the text
SH	Ovacome		Full	32	11	More recent evidence suggests in 2007 29% of ovarian cancer was diagnosed via A&E. http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis.aspx	We have amended the text for clarity, however the message remains that a significant proportion of patients sill attend as emergencies.
PR	NETSCC, Health Technology Assessment	5.27	Full	34		**3.2 Are any important limitations of the evidence clearly described and discussed?** The authors rightly note the "lack of data available to assess the burden of the disease based on the stage and the type of ovarian cancer … [and] difficulties in the collection and definitions in the minimum dataset for ovarian cancer." The conclusion that the interpretation of effectiveness of treatments is "impossible" is over-strong – "highly uncertain" would be more measured, if in practical terms not a lot different.	We have made this change
SH	Target Ovarian Cancer	33.16	Full	34	33	Target Ovarian Cancer would like in the strongest possible terms to express its desire to see a national	There is a requirement nationally that the agreed minimum datasets are collected and electronically

						minimum data set agreed for ovarian cancer, that records as a bare minimum stage and tumour type. We know that work is underway on this through the NCIN but would like to see this implemented as soon as possible as a matter of urgency. The data on the whole does exist at MDT level, and it is deplorable that it is not yet routinely available at cancer registry level. From a patient perspective, this lack of data makes informed comparisons between centres impossible, thus impeding their ability to make informed choices.	transferred from all provider organisations to cancer registries. This requirement comes into effect in December 2012 and will therefore be an obligation. The GDG cannot make a recommendation to mandate this is expedited.
SH	NCRI/RCP/RCR/ACP/JCCO	30.76	Full	36		Nearly all ovarian cancer is diagnosed at stage III / IV. Stage is an important prognostic factor, and we await with interest the results of the National population screening study which is systematically testing TV-US and CA125 screening in reducing mortality from ovarian cancer. 2 issues make successful screening challenging: (i) the low incidence and (ii) high false positive rates for imaging, for organs (ovaries) requiring laparoscopic biopsy to establish a diagnosis. Both of these factors have 'dogged' previous attempts at population screening studies. More importantly we believe that the message to primary care should emphasise the importance of ultrasound It is cheap, provides a first radiological test for imaging symptomatic women, and importantly would restore the confidence of women (subsequently diagnosed with ovarian cancer) in their GPs. It is so often the case that after a diagnosis of ovarian cancer, women reflect on previous visits to their GP with non-specific symptoms. Most of the evidence points to fairly prolonged symptoms prior to that first imaging US. Guidance should emphasise to primary care earlier use of US for non-specific abdominal symptoms including IBS.	Thank you, we agree.
SH	Central South Coast Cancer Network	24.08	Full	36	24	Our rapid referral proforma for suspected ovarian carcinoma already gives clear guidance on what GP should investigate in preparation for a rapid access appointment. This will be included as an agenda item at our next MDT business meeting and the recommendation is likely to be that we will refuse to accept requests	This guideline is not recommending population based screening for ovarian cancer. In line with DH policy and the Cancer Reform Strategy, evidence to support greater awareness of symptoms in ovarian cancer has led to these recommendations on symptom awareness (page 39). In addition the evidence to support the use of CA125 in this symptomatic population helps reduce the burden

						based on certain aspect of the NICE guidance, citing the risk to our emergency imaging service and the fact ovarian screening of this nature is unproven. We already refuse requests for ovarian screening outwith the UKFOCCS trial.	on use of ultrasound if patients were referred on symptoms alone (as recommended in previous NICE guidance – CG27). NICE would anticipate that cancer networks would commission cancer services on the basis of best evidence.
PR	NETSCC, Health Technology Assessment	5.04	Full	36	general	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** It is stated that the "potential benefits of earlier diagnosis could outweigh the potentially increased demand for investigation of women, and associated anxiety". There is limited evidence, hence the 'potential' benefits. More research is required about the combination of symptoms, duration and outcomes, as the report states.	Thank you, we agree
SH	Royal College of General Practitioners Wales	6.02	Full	36 onwards		Advice for GPs is helpful, except that not all centres will carry out a Ca125 request. It would help to be more dogmatic about performing a pelvic examination, even though detection of adnexal masses is not always easy, if detected at examination, suspicion is raised.	Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms.
PR	NETSCC, Health Technology Assessment	5.17	Full	37		Recall bias correctly identified as a source of error in case-control studies. The PPVs are especially interesting. I suppose they might be boosted by interaction terms, if a person has the full set of symptoms. The LETR paragraphs give useful context here.	Thank you
SH	Royal College of General Practitioners Wales	6.03	Full	39		Useful recommendations.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.21	Full	39	1	There is an inappropriate stress on gynaecological differential diagnosis. Many of these symptoms are related to the GI tract and would warrant GI investigation rather than gynaecological. It would be more appropriate to inform gastroenterologists to look out for ovarian cancer.	The issue that is being addressed is that only a minority of women with ovarian cancer are referred on the correct pathway initially. The guideline does not state that women with symptoms should be referred on the ovarian cancer pathway, rather it suggests that in this group the possibility of ovarian cancer should be considered in primary care and the appropriate initial tests performed to enable better secondary referral.

							In the main text of the guideline it is clear in the recommendations that patients with persistent symptoms, despite normal investigations should return to their GP for onward investigation.
SH	Central South Coast Cancer Network	24.09	Full	39	2	This guidance would result in all benign cases being referred as possible malignancies including women with fibroids	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids.
SH	Central South Coast Cancer Network	24.10	Full	39	2	2WW capacity would implode if all “pelvic masses” were referred urgently	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids.
SH	Central South Coast Cancer Network	24.11	Full	39	2	The recommendation that GPs should be carrying out tests in primary care if a woman reports having abnormal vaginal bleeding, unexplained weight loss, abdominal distension, fatigue or changes in bowel habit is not supportable.	The evidence to support this recommendation is included in the guideline (page 37-38) and the GDG’s deliberations in making this recommendation are included on page 39.
SH	North East London Cancer Network	29.00	Full	**39**	2	There is an important omission from the section of primary assessment of a woman with suspicious symptoms: this is digital rectal examination to palpate the fundus (of the pouch of Douglas.cul de sac) .This is because the limit of resolution of peritoneal nodules by ultrasound is of the order of 0.5 cms. smaller nodules can be palpated per rectum. Although some GP's may not be comfortable with vaginal examination , all should be competent at digital rectal examination	Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms. Therefore we do not think that the recommendation needs changing.
SH	Essex Cancer Network	18.05	Full	39	3	Only post-menopausal women should be referred urgently if a pelvic mass is discovered. Fibroids are the most common cause of a pelvic mass in younger women and where this may be the case an ultrasound should be requested by the G.P. first to avoid 2 week wait clinics being completely overburdened.	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids.
SH	Royal College of General Practitioners	19.00	Full	39 and 45	3 box	It would be useful to clarify whether pelvic physical examination should be undertaken for women with persistent or frequent non specific sympts (as listed). The guidance appears to suggest that checking Ca125 should be carried out instead of pelvic examination. Does a negative examination finding provide any reassurance that Ca125 is not required or is this false? Obvious pelvic mass will only be detected if examination is carried out and hence examination should be recommended for all women	We agree. Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms. We have amended the algorithm to reflect this.

						with non specific symptoms, with the clarification that negative findings should still be investigated according to the algorithm.	
SH	NHS Improvement	22.01	Full	39	3	80% of delegates at the meeting voted against this sentence of the guidance being published as written. The guidance as written would result in all benign cases being referred as possible malignancies including women with fibroids. We recommend modification: age threshold or menopausal status should be defined e.g. “over 50 years”.	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids. The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who were younger. Text explaining this decision has been added to the LETR paragraph.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.00	Full	39	3	This will result in large numbers of women with benign problems being referred leading to high levels of anxiety and overloading clinics.	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids.
SH	British Gynaecological Cancer Society 2	34.01	Full	39	3	80% of delegates at the meeting voted against this sentence of the guidance being published as written. The guidance as written would result in all benign cases being referred as possible malignancies including women with fibroids. We recommend modification: age threshold or menopausal status should be defined e.g. “over 50 years”.	We have amended the recommendation to clarify that we are talking about pelvic or abdominal mass which is not obviously uterine fibroids. The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who were younger. Text explaining this decision has been added to the LETR paragraph.
SH	Airedale NHS Foundation Trust	16.01	Full	39	5	Given the data in the age-incidence curve figure 1.4 on page 24 the parenthetic comment “especially if 50 or over” gives a false sense of security to GPs dealing with younger women; it is wrong to imply that a specified cut-off age is a valid discriminant for considering this diagnosis. Fig 1.4 suggests ~17% of cases are <50.	The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who

							were younger. Text explaining this decision has been added to the LETR paragraph.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.01	Full	39	5	Urinary urgency and frequency are very common benign problems in older women. See above	The GDG considered that there was reasonable quality, retrospective evidence that certain symptoms and signs, when experienced frequently and persistently, are suggestive of a woman having ovarian cancer, amongst other things. It was agreed that identifying those symptoms and signs which should prompt healthcare professionals to consider ovarian cancer, could lead to earlier diagnosis. The GDG believed that the potential benefits of earlier diagnosis could outweigh the potentially increased demand for investigation of women, and associated anxiety. The GDG noted that none of the existing scoring systems for symptoms were sufficiently accurate on their own to initiate an immediate urgent referral. Therefore the GDG took elements of these scoring systems to identify which symptoms warrant further investigation in primary care.
SH	Target Ovarian Cancer	33.18	Full	39	5	Women who are younger than 50, although in the minority of ovarian cancer patients do come up against barriers at their GPs due to their age. Whilst it is important to acknowledge that the large majority of women with ovarian cancer are over the age of 50, we would not want this recommendation to fuel the belief of some GPs that women under the age of 50 do not get ovarian cancer. We have examples where women have been told they could not have ovarian cancer as they were 'too young'.	The GDG recognised that women of 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut-off point for referral as this would disadvantage the 20% of women who have ovarian cancer and are younger. Therefore the GDG highlighted the 50 or over age group in the recommendations without excluding those who were younger. Text explaining this decision has been added to the LETR paragraph.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.02	NICE guidelin e	39 39	5-11 12-14	Postmenopausal bleeding should be investigated with an examination of the genital tract and a transvaginal ultrasound – this is usually organised via a rapid access clinic for the two week cancer wait	There is an already existing clinical pathway for the management of abnormal uterine bleeding (NICE GC27). Despite the fact that this symptom was linked with the existence of ovarian cancer (Hamilton et al. 2009, Goff et al. 2007) the urgent clinical pathway that is already established for abnormal uterine bleeding is likely to detect ovarian cancer as part of that investigation. Therefore we have removed this symptom from the recommendation.
SH	Royal College of General Practitioners	19.01	NICE guide	39	5-11	Re 'awareness of symptoms' it does not clarify if pelvic exam should be undertaken prior to arranging uss or bloods. Is it indicated? Not doing an exam may	Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical

						delay discovery of existing mass. Clarification is needed to explain that a negative exam means that further tests may still be indicated if trying to pick up early disease.	examination is an integral part of the assessment of any woman with symptoms. The requirement for further tests is covered by our recommendation "Advise any woman who is not suspected of having ovarian cancer to return if her symptoms become more frequent and/or persistent"
SH	Essex Cancer Network	18.06	Full	39	12	Women with these symptoms should be referred more appropriately to gynaecology, colorectal or other urgent referral clinics rather than carrying out a CA125 blood test.	Many women with ovarian cancer will have non-specific and relatively mild symptoms which would not of themselves require referral to a colorectal clinic or other urgent referral clinics. The GDG feel that in this group of patients, you need to consider the possibility of ovarian and therefore perform CA125 in primary care
SH	NHS Improvement	22.02	Full	39	12	100% of delegates voted against this sentence on the basis that women with these symptoms should be referred appropriately for other more likely diagnoses	Many women with ovarian cancer will have non-specific and relatively mild symptoms which would not of themselves require referral to a colorectal clinic or other urgent referral clinics. The GDG feel that in this group of patients, you need to consider the possibility of ovarian and therefore perform CA125 in primary care
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.02	Full	39	12	These ominous symptoms/signs should prompt urgent referral as a possible cancer.	Many women with ovarian cancer will have non-specific and relatively mild symptoms which would not of themselves require referral to a colorectal clinic or other urgent referral clinics. The GDG feel that in this group of patients, you need to consider the possibility of ovarian and therefore perform CA125 in primary care
SH	British Gynaecological Cancer Society 2	34.02	Full	39	12	100% of delegates voted against this sentence on the basis that women with these symptoms should be referred appropriately for other more likely diagnoses	Many women with ovarian cancer will have non-specific and relatively mild symptoms which would not of themselves require referral to a colorectal clinic or other urgent referral clinics. The GDG feel that in this group of patients, you need to consider the possibility of ovarian and therefore perform CA125 in primary care
SH	Ovarian Cancer Action	31.01	Full	39	13	The charity questions the credibility of including 'abnormal vaginal bleeding' in the list of symptoms for health professionals to consider. The Department of Health Key Messages for Ovarian Cancer for Health Professionals in 2009 did not identify abnormal vaginal bleeding as a symptom of ovarian cancer.	There is an already existing clinical pathway for the management of abnormal uterine bleeding (NICE GC27). Despite the fact that this symptom was linked with the existence of ovarian cancer (Hamilton et al. 2009, Goff et al. 2007) the urgent clinical pathway that is already established for abnormal uterine bleeding is likely to detect ovarian cancer as part of that investigation. Therefore we have removed this symptom from the recommendation.

SH	Ovarian Cancer Action	31.02	Full	39	14	The Department of Health Key Messages for Ovarian Cancer for Health Professionals 2009 identifies back pain as a symptom of the disease. The charity believes that there should be a consensus between all documents relating to ovarian cancer symptoms and its diagnosis, therefore back pain should be included in these guidelines.	This recommendation was based on the available evidence which did not show that back pain was a reliable indicator of ovarian cancer.
SH	NHS Improvement	22.03	Full	39	15	Consensus that appropriate assessment in a woman over 50 with persisting symptoms is indicated	The GDG feel that any patient who has persistent symptoms that are causing them concern should be encouraged, whatever age, to return for clinical assessment, despite a previous negative assessment by their GP
SH	British Gynaecological Cancer Society 2	34.03	Full	39	15	Consensus that appropriate assessment in a woman over 50 with persisting symptoms is indicated	The GDG feel that any patient who has persistent symptoms that are causing them concern should be encouraged, whatever age, to return for clinical assessment, despite a previous negative assessment by their GP
SH	NCRI/RCP/RCR/ACP/JCCO	30.22	Full	39	17-18	Although it is important to raise awareness of the potential symptom complex associated with ovarian cancer, there are concerns that ovarian cancer is considered in isolation as a potential cause of IBS type symptoms which may result in other potential more common significant underlying diagnoses being overlooked eg colorectal carcinoma. An attempt should be made to put ovarian cancer into relative context as a cause of this symptom complex	The GDG acknowledged previous NICE guidance that indicated IBS is an unlikely diagnosis, in this age category and therefore consideration should be given to ovarian cancer. This does not preclude the consideration of colorectal cancer. Many women with ovarian cancer will have non-specific and relatively mild symptoms which would not of themselves require referral to a colorectal clinic.
PR	NETSCC, Health Technology Assessment	5.34	Full	39	17-19	**Section five – additional comments** It is probably worth giving extra profile to the message about first presentation of IBS in women over 50 being unusual – Medical Indemnity Providers are likely to have claims statistics relevant to this.	The GDG believe the cross-reference to the NICE guideline on IBS is sufficient.
SH	Royal College of General Practitioners	19.04	NICE	39	17-19	I think it should say new onset IBS symptoms (it does say new diagnosis in algorithm, full guideline p 19	We have clarified in the recommendation and the algorithm that these are “symptoms within the last 12 months”
SH	Target Ovarian Cancer	33.17	Full	39	20	We would like to see a specific recommendation that GPs should advise women about why they are being tested, and provide them with information on what to expect. Whilst we understand the need not to alarm women, there is a way, if a ‘rule it out’ approach is being adopted, to communicate the referrals positively. We know from the Target Ovarian Cancer Pathfinder Study that half of the women diagnosed had no idea whatsoever that ovarian cancer could be a possibility.	We have inserted a footnote to cross-reference to ‘Referral guidelines for suspected cancer’ (CG27), which makes recommendations about support and information needs of people with suspected cancer.

SH	Airedale NHS Foundation Trust	16.02	Full	39	21	We very strongly support the paragraphs headed "Linking evidence to recommendations."	Thank you
PR	NETSCC, Health Technology Assessment	5.30	Full	40	47-50	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** "1. 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. This is likely to be a population-based study that records both the duration and frequency of symptoms." This would be a valuable study in terms of shedding light on the harms imposed by diagnostic delay.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.20	Full	40	47-50	The research recommendation for early diagnosis, based on symptoms does not include patient education strategies. Research in this area may yield more cost-effective ways to identify which patients should be referred for U/S and CA125	The research recommendation has been left deliberately broad to allow investigation of differing strategies to examine the relationship between duration and frequency of symptoms
SH	Roche Diagnostics	18.00	Full	41		In section 2.2. "Asking the right question – first tests" the question was what are the most effective tests for women with suspected ovarian cancer (symptomatic patients) in primary care. Measuring serum CA125 was recommended based on cost-effectiveness analysis. The study by Andersen et al. 2010 was referenced but the assessment and performance of HE4 vs CA125 and HE4 in combination with symptoms index was not taken into consideration. Still, the authors of the paper state " *In this study, HE4 and CA125 performed similarly overall both on their own and in combination with the SI. HE4 performed somewhat better (100% vs. 78.6% sensitivity at 95% specificity for HE4 and CA125, respectively) in high-risk women, the population of greatest interest because it is the only group for whom screening is currently recommended. This finding is consistent with recent reports that HE4 outperforms CA125 as a first-line screen due to its high sensitivity]".* The authors concluded that " *If positive predictive value is a high priority, testing by CA125 and HE4 prior to imaging may be warranted for women with ovarian cancer symptoms*	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Central South Coast Cancer	24.01	Full	41		This does not seem an evidence based change to	This guideline is not recommending population

	Network					practice. The evidence is laid out but is nothing new. There is no evidence given that supports Ca 125 as a screening procedure and particularly not for those cases where there is no ovarian mass which I find a perplexing suggestion. There would be a vast increase in referrals which would overwhelm the Fast track system if this was used or necessitate a separate ?ovarian cancer clinic. Therefore efficacy of this in preventing disease is not proven or justified outside a trial.	based screening for ovarian cancer. In line with DH policy and the Cancer Reform Strategy, evidence to support greater awareness of symptoms in ovarian cancer has led to these recommendations on symptom awareness (page 39). In addition the evidence to support the use of CA125 in this symptomatic population helps reduce the burden on use of ultrasound if patients were referred on symptoms alone (as recommended in previous NICE guidance – CG27).
SH	Abbott GmbH & Co KG	26.02	Full	41	10	Comment: Chapter 2.2 should include HE4. The complementary nature of HE4 and CA125 was demonstrated in several publications (Moore 2008, Huhtinen 2009, Nolen 2010, Abdel-Azeez 2010). We agree that no study data are available yet for ROMA in a primary care setting for patients with symptoms but no diagnosis of an abdominal mass. Therefore, we agree that it should be appropriate to recommend a referral based on initial biomarker measurement followed by Ultrasound, as Ultrasound represents the current standard of care. However, an an addition of HE4 (instead of CA125 alone), should improve the diagnosis due to the complementary nature of both markers.	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Ovacome		Full	41	11	"Symptoms alone are not sufficient to refer to secondary care" We are aware of some PCTs who currently do not allow GPs to test for CA125. Given the complex issues of interpretation of CA125 (See point 2 above) and the fact that Trans Vaginal Ultrasound by a skilled operator is the current gold standard, we are concerned that the placement of diagnosis in the general practice may lead to delays for some women. We would ask that this recommendation be discussed with Prof Ian Jacobs so that the latest findings from UKCTOCCS can be incorporated.	Thank you. Greater patient awareness of symptoms, leading to earlier pathway investigation in primary care for any cancer, including ovarian, is DH policy (Cancer Reform Strategy) which this guideline is consistent with. Unfortunately UKCTOCCS is not published and therefore the outcome from this study cannot form the basis of a recommendation.
SH	Central South Coast Cancer Network	24.13	Full	41	21	Use of Ca 125 as a screening tool not supported. CA 125 may not be raised in stage 1 disease, therefore it is not a reliable diagnostic tool in early stage disease. There is a lack of evidence base to formulate this guidance	This guideline is not recommending population based screening for ovarian cancer. In line with DH policy and the Cancer Reform Strategy, evidence to support greater awareness of symptoms in ovarian cancer has led to these recommendations on symptom awareness (page 39). In addition the

							evidence to support the use of CA125 in this symptomatic population helps reduce the burden on use of ultrasound if patients were referred on symptoms alone (as recommended in previous NICE guidance – CG27).
SH	Abbott GmbH & Co KG	26.03	Full	41	22	Add: or serum CA125 in combination with serum HE4	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Central South Coast Cancer Network	24.12	Full	41	24	GPs are not fully equipped to investigate for early ovarian ca. due to nebulous symptoms and rarity of this type of cancer. However, physical examination should be done by GP (abdominal at least if not pelvic/internal)	Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms.
SH	NCRI/RCP/RCR/ACP/JCCO	30.23	Full	41	28-31	State transvaginal ultrasound (rather than just ultrasound) to characterise the pelvis.	We have clarified different methods of performing ultrasound in the background
SH	Abbott GmbH & Co KG	26.04	Full	41	36	Insert: HE4 exhibits a similar sensitivity like CA125, but an increased specificity in patients benign gynaecologic diseases. HE4 and CA125 exhibit complementary effects and in patients with a pelvic mass a combination of both markers works better than either marker alone. If HE4 is combined with CA125 in the Risk of Ovarian Malignancy Algorithm (ROMA), sensitivity and specificity in patients with abdominal masses can be improved compared to CA125 alone.	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.05	Full	41	43	Comment: Include a paragraph to assess the efficacy of CA125 + HE4 (ROMA)	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.06	Full	43	6	Comment: Based on the direct comparison between RMI and ROMA (Moore 2010, see above), we would prefer to see the combination of CA125 + HE4 (ROMA) included in the health economic evaluation. Do the increased specificity and NPV at the relatively low cost of a serum based assay result in an overall dominating strategy?	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
PR	NETSCC, Health Technology Assessment	5.20	Full	44		The diagnostic algorithms initially evaluated in the decision model were simplified from clinical reality. One strategy not at first considered was restricted or sequential use of ultrasound as an adjunct to CA-125 testing. Although the first iteration of analyses did not	There is no borderline CA125 case – it is either abnormal (≥ 35 IU/ml) or normal (<35 IU/ml)

						support routine use of ultrasound, it begged the clinical question whether ultrasound might have a role in deciding borderline CA-125 cases. This possibility ought to be explored, because otherwise there is a risk that access would be shut down to a potentially valuable test, when applied in the right setting. The LETR method showed its value by identifying this possibility and recommending sequential ultrasound. The LETR conclusion was supported by further sensitivity analysis on the prevalence of cancer (really, the post-test probability of cancer after CA-125 testing). The economic analysis could go still further, to identify an optimal window of CA-125 values indicating ultrasound confirmation. Is the lower bound of 35IU/ml really optimal? The additional value of ultrasound in calculation of the RMI-I suggests there is no upper bound of CA-125 to obviate ultrasound.	
SH	NCRI/RCP/RCR/ACP/JCCO	30.81	NICE	45	24-35	There is an impression that a normal CA125 is falsely reassuring and further investigations can be delayed - 'patient should come back' 15 % of patients with ADVANCED ovarian cancer have a normal CA125 and 50 % of those with stage I disease have a normal CA125- precisely the group that needs to be identified early. Much more weight needs to be placed on the history/ examination and a low index of suspicion to request an U/W, a very simple procedure (1.1.2.4)	The guideline recommends patients return to their GP if symptoms persist despite normal initial CA125 test results, precisely to ensure that continued investigation is undertaken (which may include ultrasound).
SH	Airedale NHS Foundation Trust	16.03	Full	45	27	The recommendations for CA125 are somewhat simplistic given the vagaries of CA125 measurement. There should be a timescale for reassessment of ambiguous CA125 results, arguably values >20 IU/ml and abnormal results with normal ultrasound (remember PPC may be associated with ultrasonographically normal ovaries) and GPs should be reminded that normal CA125 does not disprove the diagnosis. There is a case for researching the potential of secondary care-based, possibly nurse led, assessment services for ambiguous cases to allow a low threshold for referral without excess cost. Such a service is being developed for various caner sites in Denmark.	The introduction of CA125 in primary care is a new departure to ensure patients are directed along the right cancer pathway as soon as possible. This will uncover clinical scenarios where the directive approach of a normal and abnormal CA125 cut-off does not necessarily fit every patient. These recommendations were based on evidence related to the established norms for CA125 testing. We agree that there is a case for research but we feel that the research recommendations already made by the guideline are higher priority.

SH	Abbott GmbH & Co KG	26.07	Full	45	27	Comment: Based on the comments above, reconsider to include the combination of CA125 + HE4 (ROMA) in the recommendation. Proposal: • Measure CA125 + HE4 in primary care in women with symptoms. • If CA125 is > 35 U/ml or HE4 > 70 pmol/L (Moore 2008, Huhtinen 2009), arrange ultrasound scan.	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	North East London Cancer Network	29.01	Full	45	27	• CA 125 not raised in stage 1 disease, therefore not a reliable diagnostic tool in early stage disease • Ultrasound should be caried out transvaginally • Validity of test if done by non specialist sonographer a cause for significant concern – sonographers should have appropriate training and accreditation.	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. The recommendation specifies ultrasound of the abdomen and pelvis, we do not think it needs to be more specific. We have added text to the background on this issue
SH	NCRI/RCP/RCR/ACP/JCCO	30.24	Full	45	27	The document states that the evidence is weak, and identified no association between duration of symptoms on outcomes. Yet, it recommends CA125 as a first investigation in primary care. There is no justification for this based on current evidence. How many cancers will this identify sooner, and how much sooner will they be detected? How much will this intervention cost? What will be the impact on secondary care and support services? What will be the survival benefit of this recommendation? It recommends performing an ultra-sound if the CA125 is greater than 35 IU/ml. We calculate, in a post-menopausal woman with a complex scan result that the RMI will be 315. The new policy will actually delay/prevent detection of ovarian cancers compared	The GDG recognised the need for an initial test using an objective and standardised assessment in symptomatic women because this would reduce observer variability. Serum tumour markers fulfil these criteria. High value was placed on serum CA125 as it is currently the most widely used and reliable serum tumour marker for ovarian cancer. The GDG acknowledged that the clinical evidence was of limited applicability because it did not come from symptomatic women in primary care. Although this evidence was based on data in a secondary care setting the GDG felt that it was appropriate to apply its use in the primary care setting. The health economic modelling corroborated this view by conducting sensitivity analyses including the effect of changing prevalence.

						to current practice where cases with RMI over 200 are referred to the Cancer Centre for surgery where the specificity of malignancy in such cases is 70%. There is no justification for performing a CA125 as a first test in a woman with symptoms without mention of an age cut-off. Clearly, it would be inappropriate to perform a CA125 in a 19 year old as a first test, especially as a raised CA125 is often raised in pre-menopausal women in the absence of serious pathology.	The clinical evidence demonstrated 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 (see Table 2.3), though a greater proportion of symptomatic women would be directed to the right pathway in a more timely fashion. Although the trade off in adopting a sequential strategy as recommended means that some women with ovarian cancer would be missed in the first instance, the view of the GDG was that this was a sensible and pragmatic decision as those women whose symptoms persist would subsequently re-attend and be referred.
SH	NCRI/RCP/RCR/ACP/JCCO	30.25	Full	45	27	There should be guidance for the GP in women with a raised CA125 and a normal ultrasound scan. It is inappropriate to recommend a test and then not provide any guidance as to how to manage cases with abnormal results.	We have amended the recommendation to clarify what should happen to this group of women.
SH	NHS Improvement	22.04	Full	45	27-35	Consensus that this section should be rewritten: see below (6-8).	The recommendations were based on evidence of test performance and a health economic evaluation of the most cost-effective first test. The GDG recognised the need for an initial test using an objective and standardised assessment in symptomatic women because this would reduce observer variability. Serum tumour markers fulfil these criteria. High value was placed on serum CA125 as it is currently the most widely used and reliable serum tumour marker for ovarian cancer. The GDG acknowledged that the clinical evidence was of limited applicability because it did not come from symptomatic women in primary care. Although this evidence was based on data in a secondary care setting the GDG felt that it was appropriate to apply its use in the primary care setting. The health economic modelling corroborated this view by conducting sensitivity analyses including the effect of changing prevalence.

							The clinical evidence demonstrated 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, though a greater proportion of symptomatic women would be directed to the right pathway in a more timely fashion. Although the trade off in adopting a sequential strategy as recommended means that some women with ovarian cancer would be missed in the first instance, the view of the GDG was that this was a sensible and pragmatic decision as those women whose symptoms persist would subsequently re-attend and be referred. Having identified a sequential testing strategy on clinical evidence, 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. It was recognised that there would be an impact on health service resources and women tested due to the low prevalence of ovarian cancer in the symptomatic patient group. Equally, it was felt that in order to ensure symptomatic women were placed along the correct pathway as soon as possible it could only be achieved using such a sequential testing strategy.
						A clinical examination (including as a minimum assessment of the abdomen) should be performed by the GP. A pelvic examination +/- per rectal examination are recommended. Digital rectal examination to palpate the fundus (of the pouch of Douglas.cul de sac) is recommended because the limit of resolution of peritoneal nodules by ultrasound is of the order of 0.5 cms. Smaller nodules can be palpated per rectum. Although some GP's may not be comfortable with vaginal examination , all should be competent at digital recal examination.	Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms. Therefore we do not think that the recommendation needs changing.
SH	Welsh Assembly	28.00		45	27-35	From the radiology perspective I would comment on	We have amended the recommendation to clarify

	Government			54	33-39	the following 1) In primary care setting, patients with ca125>35 but a normal ultrasound may have other pathology and may need review of the history and clinical examination findings and/or alternative investigations rather than advise to return if symptoms persist/worsen 2) I agree with recommendation for CT staging. The comment about not routinely using MRI is correct for suspected ovarian cancer but needs further clarification. There is some evidence that MRI can be very useful in triaging the less certain cases (e.g RMI 25-200, or high anaesthetic/surgical risk) where a full cancer centre surgical staging may not be in anyone's best interest, by • selecting cases for surgery in the unit vs centre • reducing the laparotomy rate for benign disease such as endometriosis, hydrosalpinx,fibroid) • prioritising the surgery upwards or downwards • aiding the surgeon in selecting the best operative plan and consenting the patient appropriately (i.e cystectomy where imaging fails to show evidence of malignancy vs "the big op")	what should happen to this group of women. The recommendations do not recommend routine use of MRI for assessing women with suspected ovarian cancer. However this does not preclude the use of MRI in selected cases such as you suggest.
SH	British Gynaecological Cancer Society 2	34.04	Full	45	27-35	Consensus that this section should be rewritten: see below (6-8). A clinical examination (including, as a minimum, assessment of the abdomen) should be performed by the GP. A pelvic examination +/- per rectal examination are recommended.	The recommendations were based on evidence of test performance and a health economic evaluation of the most cost-effective first test. The GDG recognised the need for an initial test using an objective and standardised assessment in symptomatic women because this would reduce observer variability. Serum tumour markers fulfil these criteria. High value was placed on serum CA125 as it is currently the most widely used and reliable serum tumour marker for ovarian cancer. The GDG acknowledged that the clinical evidence was of limited applicability because it did not come from symptomatic women in primary care. Although this evidence was based on data in a secondary care setting the GDG felt that it was appropriate to apply its use in the primary care setting. The health economic modelling corroborated this view by conducting sensitivity analyses including the effect of changing prevalence.

							The clinical evidence demonstrated 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, though a greater proportion of symptomatic women would be directed to the right pathway in a more timely fashion. Although the trade off in adopting a sequential strategy as recommended means that some women with ovarian cancer would be missed in the first instance, the view of the GDG was that this was a sensible and pragmatic decision as those women whose symptoms persist would subsequently re-attend and be referred. Having identified a sequential testing strategy on clinical evidence, 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. It was recognised that there would be an impact on health service resources and women tested due to the low prevalence of ovarian cancer in the symptomatic patient group. Equally, it was felt that in order to ensure symptomatic women were placed along the correct pathway as soon as possible it could only be achieved using such a sequential testing strategy. Our recommendation on page 39, implies that a physical examination is carried out as part of the assessment and we state on page 41 that clinical examination is an integral part of the assessment of any woman with symptoms. Therefore we do not think that the recommendation needs changing.
						Digital rectal examination is recommended because the limit of resolution of peritoneal nodules by ultrasound is of the order of 0.5 cms. “Smaller nodules” can be palpated per rectum. Although some GP's may not be comfortable with vaginal examination , all should be competent at digital recal examination.	
SH	Essex Cancer Network	18.07	Full	45	28	The objective of early referral and diagnosis is to enable a stage shift and hence a better prognosis. Using a flat cut off of CA125 of 35 misses 50% of stage 1 ovarian cancers – exactly those women that	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. It is

						need to be diagnosed as soon as possible. There is no evidence that diagnosing stage 3 disease earlier improves prognosis. A risk of cancer algorithm would pick up more early stage disease.	accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. If by "risk of cancer algorithm" you mean ROMA, we did not evaluate the evidence on this because HE4 was not an intervention included in this clinical question.
SH	NHS Improvement	22.06	Full	45	28	The objective of early referral and diagnosis is to enable a stage shift and hence better prognosis. Using a flat cut off of CA125 misses 50% of stage 1 ovarian cancers - those that need to be diagnosed early. There is no evidence that diagnosing Stage 3 disease earlier affects prognosis. A risk of cancer algorithm would pick up more early stage disease.	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. If by "risk of cancer algorithm" you mean ROMA, we did not evaluate the evidence on this because HE4 was not an intervention included in this clinical question.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.03	Full	45	28	CA125 is not raised in 50% of stage one disease. Suspected stage one disease should prompt referral. We have concerns regarding USS being performed by non specialist sonographers.	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. If by "risk of cancer algorithm" you mean ROMA, we did not evaluate the evidence on this because HE4 was not an intervention included in this clinical question. We have added text to the background about the need for appropriate training
SH	Ovarian Cancer Action	31.03	Full	45	28	The Department of Health Key Messages for Ovarian Cancer for Health Professionals 2009 state that for any woman who presents with the identified symptoms, both a CA125 **and** pelvic ultrasound scan should be arranged. The charity takes the view that guidance on detection of the disease should be	The DH document was not developed using the same evidence-based methodology as this NICE guideline. Therefore we feel the Key Messages should be revised in line with this NICE guideline.

						consistent, and the guidelines should propose that women who present with symptoms are referred for both investigations rather than acting on the results of the CA125 because a significant proportion of women with early stage ovarian cancer do not present with an elevated CA125 level.	
SH	British Gynaecological Cancer Society 2	34.06	Full	45	28	The objective of early referral and diagnosis is to enable a stage shift and hence better prognosis. Using a flat cut off of CA125 misses 50% of stage 1 ovarian cancers - those that need to be diagnosed early. There is no evidence that diagnosing Stage 3 disease earlier affects prognosis. A risk of cancer algorithm would pick up more early stage disease.	Symptoms alone are not specific enough to be able to ensure patients with the defined symptoms consistent with ovarian cancer embark on the most appropriate cancer diagnosis pathway. It is accepted that there are limitations with the use of CA125 but it remains the best single test currently available. The recommendations will not be detrimental and cause delay in women with early stage ovarian cancer and will speed up referral in a proportion of these patients. If by “risk of cancer algorithm” you mean ROMA, we did not evaluate the evidence on this because HE4 was not an intervention included in this clinical question.
SH	NHS Improvement	22.07	Full	45	30	Concern was expressed at the meeting that non-specialised sonographers, not experienced in pelvic ultrasound, could undertake inadequate ultrasound for the purposes of excluding ovarian cancer. It is recommended that ultrasound should be: “performed by a practitioner that is trained and accredited in transabdominal and transvaginal ultrasound of the pelvis and that transvaginal ultrasound be performed in appropriate cases” (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	We have added some of your suggested text to the background.
SH	Ovarian Cancer Action	31.04	Full	45	30	Ovarian Cancer Action proposes that it should be clearly stated that a pelvic ultrasound scan should be undertaken by a specialist who has been trained to look for ovarian cancer / ovarian mass.	We have added text to the background to clarify this issue.
SH	Target Ovarian Cancer	33.19	Full	45	30	Target Ovarian Cancer can see that NICE wishes to balance the low prevalence of ovarian cancer in the symptomatic patient group with the need to get women with symptoms onto an appropriate pathway as soon as possible. However we have already highlighted the issue of access to diagnostics and,	In reality the blood test is likely to be taken on the day of consultation whereas an ultrasound will not normally be carried out on the same day. Therefore a sequential approach is likely to speed up the pathway in a significant proportion of patients.

						given the current delays, are concerned that a sequential approach may exacerbate delays already present.	
SH	Target Ovarian Cancer	33.20	Full	45	30	See comments 4 and 5 above re pelvic/abdominal scan and timescale.	See our responses to comments 4 and 5.
SH	British Gynaecological Cancer Society 2	34.07	Full	45	30	Concern was expressed at the meeting that non-specialised sonographers, not experienced in pelvic ultrasound, could undertake inadequate ultrasound for the purposes of excluding ovarian cancer. It is recommended that ultrasound should be: **"performed by a practitioner that is trained and accredited in transabdominal and transvaginal ultrasound of the pelvis and that transvaginal ultrasound be performed in appropriate cases"** (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	We have added some of your suggested text to the background.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.03	NICE guideline	45	32-33	What do mean by ultrasound suggesting ovarian cancer – should this not be refer for urgent investigation if the ultrasound is **not** normal. Also what defines a normal scan? If the CA 125 is abnormal then it needs to be explained – refer for an opinion if normal ultrasound	The GDG prefer the current wording because not all abnormalities detected on ultrasound are necessarily suggestive of ovarian cancer e.g. uterine fibroids.
SH	NHS Improvement	22.08	Full	45	34	Based on 6 above, suggestion that a normal serum CA 125 **and** a normal ultrasound are required. Consensus amongst delegates on the following: if CA 125 greater than 35 arrange ultrasound scan (abdo/pelvis). If USS normal, but CA 125 value over 35, test should be repeated	We have amended the recommendation to clarify what should happen to this group of women.
SH	Target Ovarian Cancer	33.21	Full	45	34	See comment 6 above.	See response to comment 6.
SH	British Gynaecological Cancer Society 2	34.08	Full	45	34	Based on 6 above, suggestion that a normal serum CA 125 **and** a normal ultrasound are required. Concensus amongst delegates on the following: if CA 125 greater than 35 arrange ultrasound scan (abdo/pelvis). If USS normal, but CA 125 value over	We have amended the recommendation to clarify what should happen to this group of women.

						35, test should be repeated	
SH	Royal College of Obstetricians and Gynaecologists	14.03	Short version	45	34-35	In 1.1.2.4 need to know when a woman with a normal CA 125 or an elevated CA 125 but normal ultrasound should return to her GP if her symptoms persist	We have amended the recommendation to clarify what should happen to this group of women.
SH	Royal College of General Practitioners	19.06		45	34-35	It is highly unlikely that any GP having suspected ovarian cancer, and then explained to a by now very anxious woman that she has an abnormal blood test, is going to be happy just to sit on this result waiting for something else to happen. NICE needs to offer much clearer guidance about what GPs should do next, and consider the economic impact and workload impact of large numbers of women with false positive ca125s being referred on 2 w/w to gynaecology (the likeliest outcome from this recommendation).	We felt that little would be gained by making the recommendation more explicit and comprehensive because it is not possible to cover every possible eventuality. It is accepted that there may be increased referrals into secondary care. This is precisely the implication of the NAEDI initiative, which this guideline is consistent with. Given that previous NICE guidance recommends referral of women with symptoms alone, these recommendations are more selective.
SH	Ovarian Cancer Action	31.05	Full	45	35	The charity feels that GP's require more information about 're-assessment', as there is insufficient guidance about what tests they should arrange for the patient if symptoms persist or worsen. Is it acceptable for them to re-refer for another CA125 and pelvic ultrasound scan? What is the next recommended course of action for investigations?	We felt that little would be gained by making the recommendation more explicit and comprehensive because it is not possible to cover every possible eventuality.
SH	Abbott GmbH & Co KG	26.08	Full	45	45	Comment: The limitation of evidence for HE4 is the same that is described here for CA125. If CA125 study data are considered appropriate to recommend the marker for the primary care setting, the same principle should apply to HE4. Consequently, HE4 and ROMA should be reflected in the guideline.	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Ovacome		Full	45	46	As above, operator and interpretational skill of the investigations is of high importance in the effective diagnosis of ovarian cancer. We therefore do not believe that hospital based data is appropriate to draw the conclusions made here.	The interpretation of CA125 is simple in this context – it is either normal or abnormal.
SH	Abbott GmbH & Co KG	26.09	Full	46	2	Comment: Based on the complementary effects of HE4 and CA125, the conclusion might change based on the evaluations suggested above and HE4 should be mentioned in this paragraph.	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.10	Full	46	20	Add: Research Recommendation. Further research should be undertaken to determine the capability of	When evaluating this clinical question the GDG opted to investigate CA125 as the tumour marker

						HE4 and ROMA to guide referral decisions from a primary care setting with women symptomatic for ovarian cancer.	with the most mature data and common usage. Since we did not investigate HE4 in this setting we are not able to make recommendations on its use.
SH	NCRI/RCP/RCR/ACP/JCCO		Full	46	8	The text contains too many references to “felt strongly” or “strongly believed” or “felt this was a sensible and pragmatic decision”. The recommendations are not always consistent with main-stream practice or expert opinion. It is inappropriate to claim that the recommendations are evidence-based and then make bold recommendations in areas where the evidence has been identified to be weak.	The GDG are allowed to make recommendations based on available evidence and GDG opinion. The purpose of the LETR paragraph is to make these decisions transparent. In this specific instance the comment relates to decisions made on a theoretical cohort of women with symptoms consistent with ovarian cancer, presenting in primary care (see Table 2.3). The decision was balanced and pragmatic based on the available data.
	Abbott GmbH & Co KG	26.00	Full	49		We believe that there is ample evidence to support a stronger place for HE4 and the ROMA algorithm in the guideline as outlined below. Clearly, HE4 is more specific and sensitive than CA125 and ROMA provides a clear specificity improvement to single CA125 testing. HE4 and ROMA provide the most promising innovations and improvements to Ovarian Cancer diagnosis available to date. The related opportunity to improve patient management by use of this marker combination would be missed until the next guideline revision, if HE4 does not get a stronger weight in this version.	The evidence summary for this clinical question states that “Five studies looked at the combination of HE4 and serum CA125 (Abdel-Azeez et al., 2010; Huhtinen et al., 2009; Moore et al., 2008; Moore et al., 2009; Nolen et al., 2010). The evidence suggests that the combination of HE4 and serum CA125 is more specific, but less sensitive than either marker in isolation.” Therefore we do not feel a change to the recommendation is required
SH	NCRI/RCP/RCR/ACP/JCCO	30.77	Full	49	11-14	We agree with the requirement for tissue biopsy to make the diagnosis. Diagnostic laparoscopy can be used and can also provide more information about operability and issues like miliary disease spread which are difficult to image. Increasingly we recognise different treatments for different histological subtypes. In similar ways to other malignancies, much more information is provided by an histological biopsy, in comparison to cytology or fine needle aspirate. The gold standard should be tissue biopsy, and cytology with IHC accepted only when it is impossible to obtain histological material.	The GDG felt that having a histological diagnosis was essential to guiding future treatment, but recognised that on occasions the risks of obtaining a tissue diagnosis might not be justified. The GDG acknowledged that although there was evidence for the diagnostic yield of image-guided biopsy there was none reporting the diagnostic yield of laparoscopic biopsy. They also noted that higher associated major complication rates were reported with laparoscopic biopsy than image-guided biopsy. The GDG therefore put a high value on the outcomes of morbidity and adverse events associated with the two techniques, and agreed that the simplest and least invasive technique was image-guided biopsy.
SH	Airedale NHS Foundation	16.04	Full	49	15	Use of tumour markers: this also refers to secton 2.2	The introduction of CA125 in primary care is a new

	Trust					We know that CA125 values between 10 and 30 IU/ml convey prognostic information implying subclinically persistent tumour following chemotherapy (Crawford & Peace, Ann Oncol, 16: 47-50; 2005), information which is lost by using the standard cut-off and variation over time within the sub-35 range is assessed in the UKCTOCS screening study. The ULN is given as 35 because the signal-to-noise ratio is poor below this level, not because a value of 25 is really normal! On the other hand, the specificity of values <100 in the present clinical context of assessment of women with symptoms can be expected to be less than the figure derived from 'healthy controls;' other phenomena of no major clinical import will cause such values. Future research in this area is needed to instruct the next round of guidance but in the meantime care must be taken not to miss opportunities for timely diagnosis in the symptomatic population by being over-precise about the 35 IU/ml cut-off.	departure to ensure patients are directed along the right cancer pathway as soon as possible. This will uncover clinical scenarios where the directive approach of a normal and abnormal CA125 cut-off does not necessarily fit every patient. These recommendations were based on evidence related to the established norms for CA125 testing.
SH	NCRI/RCP/RCR/ACP/JCCO	30.26	Full	49	15	There is no mention of performing CA19-9 or CEA or CA-15-3 as a routine pre-operative investigation. The guideline must consider the value of a panel of tumour markers when determining pre-operatively whether an ovarian mass is of primary ovarian origin. These tests are also of considerable value in determining mucinous tumour of the ovary and in women with a past history of colorectal or breast cancer.	The GDG placed a high value on the outcomes of sensitivity and specificity of the different tumour marker tests for facilitating a diagnosis of ovarian cancer. At this time there is ample evidence supporting the clinical utility of serum CA125 in diagnosing ovarian cancer. The GDG acknowledged that the methodological quality of the evidence was low, with most studies being case series and not designed as prospective diagnostic or prognostic studies. This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made.
SH	Essex Cancer Network	18.08	Full	49	16 on	This discussion misses the point on how tumour markers are used in the diagnosis of ovarian cancer. CA19-9 and CEA need to be used to pick up mucinous tumours and to help exclude other primary sites. This helps both in diagnosis and in the follow up of these tumours. We know that they are less sensitive and specific than CA125 in the diagnosis of most ovarian cancers but are very useful in picking up specific sub-groups of patients and are used in conjunction with CA125. The multiple tumour marker	The GDG placed a high value on the outcomes of sensitivity and specificity of the different tumour marker tests for facilitating a diagnosis of ovarian cancer. At this time there is ample evidence supporting the clinical utility of serum CA125 in diagnosing ovarian cancer. The GDG acknowledged that the methodological quality of the evidence was low, with most studies being case series and not designed as prospective diagnostic or prognostic studies.

						panels quoted were not CA125/CA19-9/CEA combinations. Using these tumour markers effects our management (where surgery is done and by whom, type of surgery e.g. is appendix removed, and as markers in follow up) in our network on a weekly basis.	This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made.
SH	NCRI/RCP/RCR/ACP/JCCO	30.28	Full	49	43	In section 3 HE4 is stated to have better sensitivity and specificity than CA125 but then not recommended for use. Surely this should suggest further study	Given that research is currently ongoing on the role of HE4, the GDG did not feel it was a priority to recommend additional research.
SH	Airedale NHS Foundation Trust	16.05	Full	49	44	Given the evidence on HE4 (which is currently being promoted by the assay manufacturers) it seems inappropriate to omit a recommendation to research its use in this context; a nurse-led assessment clinic might be the ideal environment for such a study.	Given that research is currently ongoing on the role of HE4, the GDG did not feel it was a priority to recommend additional research.
SH	Roche Diagnostics	18.01	Full	49	44-47	Five studies comparing HE4 and serum CA125 were referenced. Two additional studies need to be taken into account. A study by Montagnana et al. (J Clin Lab Anal 2009;23(5):331-5) assessed serum levels of both HE4 and CA125 in patients with different forms of benign and malign pelvic mass and revealed that HE4 had a significantly higher area under the curve than CA125 (0.99 vs 0.91), with a sensibility and specificity of 98 and 100%, respectively. Also a study by Moore et al. (Am J Obstet Gynecol 2010 Sep;203(3):228 e1-6.)	We reviewed the Montagnana et al (2009) paper but did not include it as evidence because it compared healthy volunteers with those with ovarian cancer to estimate sensitivity and specificity and was likely to have biased estimates. The Moore et al (2010) paper was published after our cut-off date for literature searching.
SH	NCRI/RCP/RCR/ACP/JCCO	30.27	Full	49-50		Tumour markers: There is no mention of either LDH or PLAP. AFP is not raised in dysgerminomas (which are more common than yolk sac tumours) and hCG is inconsistently mildly elevated in these patients. PLAP is not universally available and the evidence for its use should be part of the review; LDH measurement should be mandatory if hCG and AFP are sent	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.
SH	Teenagers and Young Adults with Cancer (TYAC)	38.00	Full	50	35-37	This advice is ambiguous. I suggest 'All women under 40 with ovarian masses suspicious of malignancy should have AFP and hCG markers performed, which can increase the likelihood of making a pre-operative diagnosis in women with ovarian germ cell tumour. While this guidance does not include the management of germ cell tumours in its scope, the management of ovarian germ cell tumours is very different from that of ovarian carcinoma and where markers are elevated many patients can benefit	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.

						greatly from urgent multidisciplinary discussion with professionals with expertise in germ cell tumour management prior to surgery.'	
SH	NHS Improvement	22.09	Full	50	47	87% of delegates agreed with this statement. 13% voted against it to make the following point: tumour markers are used not just in diagnosis but also in planning management. In this context, not only CA125 but also CEA and CA 19-9 are important. The ratio of CA125 to CEA is clinically useful in differentiating primary and secondary ovarian cancers (see CHORUS protocol) and CA 19-9 is used in the management of mucinous tumours. A baseline measurement taken before surgery and definitive diagnosis is indicated.	The GDG placed a high value on the outcomes of sensitivity and specificity of the different tumour marker tests for facilitating a diagnosis of ovarian cancer. At this time there is ample evidence supporting the clinical utility of serum CA125 in diagnosing ovarian cancer. The GDG acknowledged that the methodological quality of the evidence was low, with most studies being case series and not designed as prospective diagnostic or prognostic studies. This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.04	Full	50	47	CA19.9 is used to in the management of mucinous tumours, and CEA may help differentiate between colorectal and ovarian cancer.	This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made.
SH	Abbott GmbH & Co KG	26.11	Full	50	47	Change first bullet point: Measure serum CA125 and HE4	The GDG noted that although the preliminary data on HE4 showed it to have a relatively high sensitivity and specificity, it was not in routine clinical use and studies about its diagnostic performance had only recently been published. 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.
SH	British Gynaecological Cancer Society 2	34.09	Full	50	47	87% of delegates agreed with this statement. 13% voted against it to make the following point: tumour markers are used not just in diagnosis but also in planning management. In this context, not only CA125 but also CEA and CA 19-9 are important. The ratio of CA125 to CEA is clinically useful in differentiating primary and secondary ovarian cancers (see CHORUS protocol) and CA 19-9 is used in the management of mucinous tumours. A baseline	The GDG placed a high value on the outcomes of sensitivity and specificity of the different tumour marker tests for facilitating a diagnosis of ovarian cancer. At this time there is ample evidence supporting the clinical utility of serum CA125 in diagnosing ovarian cancer. The GDG acknowledged that the methodological quality of the evidence was low, with most studies being case series and not designed as prospective diagnostic or prognostic studies.

						measurement taken before surgery and definitive diagnosis is indicated.	This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made.
SH	NHS Improvement	22.10	Full	50	49	96% of delegates agreed with this statement but recommend the addition of LDH.	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.
SH	NCRI/RCP/RCR/ACP/JCCO	30.29	Full	50	49	LDH is also useful in germ cell tumours (Dysgerminoma). CEA and Ca 19.9 are also useful markers in mucinous ovarian tumours and it is important to perform test before surgery. CEA. Ca 125/CEA ratio is useful in distinguishing ovarian cancer from metastatic GI malignancies in cases of advanced disease at presentation.	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation. This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made. Whilst a CA125:CEA ratio may be useful it was not considered a priority for investigation.
SH	British Gynaecological Cancer Society 2	34.10	Full	50	49	96% of delegates agreed with this statement but recommend the addition of LDH.	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.
SH	Guys and St Thomas NHS Foundation Trust	36.00	Full	50	49	LDH is also useful in germ cell tumours (Dysgerminoma). CEA and Ca 19.9 are also useful markers in mucinous ovarian tumours and it is important to perform tests before surgery. CEA. Ca 125/CEA ratio is useful in distinguishing ovarian cancer from metastatic GI malignancies in cases of advanced disease at presentation.	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation. This recommendation does not preclude the use of other tumour markers where thought to be clinically useful, as no negative recommendation has been made. Whilst a CA125:CEA ratio may be useful it was not considered a priority for investigation.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.04	NICE guidelin e	50	49-51	Also measure LDH lactate dehydrogenase Caution because there are differences in pregnancy beta hCG and tumour hCG	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.
SH	Royal College of Obstetricians and Gynaecologists	14.04	Short version	50	49-51	In 1.2.1.2 Need to add checking LDH in women under 40	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.
SH	NCRI/RCP/RCR/ACP/JCCO	30.82	NICE	50	49-51	1.2.1.2 Tumour markers: There is no mention of either LDH or PLAP. AFP is not raised in dysgerminomas (which are more common than yolk	The scope of this guideline specifically excludes germ cell tumours, reference to which has been removed from the recommendation.

						sac tumours) and hCG is inconsistently mildly elevated in these patients. PLAP is not universally available and the evidence for its use should be part of the review; LDH measurement should be mandatory if hCG and AFP are sent	
SH	Target Ovarian Cancer	33.22	Full	51	2	Target Ovarian Cancer wishes to express its concern that procedures or tests are not considered because they are 'not in routine clinical use' or only 'recently published'. This particular reference is to the commentary on data for HE4. Adopting this stance will lead to a replication of the status quo and delay the introduction of new treatments / tests. Given that CA125 in particular is poor at detecting early stage ovarian cancer, it is imperative that the status quo does not continue for any longer than it needs to. Can NICE make any comment about the quality of the data or the size of the studies in this paragraph? Target Ovarian Cancer would welcome a research recommendation for larger scale studies involving HE4 alone and in combination with other markers to provide greater clarity.	The decision made by the GDG was based on considerable discussion and consideration of the evidence. The text in the LETR paragraph captures these discussions. Given that research is currently ongoing on the role of HE4, the GDG did not feel it was a priority to recommend additional research.
SH	Abbott GmbH & Co KG	26.12	Full	51	8	Comment: All studies available clearly show that HE4 is superior to CA125 and that the combination of both is more effective than either marker alone. Due to complementary effects of the markers HE4 should not be considered instead of CA125 as currently stated but in addition to CA125. Proposed change: The GDG noted that the available data on HE4 showed it to have a relatively high sensitivity and specificity. It is not yet in routine clinical use and studies about its diagnostic performance had only recently been published. The GDG therefore did not feel the data on HE4 was substantial enough to enable it to be recommended instead of serum CA125 – the currently only serum tumour marker with widely accepted clinical utility in women with ovarian cancer. But based on the available evidence for the superiority of combined use of both markers they recommended the routine use of serum CA125 in combination with HE4 using the Risk of Ovarian Malignancy Algorithm (ROMA), which can be used as an alternative to the risk of	The GDG noted that although the preliminary data on HE4 showed it to have a relatively high sensitivity and specificity, it was not in routine clinical use and studies about its diagnostic performance had only recently been published. 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.

						malignancy I (RMI I) score.	
SH	Ovacome		Full	51	8	The GDC has chosen to not to recommend HE4 as it is a new test (even though data demonstrates greater diagnostic potential) because it is not currently in routine clinical use. We would welcome a supportive statement which alludes to its potential along with a recommendation for a technological appraisal so that it may be considered appropriately in the near future.	The decision made by the GDG was based on considerable discussion and consideration of the evidence. The text in the LETR paragraph captures these discussions. Suggestions for new technology appraisals come through the NICE topic selection team – not recommendations in guidelines. We will pass this suggestion on to them.
SH	Roche Diagnostics	18.02	Full	51		In section 3.2 " Cancer pathway management: malignancy indices" ROMA - a dual marker algorithm using HE4, CA125 and menopausal status and the overall better diagnostic performance of ROMA vs RMI was not mentioned (Moore et al. 2010). Based on a study by Moore et al. at a set specificity of 75%, ROMA had a sensitivity of 94.3% and RMI had a sensitivity of 84.6% for distinguishing benign status from EOC (P = .0029). In patients with stage I and II disease, ROMA achieved a sensitivity of 85.3% compared with 64.7% for RMI (P < .0001). The dual marker algorithm utilizing HE4 and CA125 to calculate a ROMA value achieves a significantly higher sensitivity for identifying women with EOC than does RMI.	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use. Moore et al 2010 was published after our literature search cut-off date (16 July 2010) and so was not appraised for this guideline.
SH	Roche Diagnostics	18.03	Full	51		In section 3.2 " Cancer pathway management: malignancy indices" The guideline assumes HE4 to be a high-cost marker, but the cost is similar to CA125. Additionally, even though performing HE4 adds to the cost of CA125, the combined cost is still less expensive than imaging (ultrasound).	Thank you for this information
SH	Roche Diagnostics	18.04	Full	51		Based upon current evidence HE4 and ROMA should be considered at the following steps: In women with symptoms in primary care setting (for referral to ultrasound) In women with adnexal mass for risk stratification of benign and malignant disease (for referral to a specialist - gynaecologic oncologist)	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.19	Full	52	11	Add a similar box to explain ROMA	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to

							make recommendations on its use.
SH	Abbott GmbH & Co KG	26.13	Full	51	16	Comment: Although HE4 as a new assay might come at slightly higher costs than CA125, we don't agree with the assumption that there is a significant cost difference.	We have amended the text to clarify the point you make
SH	Airedale NHS Foundation Trust	16.06	Full	51	19	Malignancy indices: If the implementation of these guidelines is successful in bringing forward the presentation to specialist care of women with ovarian cancer so that more present with early disease, the sensitivity of the RMI will decrease. A consequence of this will be a greater proportion of cases being managed, including surgical management, by gynae cancer leads in cancer units. The training of gynaecologists who are likely to take on this rôle an acute general hospitals must prepare them for this work	Thank you for this information
SH	Abbott GmbH & Co KG	26.14	Full	51	19	General comment on chapter 3.2: This paragraph does not address ROMA at all. Although it is not in routine clinical use yet, it is a well characterised index, with potentially superior performance over RMI. Therefore, it should be reflected in this paragraph.	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.15	Full	51	29	Add: … tumour markers such as serum CA125 and HE4	This is an example not an exhaustive list
SH	Abbott GmbH & Co KG	26.16	Full	51	39	Comment: The referenced systematic review (Geomini 2009) does not include the ROMA algorithm. We agree that RMI I was the best algorithm in this review. But the data from Moore 2010 should be added showing that in the direct comparison of RMI I and ROMA, ROMA was the superior algorithm.	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.17	Full	51	45	Insert an assessment of the ROMA-RMI comparison (Moore 2010)	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Abbott GmbH & Co KG		Full	51	46	Comment: The study of Raza et al. cannot be used as an evidence that RMI is the best index available. They used a higher cutoff than normally. Based on the small sample size (104 women, 26 cancers) this can only be considered as preliminary data. Due to the potential of subjective variation of the ultrasound scoring, the high cutoff needs to be assessed in a multicentric setup to assess the risk of losing sensitivity.	Whilst the Raza et al. paper was included in the evidence summary, it did not overly influence the recommendations that were made
SH	Abbott GmbH & Co KG	26.18	Full	52	6	Add ROMA as an alternative to the recommended	ROMA was not investigated as an intervention in

						RMI. RMI is the established algorithm, but there is first evidence that ROMA could be better than RMI and that it provides objective results, which may be more consistent and reproducible between centers and between regions. Proposal: Add "OR • For women with an adnexal mass calculate the ROMA score and refer all women with a high risk of malignancy to a specialist multidisciplinary team"	this clinical question and therefore we are unable to make recommendations on its use.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.01	NICE guideline	52	6-9	Malignancy indices – who is meant to do this – in primary care? Are you thinking that primary care will commission the pathway directly to the centre so saving on delays	This recommendation falls within the chapter on "Establishing a diagnosis in secondary care". In addition in our LETR paragraph, we clarify the evidence on the use of RMI I is exclusively in secondary care. Therefore we feel it is clear where the RMI I should take place.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.05	NICE guideline	52	6-9	Who should do this?	This recommendation falls within the chapter on "Establishing a diagnosis in secondary care". In addition in our LETR paragraph, we clarify the evidence on the use of RMI I is exclusively in secondary care. Therefore we feel it is clear where the RMI I should take place.
SH	Royal College of General Practitioners	19.03	NICE	52	6-9	Malignancy indicies – this is not a familiar concept in primary care: who should be carrying out this risk assessment - primary or secondary care? It would be useful to state this. (It is clear that it is a secondary care matter in the full guidance.)	This recommendation falls within the chapter on "Establishing a diagnosis in secondary care". In addition in our LETR paragraph, we clarify the evidence on the use of RMI I is exclusively in secondary care. Therefore we feel it is clear where the RMI I should take place.
SH	NHS Improvement	22.11	Full	52	6-9	79% of delegates voted against this guidance because many networks use RMI 250 (see RCOG green top guideline on management of postmenopausal cysts). There is no evidence that this should change.	In view of the lack of a definitive cut off point for RMI I the GDG are happy to amend our recommendation to be consistent with current RCOG guidelines.
SH	British Gynaecological Cancer Society 2	34.11	Full	52	6-9	79% of delegates voted against this guidance because many networks use RMI 250 (see RCOG green top guideline on management of postmenopausal cysts). There is no evidence that this should be changed.	In view of the lack of a definitive cut off point for RMI I the GDG amended the recommendation to be consistent with current RCOG guidelines.
SH	Essex Cancer Network	18.09	Full	52	7	Some networks use a RMI threshold of 250 as in the RCOG guidelines. There is no evidence as to why this should not continue.	In view of the lack of a definitive cut off point for RMI I the GDG are happy to amend our recommendation to be consistent with current RCOG guidelines.
SH	Target Ovarian Cancer	33.23	Full	52	7	It is not clear what happens to women whose RMI	These patients will be managed by the local

						falls below 200. See comment 10 above.	gynaecological oncology team. We do not feel that this needs to be specified in the recommendations.
SH	Target Ovarian Cancer	33.24	Full	52	7	This guidance is in secondary care. This may well be appropriate for those who turn out not to have ovarian cancer, but for those who do, it seems odd to have this additional step. Could the RMI not be calculated in primary care, given the results from CA125 and ultrasound by an experienced sonographer, and then patients referred to a specialist centre or local unit as appropriate?	On balance the GDG felt that the calculation and interpretation of RMI I is best carried out by a gynaecological team.
PR	NETSCC, Health Technology Assessment	5.21	Full	52	28-47	The LETR discussion on an optimal cutoff for the RMI-I score seems illogical. It notes the influence of cutoff score on disease identification, specialist referral, and cost burdens implied by benign disease. Surely there is a role for economic analysis to examine how these endpoints change with RMI-I cutoff. The GDG recommends further research – one purpose of such research would arguably be to acquire further information to inform the economic decision analysis as to optimal RMI-I cutoff. In fact economic methods could be applied to estimate the value of information forthcoming from such research and help prioritise this as a research question.	The GDG feel that an economic analysis could be carried out in conjunction with research to identify the optimal cut off of RMI I, but do not feel it is necessary to specify this in the research recommendation.
SH	Abbott GmbH & Co KG	26.20	Full	52	29	Change: "The GDG noted that there was high-quality evidence that RMI I or ROMA are the most useful indeces…"	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Abbott GmbH & Co KG	26.21	Full	52	32	Change: "RMI I to be a useful index"	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	NCRI/RCP/RCR/ACP/JCCO	30.30	Full	52	32	The guideline to use a cut-off point of RMI-I> 200 seems very specific, when it is also noted that the evidence did not indicate the optimum cut-off score for guiding management. The specific figure seems to be too prescriptive given that it is then recommended to find the optimum score.	The GDG felt it was important to recommend a cut-off value for RMI I so that this index could be used in clinical practice whilst research was being conducted to determine the optimum score.
SH	Abbott GmbH & Co KG	26.22	Full	52	44	Add: Also for the ROMA score the optimal cutoff should be determined from further multicentric studies.	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	NCRI/RCP/RCR/ACP/JCCO	30.31	Full	53	1	The research recommendation on modality of imaging is unnecessary – as standards for optimal surgery are not defined in this document and optimal resection standards vary widely in the UK	Page 53, line 1 refers to a research recommendation on RMI I. We are not sure how this comment relates to this recommendation
SH	NCRI/RCP/RCR/ACP/JCCO	30.33	Full	53	1	The document recommends prospective observational studies to investigate the RMI index.	The impact of where surgery is carried out and by whom, as a result of differing RMI I thresholds has

						This has been done, ref: Bailey, Tailor, Naik et al. Risk of malignancy index for referral of ovarian cancer cases to a tertiary center: does it identify the correct cases? (2006) IJGC. 16:30-34.	not been investigated in terms of either patient reported outcomes, impact on overall survival or economic considerations. The GDG feel this would be useful in trying to differentiate the impact of a threshold difference in applying the RMI I
PR	NETSCC, Health Technology Assessment	5.31	Full	53	1-4	"2. 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. The research should be a prospective observational cohort study evaluating women referred with suspected ovarian cancer. Diagnostic accuracy, sensitivity, specificity and cost effectiveness should be examined at the different RMI I thresholds." If the study aims to evaluate cost-effectiveness, it ideally would be prefaced by an economic analysis. This would pilot the analytic structures for interpreting cost-effectiveness data, and prioritise study endpoints in terms of their relevance to the economic decision problem.	The GDG feel that an economic analysis could be carried out in conjunction with research to identify the optimal cut off of RMI I, but do not feel it is necessary to specify this in the research recommendation.
SH	NHS Improvement	22.12	Full	53	1-4	79% voted against this research recommendation on the basis that the RMI is not an absolute measure. Arbitrary thresholds are selected on the basis of clinical and economic implications.	The use of arbitrary thresholds has an impact on patients, which is why the GDG feel this research recommendation was important. The impact of where surgery is carried out and by whom, as a result of differing RMI I thresholds has not been investigated in terms of either patient reported outcomes, impact on overall survival or economic considerations.
SH	British Gynaecological Cancer Society 2	34.12	Full	53	1-4	79% voted against this research recommendation on the basis that the RMI is not an absolute measure. Arbitrary thresholds are selected on the basis of clinical and resource implications.	The use of arbitrary thresholds has an impact on patients, which is why the GDG feel this research recommendation is important. The impact of where surgery is carried out and by whom, as a result of differing RMI I thresholds has not been investigated in terms of either patient reported outcomes, impact on overall survival or economic considerations.
SH	Abbott GmbH & Co KG	26.23	Full	53	2	Change: "Further research should be undertaken to determine the optimum RMI I and ROMA thresholds…"	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to make recommendations on its use.
SH	Essex Cancer Network	18.10	Full	53	6	This discussion also misses the point as to how imaging is used in the diagnosis of ovarian cancer. CT is ideal where the diagnosis is clear, but a common dilemma is whether an ovarian cyst is	The recommendations do not recommend routine use of MRI for assessing women with suspected ovarian cancer. However this does not preclude the use of MRI in selected cases such as you suggest.

						benign, borderline or malignant in the absence of any other disease. In most hands MR is by far the best tool in this context.	
SH	NCRI/RCP/RCR/ACP/JCCO	30.32	Full	53	11	Typo: Principal not principle.	This change has been made.
SH	Airedale NHS Foundation Trust	16.07	Full	53	27	Imaging in the diagnostic pathway: which procedures? In Networks with an established practice of using MRI to characterise ovarian masses the issue of lack of availability is irrelevant.	In reality, access to MRI varies across the country and therefore this text is still appropriate to include.
SH	NCRI/RCP/RCR/ACP/JCCO	30.35	Full	54	33	There is no good evidence to support CT scans as a routine test in cases suspected to be ovarian cancer. The contents of the publication: “Byrom, Redman et al” were heavily criticised in a subsequently published letter and should not be referenced in this document. There is certainly no good evidence to support a CT scan of the thorax as a routine investigation in these	There was good quality evidence from systematic reviews on which to base the recommendations on diagnosis. The GDG agreed that the sensitivity and specificity of ultrasound and CT for establishing a diagnosis, were shown to be broadly equivalent, but that the evidence did not specify which of these imaging modalities was the most effective. Given that ultrasound and CT had been shown to have equivalent sensitivity and specificity, and that ultrasound is more readily available, less costly and involves no radiation unlike CT, the GDG felt it was appropriate to recommend ultrasound as the initial imaging test for women with suspected ovarian cancer. The GDG noted that the evidence for the staging of ovarian cancer was sparse. The GDG recognised that ultrasound is subjective and operator dependent and has limitations in detecting peritoneal disease, whereas multi-slice CT has high spatial resolution and is more sensitive for assessment of omental and peritoneal disease, and abdominal and pelvic lymph nodes. CT is the investigation of choice for staging thoracic disease. For these reasons the GDG chose CT to be the investigation of choice for staging. The Byrom et al paper was identified during a systematic search of the literature as being relevant to this clinical question and was critically appraised by an independent reviewer, in line with NICE methodology. We have amended this recommendation to include CT of the thorax where clinically indicated.

						cases either. The lack of evidence in support of CT scans predicting cytoreduction rates is largely due to the great variation in cytoreduction rates between individual surgeons. This variation would need to be addressed before any coherent recommendations can be confidently made regards the value of CT scans as a predictive test in achieving optimal/complete cytoreduction. To date, there is no reassuring evidence to suggest that CT scans can be used to select cases that are not cytoreducable.	We note your point but the GDG believe that the ability to predict preoperatively whether optimal surgery is feasible would be a useful research question to answer. The design of the study could address the surgical issue by only recruiting from centres that have satisfactory optimal cytoreduction rates. The GDG would consider that acceptable variation of surgical effectiveness in cytoreduction is questionable if the ultimate aim is improving survival and outcome.
SH	NHS Improvement	22.13	Full	54	37	There are 2 separate areas of concern related to this statement: 1. The use of CT in all patients with suspected ovarian cancer based on the US alone would be highly unusual and against published evidence. There is an important category of patients in which the ultrasound demonstrates features of *possible* malignancy but the mass remains indeterminate based on factors such as patient age, CA125 level and clinical history. In such cases of 'indeterminate adnexal mass', published evidence suggests that MRI is more specific in differentiating malignant lesions from complex benign lesions such as endometriosis or dermoid cysts. This is a very important issue, as the radiation dose due to CT of the chest, abdomen and pelvis would be inappropriate. We would suggest an alteration of wording to state: **'If the ultrasound, CA125, and clinical status suggest ovarian cancer, perform a CT…'** 2. The routine inclusion of chest CT, in addition to CT of the abdomen and pelvis, in every patient with suspected ovarian cancer would institute a significant change in practice in many tertiary referral centres, based on limited evidence. The likelihood of changing the patients' stage of disease is very low, as pleural effusions and pre-cardiac lymphadenopathy will be detected on the upper slices of the abdominal CT. In addition, the detection of	We have changed the recommendation to read "If the ultrasound, CA125 and clinical status suggests ovarian cancer, perform a CT scan of the pelvis and abdomen to establish the extent of disease. The thorax may be included where clinically indicated."

						incidental pulmonary nodules can lead to anxiety and repeat follow-up chest CT despite pulmonary metastases being rare (Sahdev et al). However, we accept that in some circumstances, inclusion of chest CT would be appropriate based on the clinician's discretion. We would suggest changing the wording to: **'perform a CT scan of the pelvis and abdomen. The thorax may be included where clinically indicated.'** (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	
SH	British Gynaecological Cancer Society 2	34.13	Full	54	37	There are 2 separate areas of concern related to this statement: 1. The use of CT in all patients with suspected ovarian cancer based on the US alone would be highly unusual and against published evidence. There is an important category of patients in which the ultrasound demonstrates features of *possible* malignancy but the mass remains indeterminate based on factors such as patient age, CA125 level and clinical history. In such cases of 'indeterminate adnexal mass', published evidence suggests that MRI is more specific in differentiating malignant lesions from complex benign lesions such as endometriosis or dermoid cysts. This is a very important issue, as the radiation dose due to CT of the chest, abdomen and pelvis would be inappropriate. We would suggest an alteration of wording to state: **'If the ultrasound, CA125, and clinical status suggest ovarian cancer, perform a CT…'** 2. The routine inclusion of chest CT, in addition to CT of the abdomen and pelvis, in every patient with suspected ovarian cancer would institute a significant change in practice in many tertiary referral centres, based on limited evidence. The likelihood of changing the patients' stage of disease is very low, as pleural effusions and pre-cardiac lymphadenopathy will be detected on the upper slices	We have changed the recommendation to read "If the ultrasound, CA125 and clinical status suggests ovarian cancer, perform a CT scan of the pelvis and abdomen to establish the extent of disease. The thorax may be included where clinically indicated."

						of the abdominal CT. In addition, the detection of incidental pulmonary nodules can lead to anxiety and repeat follow-up chest CT despite pulmonary metastases being rare (Sahdev et al). However, we accept that in some circumstances, inclusion of chest CT would be appropriate based on the clinician's discretion. We would suggest changing the wording to: **'perform a CT scan of the pelvis and abdomen. The thorax may be included where clinically indicated.'** (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.06	NICE guidelin e	54	37-38	Why CT abdo/pelvic and chest – why not just CXR and CT AP?	We have now changed the recommendation to "…perform a CT scan of the pelvis and abdomen. The thorax may be included where clinically indicated." The literature search did not identify any evidence on the use of chest x-ray
SH	Airedale NHS Foundation Trust	16.08	Full	54	39	Given comment 8 above, this recommendation is unnecessarily proscriptive.	In reality, access to MRI varies across the country and therefore this text is still appropriate to include.
SH	NHS Improvement	22.14	Full	54	39	There is concern that the use of MRI for evaluation of indeterminate adnexal masses, as described above in 13, has not been included in the NICE guidance. The statement given on page 54 line 39 could be misinterpreted. We would suggest that there should be a further statement for clarification: **The use of MRI should be considered in the evaluation of the indeterminate adnexal mass.** There is extensive published evidence to support the role of MRI in evaluation of adnexal masses. We include the references as follows: 1.: Kurtz AB, Tsimikas JV, Tempany CM, Hamper UM, Arger PH, Bree RL, Wechsler RJ, Francis IR, Kuhlman JE, Siegelman ES, Mitchell DG, Silverman SG, Brown DL, Sheth S, Coleman BG, Ellis JH, Kurman RJ, Caudry DJ, McNeil BJ. Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging	Not using MRI routinely in assessing women with ovarian cancer, does not preclude the use of MRI where clinically indicated e.g. evaluation of the indeterminate adnexal mass.

						correlated with surgery and histopathologic analysis--report of the Radiology Diagnostic Oncology Group. Radiology. 1999 Jul;212(1):19-27. PubMed PMID: 10405715. 2: Sohaib SA, Mills TD, Sahdev A, Webb JA, Vantrappen PO, Jacobs IJ, Reznek RH. The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clin Radiol. 2005 Mar;60(3):340-8. PubMed PMID: 15710137. 3: Adusumilli S, Hussain HK, Caoili EM, Weadock WJ, Murray JP, Johnson TD, Chen Q, Desjardins B. MRI of sonographically indeterminate adnexal masses. AJR Am J Roentgenol. 2006 Sep;187(3):732-40. PubMed PMID: 16928938. 4: Kinkel K, Lu Y, Mehdizade A, Pelte MF, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization--meta-analysis and Bayesian analysis. Radiology. 2005 Jul;236(1):85-94. Epub 2005 Jun 13. PubMed PMID: 15955864. 5: Forstner R, Sala E, Kinkel K, Spencer JA. ESUR guidelines: ovarian cancer staging and follow-up. Eur Radiol. 2010 Sep 14. [Epub ahead of print] PubMed PMID: 20839002. 6: Spencer JA, Weston MJ, Saidi SA, Wilkinson N, Hall GD. Clinical utility of image-guided peritoneal and omental biopsy. Nat Rev Clin Oncol. 2010 Nov;7(11):623-31. PubMed PMID: 20981128. 7: Spencer JA, Ghattamaneni S. MR imaging of the sonographically indeterminate adnexal mass. Radiology. 2010 Sep;256(3):677-94. Review. PubMed PMID: 20720065. 8: Spencer JA, Perren TJ. Recent EORTC and MRC UK studies: implications for imaging ovarian cancer. Cancer Imaging. 2010 Jul 6;10:135-6. Review. PubMed PMID: 20605760. 9: Spencer JA, Forstner R, Cunha TM, Kinkel K;	

						ESUR Female Imaging Sub-Committee. ESUR guidelines for MR imaging of the sonographically indeterminate adnexal mass: an algorithmic approach. Eur Radiol. 2010 Jan;20(1):25-35. PubMed PMID: 20069737. (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.05	Full	54	39	MRI should not be excluded, especially in the case of early stage ovarian cancer. MRI is useful in differentiating between endometrioma and cancer (both cause elevated CA125 levels).	Not using MRI routinely in assessing women with ovarian cancer, does not preclude the use of MRI where clinically indicated e.g. evaluation of the indeterminate adnexal mass.
SH	NCRI/RCP/RCR/ACP/JCCO	30.34	Full	54	39	MRI is very useful in characterisation of ovarian masses and more objective than U/S. The guideline should include situations in which MRI could be considered (clinical suspicion of endometrioma, etc)	Not using MRI routinely in assessing women with ovarian cancer, does not preclude the use of MRI where clinically indicated e.g. evaluation of the indeterminate adnexal mass.
SH	British Gynaecological Cancer Society 2	34.14	Full	54	39	There is concern that the use of MRI for evaluation of indeterminate adnexal masses, as described above in 13, has not been included in the NICE guidance. The statement given on page 54 line 39 could be mis-interpreted. We would suggest that there should be a further statement for clarification: **The use of MRI should be considered in the evaluation of the indeterminate adnexal mass.** There is extensive published evidence to support the role of MRI in evaluation of adnexal masses. We include the references for the evidence and supporting expert opinion as follows: 1.: Kurtz AB, Tsimikas JV, Tempany CM, Hamper UM, Arger PH, Bree RL, Wechsler RJ, Francis IR, Kuhlman JE, Siegelman ES, Mitchell DG, Silverman SG, Brown DL, Sheth S, Coleman BG, Ellis JH, Kurman RJ, Caudry DJ, McNeil BJ. Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging	Not using MRI routinely in assessing women with ovarian cancer, does not preclude the use of MRI where clinically indicated e.g. evaluation of the indeterminate adnexal mass.

						correlated with surgery and histopathologic analysis--report of the Radiology Diagnostic Oncology Group. Radiology. 1999 Jul;212(1):19-27. PubMed PMID: 10405715. 2: Sohaib SA, Mills TD, Sahdev A, Webb JA, Vantrappen PO, Jacobs IJ, Reznek RH. The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clin Radiol. 2005 Mar;60(3):340-8. PubMed PMID: 15710137. 3: Adusumilli S, Hussain HK, Caoili EM, Weadock WJ, Murray JP, Johnson TD, Chen Q, Desjardins B. MRI of sonographically indeterminate adnexal masses. AJR Am J Roentgenol. 2006 Sep;187(3):732-40. PubMed PMID: 16928938. 4: Kinkel K, Lu Y, Mehdizade A, Pelte MF, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization--meta-analysis and Bayesian analysis. Radiology. 2005 Jul;236(1):85-94. Epub 2005 Jun 13. PubMed PMID: 15955864. 5: Forstner R, Sala E, Kinkel K, Spencer JA. ESUR guidelines: ovarian cancer staging and follow-up. Eur Radiol. 2010 Sep 14. [Epub ahead of print] PubMed PMID: 20839002. 6: Spencer JA, Weston MJ, Saidi SA, Wilkinson N, Hall GD. Clinical utility of image-guided peritoneal and omental biopsy. Nat Rev Clin Oncol. 2010 Nov;7(11):623-31. PubMed PMID: 20981128. 7: Spencer JA, Ghattamaneni S. MR imaging of the sonographically indeterminate adnexal mass. Radiology. 2010 Sep;256(3):677-94. Review. PubMed PMID: 20720065. 8: Spencer JA, Perren TJ. Recent EORTC and MRC UK studies: implications for imaging ovarian cancer. Cancer Imaging. 2010 Jul 6;10:135-6. Review. PubMed PMID: 20605760. 9: Spencer JA, Forstner R, Cunha TM, Kinkel K;	

						ESUR Female Imaging Sub-Committee. ESUR guidelines for MR imaging of the sonographically indeterminate adnexal mass: an algorithmic approach. Eur Radiol. 2010 Jan;20(1):25-35. PubMed PMID: 20069737. (this response was discussed at the meeting, circulated to members, and then formulated by the Radiologist on BGCS Council after consultation with peers)	
SH	Guys and St Thomas NHS Foundation Trust	36.01	Full	54	39	MRI is very useful in characterisation of ovarian masses and more objective than U/S. The guideline should include situations in which MRI could be considered (clinical suspicion of endometrioma, etc).	Not using MRI routinely in assessing women with ovarian cancer, does not preclude the use of MRI where clinically indicated e.g. evaluation of the indeterminate adnexal mass.
SH	Central South Coast Cancer Network	24.07	Full	55	1	As a result of this NICE guidance, both our heads of biochemistry and ultrasound have voiced their concerns. Already there appears to be an increase in primary care referrals as a result which in turn is compromising our emergency ultrasound availability. My view is that whomsoever requests an investigation, is responsible for acting on the result such that if that clinician does not have the necessary specialist expertise to act on the result, then that investigation should only be requested by, or on the advice of someone who does.	The recommendations on the use of tumour marker tests and ultrasound as outlined in this guideline, will allow primary care to make decisions on where to refer patients in the management of their suspected ovarian cancer.
SH	NCRI/RCP/RCR/ACP/JCCO	30.36	Full	55	16	Either the study should be randomised or both imaging modalities should be performed for each woman and the accuracy compared.	Whilst an RCT would be preferable, there are questions about the feasibility of conducting a straight randomised trial of CT vs MRI, given the implication on services and availability
SH	NCRI/RCP/RCR/ACP/JCCO	30.37	Full	55	16	A study of MR vs CT in terms of predicting debulkability may not be helpful or effective. Debulkability is in part related to surgical intent, skills, threshold for stopping and the biological nature of the disease.	We note your comment that such a study may not be helpful or effective. On the other hand, it might be because debulkability is related to all the factors you mention but also to the extent of spread of disease.
SH	NCRI/RCP/RCR/ACP/JCCO	30.38	Full	55	19	It should be made clear that cytology can be used as a last resort in advanced disease but is not appropriate for cases of suspected stage I disease.	Given that the clinical question concerns the best method of tissue diagnosis before chemotherapy, this implies that we are not dealing with stage I disease.
PR	NETSCC, Health Technology Assessment	5.24	Full	55	19-21	Case-control studies are a reasonable format for comparing CT to MRI.	Thank you
PR	NETSCC, Health Technology Assessment		Full	55	19-21	“3. Large multicentre case–control studies should be conducted to compare the accuracy of CT versus MRI for staging and for predicting optimal	Thank you

						cytoreduction. A prospective study in women undergoing primary surgery would be feasible." Agreed, with the caveat that accuracy of these technologies is a moving target.	
	NHS Improvement	22.15	Full	55	19-21	44% of delegates voted against this guidance on the basis that resectability of disease is surgeon-dependent (Gynecol Oncol. 2003 Aug;90(2):390-6; J Clin Oncol 2002;20:1248-59; J Clin Oncol. 2005 Dec 1;23(34):8802-11) and surgical standards and optimal cytoreduction rates are very variable in the UK In the absence of recommendations on surgical standards later in the document*, this research recommendation is a nonsense *The guidance does not include any recommendations on surgery in the section entitled "Management of advanced…ovarian cancer". As such, the end point of this research recommendation is not consistent with opinions expressed later in the document (pgs 76-77)	We note your point but the GDG believe that the ability to predict preoperatively whether optimal surgery is feasible would be a useful research question to answer. The design of the study could address the surgical issue by only recruiting from centres that have satisfactory optimal cytoreduction rates. The GDG would consider that acceptable variation of surgical effectiveness in cytoreduction is questionable if the ultimate aim is improving survival and outcome.
SH	NCRI/RCP/RCR/ACP/JCCO	30.90	NICE Full	55	19-21	4.3 MRI v CT. It is unclear what value a study comparing these modalities would achieve. The decision about primary or delayed surgery is made principally on the extent of disease in the upper abdomen. Comparing CT and MRI in the pelvis will not help to identify operable cases. It is also unclear what value a case-control study would have in this setting. Furthermore, the evidence emerging from RCTs is that delaying primary surgery has not deleterious effect on outcome. If the question of operability versus non operability is considered important, then one might want a trial with laparoscopic assessment or not. A far more important research question is to ensure that adequate tumour samples are taken at the outset and again at delayed surgery, if done so that research into predictive and prognostic biomarkers can move forward rapidly.	The research recommendation is about investigating the accuracy of CT vs MRI for staging and predicting optimal cytoreduction. It does not limit the use of CT and MRI to only the pelvis, nor is it trying to predict operability. Whilst an RCT would be preferable, there are questions about the feasibility of conducting a straight randomised trial of CT vs MRI, given the implication on services and availability. It is a valid point that as part of a trial, adequate samples are obtained to allow translational research in relation to predictive and prognostic response.
SH	British Gynaecological Cancer Society 2	34.15	Full	55	19-21	44% of delegates voted against this guidance on the basis that resectability of disease is surgeon-dependent (Gynecol Oncol. 2003 Aug;90(2):390-6; J Clin Oncol 2002;20:1248-59; J Clin Oncol. 2005 Dec 1;23(34):8802-11) and surgical standards and optimal cytoreduction rates are very variable in the UK	We note your point but the GDG believe that the ability to predict preoperatively whether optimal surgery is feasible would be a useful research question to answer. The design of the study could address the surgical issue by only recruiting from centres that have satisfactory optimal cytoreduction

						In the absence of recommendations on surgical standards later in the document*, this research recommendation is a nonsense *The guidance does not incude any recommendations on surgery in the section entitled "Management of advanced…ovarian cancer". As such, the end point of this research recommendation is not consistent with opinions expressed later in the document (pgs 76-77)	rates. The GDG would consider that acceptable variation of surgical effectiveness in cytoreduction is questionable if the ultimate aim is improving survival and outcome.
SH	NCRI/RCP/RCR/ACP/JCCO	30.39	Full	55	20	An important research question is the value of MRI in diagnosing malignant ovarian masses in comparison with risk malignancy index (RMI) calculation. Quite a few patients present with inappropriate surgery because malignancy was not suspected at initial assessment.	This clinical question related to optimal cytoreduction as predicted by imaging and did not investigate the relationship between RMI and subsequent diagnosis. Therefore we are not able to recommend research on this.
SH	Guys and St Thomas NHS Foundation Trust	36.02	Full	55	20	An important research question is the value of MRI in diagnosing malignant ovarian masses in comparison with risk malignancy index (RMI) calculation. Quite a few patients come to us with inappropriate surgery because malignancy was not suspected at initial assessment as their RMI was low.	This clinical question related to optimal cytoreduction as predicted by imaging and did not investigate the relationship between RMI and subsequent diagnosis. Therefore we are not able to recommend research on this.
SH	Royal College of Pathologists	13.00	**Chapter 3- section on tissue diagnosis.**	55		I would agree that in all bar very exceptional cases a tissue biopsy should be obtained before offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer. Cytology should not be relied upon except in rare cases. There are a number of reasons for this, including the fact that the underlying architecture cannot be appreciated on cytology and that a large number of immunostains may need to be performed for confirmation of an ovarian, tubal or peritoneal origin and for tumour typing and grading (while these immunostains can be performed on cytological preparations, they are not as reliable as on tissue biopsy and in many cases only a limited number of cells are present even if a cell block preparation is made which is desirable in those rare cases where cytology alone is used for diagnosis). Overall, much more information can be garnered from a biopsy rather than a cytology specimen (either ascitic fluid or fine needle aspirate). Some patients do not undergo resection after chemotherapy and so the morphology of the tumour may never be seen. If the tumour is resected	Thank you

						following chemotherapy, it may have a significantly different morphology due to chemotherapy effect, making typing difficult. In other cases, no residual tumour is present following chemotherapy. It is also desirable that archival tissue is present should targeted therapies become available in the future or if further markers need to be done at some point. While the best means of obtaining a tissue biopsy are essentially a clinical decision, I consider that percutaneous needle core biopsies are generally suitable specimens for tumour diagnosis, typing and immunohistochemical studies.	
SH	NHS Improvement	22.20	Full	55	37	This statement is not evidence-based and should be removed (see 19)	This is the background to the topic. It is not a summary of the evidence, nor is it a recommendation.
SH	NCRI/RCP/RCR/ACP/JCCO	30.40	Full	55	37	The mention of frozen section under tissue diagnosis is mis-placed. This should be in the section relating to staging of early stage ovarian cancer.	We disagree. Frozen section is a method used for tissue diagnosis. In addition, reference will now be made to this in the background to section 5.1
SH	British Gynaecological Cancer Society 2	34.20	Full	55	37	This statement is not evidence-based and should be removed (see 19)	This is the background to the topic. It is not a summary of the evidence, nor is it a recommendation.
SH	NCRI/RCP/RCR/ACP/JCCO	30.42	Full	55-56		We would agree that in all bar very exceptional cases a tissue biopsy should be obtained before offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer. Cytology should not be relied upon except in very rare cases. There are a number of reasons for this, such as the fact that the underlying architecture cannot be appreciated on cytology and that a large number of immunostains may need to be performed (while this can sometimes be done on cytology, it is not as reliable as on tissue biopsy and in many cases only a limited number of cells are present even if a cell block preparation is made). Overall, much more information can be garnered from a biopsy rather than a cytology specimen. Some patients do not undergo resection after chemotherapy and so the tumour may never be seen. It may also look totally different after chemotherapy. It is also desirable that archival tissue is present should targeted therapies become available in the future and it is also desirable to have tissue should, for example, further markers need to	Thank you

						be done in the future for any reason.	
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.07	NICE guideline	56	26-34	Tissue diagnosis versus cytology – this represents a delay and very few cases will be inadvertently treated if positive adenocarcinoma cells on cytology and the appearances of advanced disease on CT including ascites. Recent MRC study allowed study entry using cytology	The GDG felt that having a histological diagnosis was essential to guiding future treatment, but recognised that on occasions the risks of obtaining a tissue diagnosis might not be justified. In these circumstances, the risk of giving chemotherapy when the diagnosis is uncertain has to be weighed against the potential risks of obtaining histological confirmation.
SH	Target Ovarian Cancer	33.25	Full	56	27	Target Ovarian Cancer supports this recommendation in terms of making sure women are not given cytotoxic drugs unnecessarily.	Thank you
SH	NHS Improvement	22.16	Full	56	27-29	93% of delegates agreed with this statement. I include comments from Dr Raji Ganesan, pathology representative on BGCS: I am commenting on the draft NICE guidelines "**Ovarian cancer: the recognition and initial management of ovarian cancer**". These comments are submitted in my capacity as pathology representative on the BGCS Council. These comments have been endorsed by three council members of the British Association of Gynaecological Pathologists (Professor Glenn McCluggage, Dr Lynn Hirschowitz and myself), the two pathology representatives on the ovarian subgroup of the NCRI Gynaecological Clinical Studies Group (Dr Nafisa Wilkinson and myself) and two authors of the RCPath datasets for reporting of neoplasms of the ovaries, fallopian tubes and peritoneum (Professor Glenn McCluggage and Dr Nafisa Wilkinson). These comments include the opinion of pathologists who use frozen sections especially in those cases where no pre-op diagnosis exists. **1.2.4-section on tissue diagnosis:** Agreement that in all bar very exceptional cases a tissue biopsy should be obtained before offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer. It is also desirable that archival tissue is present should targeted therapies become available in the future and it is also desirable to have tissue should, for example, further markers	Thank you for your support for this recommendation. The GDG feel that the debate outlined would be best considered by the BCGS and once resolved, may form the basis on which evidence may be sought.

						need to be done in the future for any reason. Tissue obtained after neoadjuvant therapy is not a substitute as some patients do not undergo resection after chemotherapy and so the tumour may never be seen. It may also look totally different after chemotherapy. It may also imply that only chemoresistant clones are available for examination. In exceptional cases, where tissue diagnosis cannot be obtained (such as in possible primary peritoneal carcinomas presenting as pelvic serous carcinomas) cytology can be a substitute. Cell blocks must be made so that IHC can be done if required and material can be available for the future. There are a number of reasons for this preference, such as the fact that the underlying architecture cannot be appreciated on cytology and that a large number of immunostains may need to be performed (while this can sometimes be done on cytology, it is not as reliable as on tissue biopsy). **Debate:** 1. Whether IHC should be recommended as mandatory for diagnosis. There is very reasonable body of opinion that serous carcinomas are very distinctive morphologically and therefore IHC is not necessary. On the other hand, not all biopsied tumours will be serous carcinomas and IHC will aid confirmation of primary vs secondary nature as well as the tumour type. Also the ability for reliable morphologic diagnosis is more pathologist dependant than interpretation of immunostains. The recommended markers include CK7, CK20, WT1,p53, CA- 125, CEA-M. 2. Frozen sections for primary intraoperative diagnosis. 3. Women with symptomatic ascites frequently undergo paracentesis for symptomatic relief, and cell block cytology is readily available on this sample of ascitic fluid. In the situation where cytology and immunohistochemistry on cell block are consistent with ovarian malignancy and the	

						diagnosis of advanced stage ovarian cancer is supported by CT scan evidence and tumour markers (high Ca125 with Ca125:CEA ratio > 25:1), the gynaecological cancer centre MDT may decide that neoadjuvant chemotherapy is appropriate without the need to subject the patient to further invasive procedures (scan guided biopsy or laparoscopy). This process was deemed adequate for diagnosis of advanced ovarian cancer for the EORTC 55971 and the MRC CHORUS clinical trials and is commonly used in gynae oncology centres throughout the UK. 4. The NSSG Leads did not support the initiation of chemotherapy in the absence of a diagnosis confirmed by histology or cytology	
SH	British Gynaecological Cancer Society 2	34.16	Full	56	27-29	93% of delegates agreed with this statement. I include comments from Dr Raji Ganesan, pathology representative on BGCS: I am commenting on the draft NICE guidelines "**Ovarian cancer: the recognition and initial management of ovarian cancer**". These comments are submitted in my capacity as pathology representative on the BGCS Council. These comments have been endorsed by three council members of the British Association of Gynaecological Pathologists (Professor Glenn McCluggage, Dr Lynn Hirschowitz and myself), the two pathology representatives on the ovarian subgroup of the NCRI Gynaecological Clinical Studies Group (Dr Nafisa Wilkinson and myself) and two authors of the RCPath datasets for reporting of neoplasms of the ovaries, fallopian tubes and peritoneum (Professor Glenn McCluggage and Dr Nafisa Wilkinson). These comments include the opinion of pathologists who use frozen sections especially in those cases where no pre-op diagnosis exists. **<u>1.2.4-section on tissue diagnosis:</u>** Agreement that in all bar very exceptional cases a tissue biopsy should be obtained before offering	Thank you for your support for this recommendation. The GDG feel that the debate outlined would be best considered by the BCGS and once resolved, may form the basis on which evidence may be sought.

						cytotoxic chemotherapy to women with suspected advanced ovarian cancer. It is also desirable that archival tissue is present should targeted therapies become available in the future and it is also desirable to have tissue should, for example, further markers need to be done in the future for any reason. Tissue obtained after neoadjuvant therapy is not a substitute as some patients do not undergo resection after chemotherapy and so the tumour may never be seen. It may also look totally different after chemotherapy. It may also imply that only chemoresistant clones are available for examination. In exceptional cases, where tissue diagnosis cannot be obtained (such as in possible primary peritoneal carcinomas presenting as pelvic serous carcinomas) cytology can be a substitute. Cell blocks must be made so that IHC can be done if required and material can be available for the future. There are a number of reasons for this preference, such as the fact that the underlying architecture cannot be appreciated on cytology and that a large number of immunostains may need to be performed (while this can sometimes be done on cytology, it is not as reliable as on tissue biopsy). **Debate:** 5. Whether IHC should be recommended as mandatory for diagnosis. There is very reasonable body of opinion that serous carcinomas are very distinctive morphologically and therefore IHC is not necessary. On the other hand, not all biopsied tumours will be serous carcinomas and IHC will aid confirmation of primary vs secondary nature as well as the tumor type. Also the ability for reliable morphologic diagnosis is more pathologist dependant than interpretation of immunostains. The recommended markers include CK7, CK20, WT1,p53, CA- 125, CEA-M. 6. Frozen sections for primary intraoperative diagnosis.	
SH	Northern Ireland Cancer	25.06	Full	56	30	This is too ambiguous.	We have amended the recommendation to clarify

	Network & Belfast Health and Social Care Trust						that where a confirmed tissue diagnosis is not possible, cytological diagnosis is required before offering the patient chemotherapy.
SH	NCRI/RCP/RCR/ACP/JCCO	30.41	Full	56	30	Chemotherapy should not be given without confirmed diagnosis of malignancy. Although histological diagnosis is preferred, in exceptional circumstances chemotherapy can be used with cytological diagnosis.	We have amended the recommendation to clarify that where a confirmed tissue diagnosis is not possible, cytological diagnosis is required before offering the patient chemotherapy.
SH	Guys and St Thomas NHS Foundation Trust	36.03	Full	56	30	Chemotherapy should not be given without confirmed diagnosis of malignancy. Although histological diagnosis is preferred, in exceptional circumstances only, chemotherapy can be used with cytological diagnosis.	We have amended the recommendation to clarify that where a confirmed tissue diagnosis is not possible, cytological diagnosis is required before offering the patient chemotherapy.
SH	NHS Improvement	22.17	Full	56	30-34	Although 93% of delegates agreed with the first part of this guidance, 87% voted against lines 30-34 making the following comments: • The wording is ambiguous • It should be emphasised that in the exceptional circumstances when a tissue biopsy is not obtained, cytology must be used in planning management	We have amended the recommendation to clarify that where a confirmed tissue diagnosis is not possible, cytological diagnosis is required before offering the patient chemotherapy.
SH	British Gynaecological Cancer Society 2	34.17	Full	56	30-34	Although 93% of delegates agreed with the first part of this guidance, 87% voted against lines 30-34 making the following comments: • The wording is ambiguous • It should be emphasised that in the exceptional circumstances when a tissue biopsy is not obtained, cytology must be used in planning management	We have amended the recommendation to clarify that where a confirmed tissue diagnosis is not possible, cytological diagnosis is required before offering the patient chemotherapy.
SH	NCRI/RCP/RCR/ACP/JCCO	30.43	Full	57	36	Despite the lack of evidence relating to laparoscopic biopsies, it has been assumed that the morbidity is less with radiologically assisted biopsies. We believe that it is inappropriate to make this assumption and the corresponding recommendation. There has been no mention of the evidence relating to the value of laparoscopy in determining the likelihood of achieving optimal cytoreduction. If this was to be considered in select cases, then there would be no value in performing the radiologically assisted biopsy and subjecting the patient to two procedures.	We disagree. We feel that a general anaesthetic based procedure will have a greater morbidity compared with a local anaesthetic based procedure. The GDG have made changes to the recommendation to clarify this issue
SH	Royal College of	14.05	Short	57	36-41	In 1.2.4.3 need to clarify that for those cases with	We have made changes to the recommendation for

	Obstetricians and Gynaecologists		version			advanced disease (stages 2,3 and 4) percutaneous image guided biopsy is preferable to laparoscopy and biopsy. This does not apply to stage 1 disease where tissue for diagnosis is obtained at laparotomy.	clarity
SH	NHS Improvement	22.18	Full	57	36-41	Although 68% of delegates agreed with this statement, 32% did not on the basis that: • laparoscopy is used in a number of centres to assess resectability of disease before proceeding with cytoreductive surgery. A biopsy taken during the procedure would be appropriate in such cases. Concern was voiced that this guidance might prevent laparoscopy being performed for this reason in the future. • Evidence for statement weak	We have made some amendments to this recommendation. The revised recommendation does not preclude the use of laparoscopy as you suggest. The LETR paragraph acknowledges that the evidence base for this question is weak.
SH	British Gynaecological Cancer Society 2	34.18	Full	57	36-41	Although 68% of delegates agreed with this statement, 32% did not on the basis that: • laparoscopy is used in a number of centres to assess resectability of disease before proceeding with cytoreductive surgery. A biopsy taken during the procedure would be appropriate in such cases. Concern was voiced that this guidance might prevent laparoscopy being performed for this reason in the future. • Evidence for statement weak	We have made some amendments to this recommendation. The revised recommendation does not preclude the use of laparoscopy as you suggest. The LETR paragraph acknowledges that the evidence base for this question is weak.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.07	Full	57	40	Laparoscopy may also be used to determine respectability at time of biopsy and therefore this line should not be so proscriptive.	We have made some amendments to this recommendation. The revised recommendation does not preclude the use of laparoscopy as you suggest. The LETR paragraph acknowledges that the evidence base for this question is weak.
PR	NETSCC, Health Technology Assessment	5.25	Full	58	2-7	Agreed lower priority for economic evaluation.	Thank you
SH	Royal College of Pathologists	13.01	**Chapter 4- section on management of suspected early (stage 1) ovarian**	61		This is an area which has engendered considerable debate. Systematic retroperitoneal lymphadenectomy is standard practice in many centres in the UK and elsewhere for stage 1 ovarian cancer. My own view is that this is something that should be decided upon by gynaecological and medical oncologists and this is not primarily a pathological issue. If it is decided that full staging (including systematic retroperitoneal lymphadenectomy) is to be undertaken then there will need to be local and national debate to discuss the optimal way to do this. There has been considerable	Thank you for your comments. Systematic retroperitoneal lymphadenectomy (SRL) may be standard practise in some centres (we don't know how many) and we have no data to indicate how 'systematic' some of these lymphadenectomies are. Equally, there are many centres that do not perform systematic retroperitoneal lymphadenectomy, and possibly some that don't even perform lymph node sampling. We agree. The clinical question concerned the

			cancer			debate about the use of frozen section in such instances. I feel it is premature to discuss the value of frozen section at this time (although I consider this an acceptable way of establishing the need for lymphadenectomy in suspected stage 1 ovarian cancer and better than performing a second operation following pathological diagnosis of a stage 1 ovarian carcinoma or performing lymphadenectomy without a confirmed tissue diagnosis in a suspected stage 1 carcinoma). Should a decision be taken in the future to carry out frozen sections for the purpose of staging early ovarian cancer, this may have resource implications in some institutions which will need to be considered and appropriately addressed.	effectiveness of systematic retroperitoneal lymphadenectomy (SRL) versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic.
SH	Central South Coast Cancer Network	24.02	Full	61		**Management of early ovarian cancer** As stage 1 ovarian cancer represents the group of ovarian cancer patients whom cure is a potential possibility it seems unusual that the guideline seems reticent to accept trade offs that might improve the survivability of this group of patients albeit with higher potential morbidity. There is a logical inconsistency within the draft guideline regarding the management of early ovarian cancer. The guideline emphasises in several areas, and quotes the evidence from the systematic review of (Winter – Roach *et al* 2009), that 'complete' surgical staging, including lymphadenectomy, can improve survival. The guideline however advocates against systematic lymphadenectomy in presumed stage 1 ovarian cancer. This by implication would imply that the guideline advocates non-complete staging for stage 1. The guideline then indicates that adjuvant systemic chemotherapy is not required in patients who have optimal/ complete staging. The guideline should be more explicit and indicate, if this is in fact their advice, that lymphadenectomy is not indicated and thus by implication <u>all</u> patients who are found with "stage 1" ovarian cancer should receive chemotherapy. This means that all patients with ovarian cancer would be advised to have chemotherapy.	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed.

						If this is the guideline's recommendation then this statement should be made explicate	
SH	NCRI/RCP/RCR/ACP/JCCO	30.78	Full	61		Retroperitoneal lymphadenectomy should be confined to patients who can potentially avoid chemotherapy by the procedure i.e. patients with stage IA low grade disease. All other patients will receive chemotherapy. We do not believe that retroperitoneal lymphadenectomy has been proven as an additional therapeutic procedure in its own right, in addition to chemotherapy.	The GDG agrees that SRL has not been proven as an additional therapeutic procedure. However, the implication of the ACTION study was that retroperitoneal lymphadenectomy, if performed and the lymph nodes were negative, then adjuvant chemotherapy was not indicated, irrespective of histological type/grade. Whilst the ACTION study was randomised for chemotherapy, it was not randomised for the subgroup analysis on retroperitoneal lymphadenectomy. Consequently, it was not included in the evidence review for this topic. Therefore it is not possible to recommend retroperitoneal lymphadenectomy on this basis. But this possibility is one of the arguments that surgical oncologists put forward in support of retroperitoneal lymphadenectomy i.e. that has a therapeutic value
SH	NCRI/RCP/RCR/ACP/JCCO	30.44	Full	61	11	The definition of optimal surgery is ambiguous, especially with respect of lymph node assessment and the reference used to support the data is inadequate.	The guideline quotes the definition of optimal staging used by Winter-Roach 2009 – it does not specifically state what assessment refers to. We agree that this has potential for confusion and contributes to/reflects the current variation in practise.
SH	Guys and St Thomas NHS Foundation Trust	36.04	Full	61	11	The definition of optimal surgery is ambiguous, especially with respect of lymph node assessment and the reference used to support the data is inadequate.	The guideline quotes the definition of optimal staging used by Winter-Roach 2009 – it does not specifically state what assessment refers to. We agree that this has potential for confusion and contributes to/reflects the current variation in practise.
SH	NCRI/RCP/RCR/ACP/JCCO	30.46	Full	61	15	The document refers to "assessment" of the retroperitoneal nodes without specifically stating what "assessment" refers to. This requires clarification otherwise it could be misleading and potentially dangerous especially when important decisions relating to adjuvant chemotherapy are based on this "assessment". There is no mention of frozen section analysis in this section. A number of publications have identified the significant value of this including Naik et al (2006, IJGC), Kokka et al (2009, Histopathology), Medeiros	The guideline quotes the definition of optimal staging used by Winter-Roach 2009 – it does not specifically state what assessment refers to. We agree that this has potential for confusion and contributes to/reflects the current variation in practise. The GDG has tried to tackle this problem and is unable to recommend systematic retroperitoneal lymphadenctomy as a norm but does advocate lympth node samplng The clinical question concerned the effectiveness of systematic retroperitoneal lymphadenectomy (SRL) versus lymph node sampling not ways of making SRL more effective. In the absence of any

						et al (2005, IJGC) in identifying accurately the women who will benefit from a staging procedure at the initial laparotomy thereby allowing the option of avoiding chemotherapy in fully staged stage I cases. There is no mention of re-staging procedures in this section. We believe that it is inappropriate to exclude the results of the systematic review performed by Kim et al on the basis of insufficient quality of included studies. The quality of these included studies is of higher quality than other studies referenced elsewhere in the document on which bold and sweeping recommendations have been based.	proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic. Kim 2010 was not excluded from the evidence review. However the studies included in Kim were also appraised individually. The GDG based their recommendations on all of this evidence. We accept that in these guidelines there is variation on the quality of evidence needed to make or not to make a recommendation but that reflects the individual context of the topic in question. In this case, there already exists a consensus that assessment should be undertaken – the debate is whether it should be systematic retroperitoneal lymphadenectomy or sampling and these data is not sufficient to change current clinical practice whatever it might be, other than to recommend that sampling is undertaken..
SH	Central South Coast Cancer Network	24.14	Full	61	33	Recommendation not to undertake retroperitoneal lymph node assessment in early disease is not supported. Retroperitoneal lymph node assessment is standard practice in staging early ovarian cancer in many Centres. This is part of "optimal staging" as defined in the full guidance.	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is

							performed. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed.
SH	NCRI/RCP/RCR/ACP/JCCO	30.45	Full	61	40	Whilst stating the evidence is weak for systematic retroperitoneal lymphadenectomy (SRL), the draft guideline then recommends omitting the procedure of SRL. There is no justification for this. Not when there is evidence to show that SRL is likely to detect nodal disease in 22% of cases compared to sampling which identifies 9% of nodal disease only. The rationale to omit chemotherapy in early stage cases therefore would be inappropriate when there is a risk of leaving nodal disease in situ. The ACTION Trial recommended a sampling of retroperitoneal lymph nodes as a minimum for the staging procedure to be considered optimal. Further analysis of the ACTION data recently published showed that the lack of benefit of adjuvant chemotherapy was directly related to the quality of the retroperitoneal lymph node dissection, i.e. the confidence with which it can be considered safe to omit chemotherapy is directly proportional to the quality of the staging procedure and in particular the quality of the retroperitoneal lymphadenectomy. Large retrospective series by Chan and the recently published Rouzier et al (BJOG, 2010) on over 49,000 cases confirm these results.	The GDG does not dispute that it is possible SRL may detect more involved nodes but the evidence on the basis of study quality assessed according to GRADE was limited and of poor quality. There was no survival benefit from systematic retroperitoneal lymphadenectomy. They also noted that no studies reported on quality of life. The GDG noted the complications and likely increased costs associated with performing systematic retroperitoneal lymphadenectomy and were unable to recommend its use in women whose disease appears to be confined to the ovaries. We have, however, amended the recommendations to emphasise that lymph node assessment is required .The effects noted in both the Chan and Rouzier papers can be attributed to selection bias and stage migration ('Will Roger's effect')
SH	Target Ovarian Cancer	33.26	Full	61	9	See comment 7 above.	See response to comment 7
SH	NCRI/RCP/RCR/ACP/JCCO	30.47	Full	61-62		Many consider that the statement that systematic retroperitoneal lymphadenectomy should not be part of the standard surgical treatment of stage 1 ovarian cancer is flawed. The NICE statement about being able to omit chemotherapy in selected fully staged cases makes little sense if the recommendation is not to fully stage. Systematic retroperitoneal lymphadenectomy is standard practice in many centres in the UK and elsewhere for stage 1 ovarian	Thank you for your comments. Systematic retroperitoneal lymphadenectomy (SRL) may be standard practise in some centres (we don't know how many) and we have no data to indicate how 'systematic' some of these lymphadenectomies are. Equally, there are many centres that do not perform systematic retroperitoneal lymphadenectomy, and possibly some that don't even perform lymph node sampling.

						cancer. It is the view of some experts that this is something that should be decided upon by gynaecological and medical oncologists and this is not primarily a pathological issue. If it is decided that full staging is to be done then there will need to be local arrangements to discuss the optimal way to do this. It is then that the issues of frozen section can be discussed. As stands it is perhaps premature to discuss this in detail at this point. Most would consider frozen section to be the way to do this so that the lymphadenectomy can be performed at the initial operation (we would however, not recommend this for mucinous tumours or in every patient with an ovarian mass since there is the potential for this to be abused). One view is that the indication for frozen section is that the result will influence the immediate surgical management and clearly if lymphadenectomy is being considered, this is a legitimate use of frozen section. There is a growing acceptance in the gynaecological pathology community for performing frozens in such instances, although there is still some reluctance and there may be local problems with regard to availability of frozens at the site of operation. Some also feel that frozen section is of proven utility in such cases. An unacceptable (in the view of many) alternative is that lymphadenectomy is done without a diagnosis in all cases of suspected stage 1 ovarian carcinoma. There will obviously be occasional cases where a totally unexpected carcinoma will be picked up and staging will require a further operation. Debate about frozen section in this situation would be better after it is determined that systematic lymphadenectomy should be performed for stage 1 ovarian cancer.	We agree. The clinical question concerned the effectiveness of systematic retroperitoneal lymphadenectomy (SRL) versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic.
SH	NCRI/RCP/RCR/ACP/JCCO	30.48	Full	61-67, 74		Statements relating to lymphadenectomy in early and late stage disease and recommendations about chemotherapy for patients with Stage 1a\b Grade1-2 disease are linked in clinical practice but not in the document. The literature shows that 10-30% patients with apparent Stage 1a\b disease have lymph node involvement (Timmers et al International Journal of Gynecological Cancer 2010). Thus one cannot recommend observation for any patient with early	You have highlighted the problem well. Unfortunately we do not know the answer and hence the GDG is not able to recommend systematic retroperitoneal lymphadenectomy with its attendent risks and resource implications. This is the rationale for the research recommendation

						stage disease unless there has been a systematic dissection of the lymph nodes	
SH	NCRI/RCP/RCR/ACP/JCCO	30.79	Full	67		The intended comparison between adequately and inadequately stage is not made needs correcting.	We are not clear on the intended meaning of this comment
SH	North East London Cancer Network	29.02	Full	67	1	• Retroperitoneal lymph node assessment is standard practice in staging early ovarian cancer in many Centres. This is part of "optimal staging" as defined on page 74 of 144 (full guidance) • Recommendation condones suboptimal practice • Frozen section relevant here but not reviewed • ACTION trial not mentioned - this also suggests a lack of expertise in selecting relevant literature • Wording confusing • The role of lymph node "assessment" or "dissection" is not discussed • At a one day meeting on the optimal management of early stage ovarian cancer (Belfast, March 2010) 75% of delegates voted that retroperitoneal node dissection (para-aortic and pelvic) should be performed if frozen section reported malignancy • The relevant Cochrane Review (Winter-Roach) states that "there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy". Not performing this procedure reduces options for patients • The last is particularly relevant in women wishing to retain fertility.	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic. The ACTION trial was designed to investigate the use of adjuvant chemotherapy in patients with early stage ovarian cancer. Therefore it was not identified by the literature search for the topic on systematic retroperitoneal lymphadenectomy. In addition, the subgroup analysis in ACTION, of optimal vs sub-optimal surgery was done post hoc

							and was not powered to assess this comparison. Therefore these results would have been difficult to interpret with certainty. We have revised the background to clarify why we are looking at this topic and to ensure that all definitions are made explicit. The text you refer to are the key priorities for implementation. The background to lymph node assessment is in chapter 4. The guideline has not recommended that optimal surgical staging should not be performed.
SH	Royal College of Obstetricians and Gynaecologists	14.01	Short version	67	1-4	Guideline states that systematic retroperitoneal lymphadenectomy should not be done as part of the standard surgical staging procedure. This statement is based on the lack of evidence from randomised trials for the beneficial effect on improvement of overall survival of the procedure. However, good data from several descriptive studies does confirm that retroperitoneal lymphadenectomy does identify the presence of metastatic disease in cases where gross disease is confined to the ovaries in 10 - 20% of cases. Whilst this data does not support the view that lyphadenectomy is a therapeutic procedure it certainly does identify true stage 1 cases from those cases where disease is only confined to the ovaries on clinical assessment but which do have occult nodal disease. This latter group should in theory have a worse prognosis and hence if identified at diagnosis could be given a different chemotherapy regime in comparison with those cases where disease is definitely only confined to the ovaries.	Thank you for your comments. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. What is not known is whether systematic retroperitoneal lymphadenectomy would confer additional value which is why the GDG felt unable to recommend this procedure as a routine part of staging.
SH	Royal College of Obstetricians and Gynaecologists	14.06	Short version	67	1-4	In section 1.3.1.1 need to distinguish between systematic retroperitoneal lymphadenectomy (no randomised data to support its routine use), and retroperitoneal lymph node sampling for which there is good data from the ACTION study. Guideline development group need to have a statement saying in stage 1 disease (where disease appears to be confined to the ovaries) optimal surgical staging should include peritoneal biopsies from pelvis and abdomen as well as retroperitoneal lymph node sampling.	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes.

							Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed.
SH	NHS Improvement	22.19	Full	67	1-4	100% of delegates at the meeting rejected this guidance. • Retroperitoneal lymph node dissection is part of the FIGO staging of ovarian cancer. It is currently performed in a number of Centres in the UK consistent with international best practice guidelines (EORTC-GCG Quality indicators, NCCN guidelines). A lack of evidence should not dictate that a clinical practice currently in use must stop. • Retroperitoneal lymph node assessment is part of "optimal staging" as defined on page 74 (full guidance) • "Optimal staging", as defined in the studies constituting the evidence for the statement on page 74, recommended "systematic retroperitoneal lymphadenectomy" and "optimal staging to include pelvic and para-aortic retroperitoneal node dissection" (Winter Roach et al, 2009 Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 3: CD004706) • This recommendation (p67) condones suboptimal practice	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any

						• ACTION trial not mentioned here suggesting a lack of expertise in selecting relevant literature • Wording confusing and the exact interpretation of lymph node "assessment" is not discussed • At a one day meeting on the optimal management of early stage ovarian cancer (Belfast, March 2010) 75% of delegates voted that retroperitoneal node dissection (para-aortic and pelvic) should be considered if frozen section reported malignancy • The relevant Cochrane Review (Winter-Roach) states that "there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy". Not performing this procedure reduces options for patients • The last is particularly relevant in women wishing to retain fertility. Frozen section is dismissed earlier in the document (page 55 line 37): see below. Comment was made at the meeting of BGCS members on 15th October that frozen section is used in a number of Centres in the UK to determine the extent of surgery with or without lymphadenectomy. This was confirmed in email correspondence after the meeting The following statement is presented by Dr Raji Ganesan (see 16) on behalf of Histopathology and is relevant here: Dr Raji Ganesan writes: **Agreement** This is obviously an area which has engendered considerable debate and although pathology and pathologists are involved in the process, this is something that should be decided upon by gynaecological and medical oncologists and is not primarily a pathological issue. **Debate:**	proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic. The ACTION trial was designed to investigate the use of adjuvant chemotherapy in patients with early stage ovarian cancer. Therefore it was not identified by the literature search for the topic on systematic retroperitoneal lymphadenectomy. In addition, the subgroup analysis in ACTION, of optimal vs sub-optimal surgery was done post hoc and was not powered to assess this comparison. Therefore these results would have been difficult to interpret with certainty. We have revised the background to clarify why we are looking at this topic and to ensure that all definitions are made explicit. The text you refer to are the key priorities for implementation. The background to lymph node assessment is in chapter 4. The guideline has not recommended that optimal surgical staging should not be performed.

						1. Whether frozen section is to be used for intraoperative diagnosis and staging Opinions include: a. The debate about frozen section is not the direct remit of the NICE Ovarian guidelines but is clearly an issue that needs addressing at national level after a decision on the role of systematic lymphadenectomy in stage 1 ovarian cancer. b. Detailed imaging, use of tumour markers, histology/cytology results and robust multidisciplinary interaction are sufficient for preoperative decisions on staging. c. The NICE guidance should at least acknowledge that FS can be of use in cases where preoperative diagnosis is not available and guide staging in these cases. d. Feasibility debate should include provision of service when the pathology service is remote from the surgical site and the resource implications of such a move.	
SH	British Gynaecological Cancer Society 2	34.19	Full	67	1-4	100% of delegates at the meeting rejected this guidance. • Retroperitoneal lymph node dissection is part of the FIGO staging of ovarian cancer. It is currently performed in a number of Centres in the UK consistent with international best practice guidelines (EORTC-GCG Quality indicators, NCCN guidelines). A lack of evidence should not dictate that a clinical practice currently in use must stop. • Retroperitoneal lymph node assessment is part of "optimal staging" as defined on page 74 (full guidance) • "Optimal staging", as defined in the studies	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to

						constituting the evidence for the statement on page 74, recommended "systematic retroperitoneal lymphadenectomy" and "optimal staging to include pelvic and para-aortic retroperitoneal node dissection" (Winter Roach et al, 2009 Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 3: CD004706) • This recommendation (p67) condones suboptimal practice • ACTION trial not mentioned here suggesting a lack of expertise in selecting relevant literature • Wording confusing and the exact interpretation of lymph node "assessment" is not discussed • At a one day meeting on the optimal management of early stage ovarian cancer (Belfast, March 2010) 75% of delegates voted that retroperitoneal node dissection (para-aortic and pelvic) should be considered if frozen section reported malignancy • The relevant Cochrane Review (Winter-Roach) states that "there is strong evidence that optimal surgical staging identifies patients who have either little or nothing to gain from adjuvant chemotherapy". Not performing this procedure reduces options for patients • The last is particularly relevant in women wishing to retain fertility. Frozen section is dismissed earlier in the document (page 55 line 37): see below. Comment was made at the meeting of BGCS members on 15th October that frozen section is used in a number of Centres in the UK to determine the extent of surgery with or without lymphadenectomy. This was confirmed in email correspondence after the meeting The following statement is presented by Dr Raji Ganesan (see 16) on behalf of Histopathology and is relevant here:	support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic. The ACTION trial was designed to investigate the use of adjuvant chemotherapy in patients with early stage ovarian cancer. Therefore it was not identified by the literature search for the topic on systematic retroperitoneal lymphadenectomy. In addition, the subgroup analysis in ACTION, of optimal vs sub-optimal surgery was done post hoc and was not powered to assess this comparison. Therefore these results would have been difficult to interpret with certainty. We have revised the background to clarify why we are looking at this topic and to ensure that all definitions are made explicit. The text you refer to are the key priorities for implementation. The background to lymph node assessment is in chapter 4. The guideline has not recommended that optimal surgical staging should not be performed.

						Dr Raji Ganesan writes: **Agreement** This is obviously an area which has engendered considerable debate and although pathology and pathologists are involved in the process, this is something that should be decided upon by gynaecological and medical oncologists and is not primarily a pathological issue. **Debate:** 2. Whether frozen section is to be used for intraoperative diagnosis and staging Opinions include: a. The debate about frozen section is not the direct remit of the NICE Ovarian guidelines but is clearly an issue that needs addressing at national level after a decision on the role of systematic lymphadenectomy in stage 1 ovarian cancer. b. Detailed imaging, use of tumour markers, histology/cytology results and robust multidisciplinary interaction are sufficient for preoperative decisions on staging. c. The NICE guidance should at least acknowledge that FS can be of use in cases where preoperative diagnosis is not available and guide staging in these cases. d. Feasibility debate should include provision of service when the pathology service is remote from the surgical site and the resource implications of such a move.	
SH	Essex Cancer Network	18.11	Full	67	2	Any suggestion that at least a thorough lymph node sampling is not carried out in apparent Stage 1 disease goes against what is established practice throughout most of the world, and there is no good evidence to support this change. The use of frozen	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy;*

						section is not adequately addressed – this is routinely used in most cancer centres.	*biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4 and there is no evidence to support such a systematic approach as part of the standard surgical treatment of suspected ovarian cancer in women whose disease appears to be confined to the ovaries. We agree that retroperitoneal lymph node assessment, should be standard practice in staging early ovarian cancer and have added a recommendation that this is performed. The clinical question concerned the effectiveness of SRL versus lymph node sampling not ways of making SRL more effective. In the absence of any proven benefit of SRL, the use of frozen section was not considered relevant to investigate as a separate topic.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.08	Full	67	2	This is standard practice in our centre based on the best evidence –the ACTION trial. Over 75% of Gynae oncologist support lymphadenectomy in apparent early disease with between 15 to 30% of women being upstaged. This guideline is at variance with international practice and standards (FIGO etc).	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on

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SH	NCRI/RCP/RCR/ACP/JCCO	30.49	Full	67	2	Recommendations should include a clear definition of what constitutes evidence based optimal surgical staging rather than the role of lymphadenectomy. One of the most important findings of the adjuvant trials was the number of incompletely staged patients. To focus the whole surgical discussion in the role of lymphadenectomy (with poor quality evidence) misses the point.	The question that was addressed focused on the effectiveness of systematic retroperitoneal lymphadenectomy in a particular patient group. It is not possible for us to make recommendations outside of this issue.
SH	Guys and St Thomas NHS Foundation Trust	36.05	Full	67	2	Recommendations should include a clear definition of what constitutes evidence based optimal surgical staging rather than the role of lymphadenectomy. One of the most important findings of the adjuvant trials was the number of incompletely staged patients. To focus the whole surgical discussion in the role of lymphadenectomy (with poor quality evidence) misses the point.	The question that was addressed focused on the effectiveness of systematic retroperitoneal lymphadenectomy in a particular patient group. It is not possible for us to make recommendations outside of this issue.
SH	NCRI/RCP/RCR/ACP/JCCO	30.50	Full	67	15	To undertake a RCT of lymphadenectomy in early ovarian cancer would be extremely difficult with a relatively low rate of events and considerable scope for confounding by adjuvant therapy. We would recommend that the NCRI CSG should consider whether such a study would be valuable and feasible.	This represents about a quarter of patients with ovarian cancer and the GDG feel it is both an important topic for research and feasible.
SH	NCRI/RCP/RCR/ACP/JCCO	30.51	Full	67	16	The research recommendation on systemic lymphadenectomy seems inappropriate. Despite multiple reports there is really no good evidence that this is worth pursuing. There are many other questions that would be better addressed than this.	From the data available, it is not clear whether there is or is not a therapeutic or survival benefit from systematic retroperitoneal lymphadenectomy compared to lymph node sampling. Therefore research is required.

SH	Airedale NHS Foundation Trust	16.09	Full	67	20	We agree with the need for proper research into the rôle of lymphadenectomy and with the proscription of performing this procedure before such evidence is available.	Thank you
PR	NETSCC, Health Technology Assessment	5.32	Full	67	20-23	"4. A prospective randomised trial should be undertaken to evaluate the cost effectiveness and associated risks of systematic retroperitoneal lymphadenectomy in women with ovarian cancer whose disease appears to be confined to the ovaries. Researchers should be encouraged to develop a prospective randomised trial with international collaboration to answer this question in a timely manner." I also note that "This clinical question was agreed as a low priority for health economic evaluation because of the lack of good quality RCT data in this area." – this recommendation clashes with the idea of setting up a, presumably pragmatic, RCT to evaluate cost-effectiveness. Research for the purpose of informing an economic analysis should be prefaced by economic analysis to identify the areas of sensitivity.	The text you refer to is part of the LETR paragraph which accompanies the recommendations, not a recommendation itself. The purpose of this text is to clarify why it was not possible to conduct an economic analysis for this topic, not to say that an economic analysis should not be conducted.
SH	Medical Research Council Clinical Trials Unit	21.00	Full	67	38-41	When you reference TA55 I think you should mention that the first-line trials considered in that appraisal were not carried out specifically in women with stage I disease; and that GOG111 and 132 included only FIGO stage III-IV, OV10 was >90% stage III-IV, and that in ICON3 9% of women had stage I disease. Is it not also relevant to state that there are no randomised studies specifically comparing carboplatin vs. carboplatin-paclitaxel in early stage disease and that ICON1 and ACTION (and the other studies included in the Cochrane review) did not include platinum-taxane in their combination regimens (due to the age of the studies)? ie. We're largely extrapolating our choice of regimen from studies in advanced disease. It could also be mentioned, however, that the ICON3 subgroup analysis by stage was consistent with the main findings of the trial of no evidence of benefit for the addition of paclitaxel to carboplatin in patients with stage I disease; and that the majority of patients in ICON1/ACTION received single agent carboplatin (57% in the combined analysis) as evidence to support the recommendation (p 74) for using single agent carboplatin.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.

						I acknowledge there is a paragraph re: choice of chemotherapy on p74 lines 30-35 but think that it would be helpful to give more details on the evidence.	
SH	Medical Research Council Clinical Trials Unit	21.01	Full	68	2	**"Clinical question: For women with stage I ovarian cancer, what is the most effective first-line chemotherapy?"** In this clinical evidence section several questions are addressed: 1. Do patients with stage I disease benefit from adjuvant chemotherapy 2. Which sub-groups of patients with stage I disease might benefit/not benefit from adjuvant chemo 3. Should 3 vs 6 cycles of carboplatin-paclitaxel be used, but not actually what is the most effective chemotherapy. Would it be better to split this into 2 questions? 1. Which patients with stage I ovarian cancer may benefit from adjuvant chemotherapy 2. What is the optimum chemotherapy regimen in stage I ovarian cancer	Stakeholders were consulted about the proposal to include this topic in the scope of the guideline. The clinical question derived from this topic was then searched and appraised in line with NICE methodology. It is not possible to change the clinical question at this stage in guideline development.
SH	NCRI/RCP/RCR/ACP/JCCO	30.53	Full	68	22	The problem here is that the long term results of ICON1 have not been peer reviewed and published. These results are relevant to UK practice whereas ACTION is more appropriate for European practice. We believe that it is premature to implement withholding of adjuvant therapy to low risk ovarian ca (other than grade I stage Ia disease) until ICON1 has been published.	The ICON1 10 year follow up data has not been published, therefore we are unable to consider it as evidence.
SH	Medical Research Council Clinical Trials Unit	21.03	Full	68	2-48	Although the clinical recommendations on p74 for offering adjuvant chemotherapy differentiate between patients with low-risk vs high-risk stage I disease, no evidence specifically related to this recommendation is presented. The 10-year update of the ICON1 trial (the largest trial investigating adjuvant chemotherapy for early stage ovarian cancer) presented at ASCO 2007	The ICON1 10 year follow up data has not been published, therefore we are unable to consider it as evidence.

						showed evidence of a continued benefit in favour of adjuvant chemotherapy in the full trial population, and (on sub-group analysis) that the benefit was clear in high-risk patients but not in low-risk. Reference: Swart AC. *et al*., on behalf of ICON collaborators. (2007) Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON1). Journal of Clinical Oncology (Meeting Abstracts). 25(18_suppl): 5509.	
SH	Medical Research Council Clinical Trials Unit	21.02	Full	68	30	Shouldn't it be noted that the optimal vs sub-optimal surgery analysis in ACTION was a sub-group analysis and that the trial was not powered for this comparison?	The ACTION trial was not appraised individually as it was included within a systematic review by Winter-Roach et al. The authors of the Winter-Roach review did not comment on this issue, therefore it would not be appropriate for us to do so.
SH	NCRI/RCP/RCR/ACP/JCCO	30.54	Full	68	34	The problem here is that the Chan paper did not find a difference between subtypes when they looked at it suggesting that 6 is still possibly better than 3 cycles.	The recommendation on p 74, lines 8-10 has been deleted
SH	NCRI/RCP/RCR/ACP/JCCO	30.52	Full	68	8	Regimen not regime	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.87	FULL	74		The analysis of the Bell et al paper is superficial. Firstly, many of the patients did not have serous cancer, and the proportion of with grade 3 tumours was low. These factors have important prognostic value in relation to the probability of recurrence. If a large number of patients were unlikely to benefit from chemotherapy at all (non serous, or low grade tumours) then clearly 3 cycles is equivalent to 6 cycles which is equivalent to 0 cycles. To summarise this in the algorithm that carboplatin/paclitaxel x3 is equivalent to carboplatin x 6 (pg 24 appendix C Draft guidance) is based on no scientific evidence whatsoever. This algorithm referred to elsewhere in the context of lymphadenectomy for stage I disease should be removed or undergo major revision. The recommendations are not based on evidence, the views of specialist international Gynaecological Cancer groups, or practice within the majority of UK Gynaecological Cancer Centres	The recommendation on p 74, lines 8-10 has been deleted We have added a recommendation that retroperitoneal lymph node assessment should be performed and amended the algorithm to reflect this.
SH	NCRI/RCP/RCR/ACP/JCCO	30.55	Full	74	1	As above, we believe that the first point is premature and can only be applied to the UK population when we have the mature results of ICON1 published.	The ICON1 10 year follow up data has not been published, therefore we are unable to consider it as evidence.

						There should be some discussion of young women and how to manage potentially fertile women with suspected early stage ovarian cancer. This is a big problem that should be addressed. Point 4 feels premature and not sufficiently backed up by evidence. ICON1 and ACTION were based on 6 cycles and these were the trials that proved the efficacy of adjuvant therapy.	The guidance is not meant to cover all aspects of ovarian cancer management. Individual patient needs may require individual care plans and fertility is one such area where clinical judgement in consultation with the patient may require different approaches to treatment. In women whose risk of relapse was small the GDG felt the adverse effects and costs of adjuvant treatment would significantly outweigh any benefit from treatment and therefore did not recommend adjuvant chemotherapy.
SH	Royal College of Obstetricians and Gynaecologists	14.02	Short version	74	1-3	Guideline states adjuvant chemotherapy should not be given to women who have had optimal surgical staging ie retroperitoneal lymph node assessment. This statement WILL CAUSE A LOT OF CONFUSION because the guideline does not clearly state that unlike systematic retroperitoneal lymphadenectomy there is good evidence for doing random biopsies of the pelvic and abdominal peritoneum as well as retroperitoneal lymph node sampling. Guideline development group need to include under staging that optimal staging in cases with disease apparently only confined to the ovaries on clinical assessment includes retroperitoneal lymph node assessment (not systematic retroperitoneal lymphadenectomy) and peritoneal biopsies.	We have added a recommendation that retroperitoneal lymph node assessment should be performed
SH	NHS Improvement	22.21	Full	74	2	Although the delegates agreed with this guidance significant concern was expressed: • This statement is inconsistent with page 67 lines 1-4 (see 19). • Contradiction in terms: definition of optimal staging – how is optimal staging possible if lymph nodes are not assessed (see previous recommendations)? • In this context, the definition of optimal surgical staging and “retroperitoneal lymph node assessment”must be clarified	This guidance has defined optimal staging as comprising *“midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)”.* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the

							renal veins. It is the latter that is referred to on page 67, lines 1-4. Therefore we do not believe there is a contradiction. We have however added a recommendation that retroperitoneal lymph node assessment should be performed
SH	British Gynaecological Cancer Society 2	34.21	Full	74	2	Although the delegates agreed with this guidance significant concern was expressed: • This statement is inconsistent with page 67 lines 1-4 (see 19). • Contradiction in terms: definition of optimal staging – how is optimal staging possible if lymph nodes are not assessed (see previous recommendations)? • In this context, the definition of optimal surgical staging and "retroperitoneal lymph node assessment" must be clarified in the guidance.	This guidance has defined optimal staging as comprising *"midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsieis of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter Roach et al 2009)".* This includes retroperitoneal lymph node assessment which may include palpation and excision of lymph nodes. Specifically this guidance defines systematic retroperitoneal lymphadenectomy (SRL), as a systematic stripping of all lymph nodes from the pelvis and para-aortic region to the level of the renal veins. It is the latter that is referred to on page 67, lines 1-4. Therefore we do not believe there is a contradiction. We have however added a recommendation that retroperitoneal lymph node assessment should be performed
SH	NHS Improvement	22.22	Full	74	4	Delegates abstained from voting on the basis that this is not an appropriate statement because: • A woman who has had suboptimal staging has "presumed stage 1" disease, not "stage 1" by definition • If sub-optimally staged, re-staging as a second procedure prior to offering chemotherapy is an option – this should be discussed. • Furthermore, the document has not discussed the relevance of histological sub-types	The GDG recognise the potential confusion that could arise from the initial draft and have modified the recommendations on systematic retroperitoneal lymphadenectomy so that they now state lymph node assessment should be performed The GDG assume that when "presumed" stage 1 disease is considered that the guidance on the discussion of risks and benefits of chemotherapy is still relevant. The risks and benefits of second surgery would presumably be included in this discussion as suggested. Different histological subtypes were not specified in the clinical question. Therefore it is not possible for the GDG to make recommendations for different subtypes.
SH	NCRI/RCP/RCR/ACP/JCCO	30.56	Full	74	4	We should aim to complete optimal staging in those	We agree

						patients with low risk rather than discussion with the patient. Or even better to perform adequate staging in the first place.	
SH	British Gynaecological Cancer Society 2	34.22	Full	74	4	Delegates abstained from voting on the basis that this is not an appropriate statement because: • A woman who has had suboptimal staging has "presumed stage 1" disease, not "stage 1" by definition • If sub-optimally staged, re-staging as a second procedure prior to offering chemotherapy is an option – this should be discussed. • Furthermore, the document has not discussed the relevance of histological sub-types	The GDG recognise the potential confusion that could arise from the initial draft and have modified the recommendations on systematic retroperitoneal lymphadenectomy so that they now state lymph node assessment should be performed The GDG assume that when "presumed" stage 1 disease is considered that the guidance on the discussion of risks and benefits of chemotherapy is still relevant. The risks and benefits of second surgery would presumably be included in this discussion as suggested. Different histological subtypes were not specified in the clinical question. Therefore it is not possible for the GDG to make recommendations for different subtypes.
SH	Guys and St Thomas NHS Foundation Trust	36.06	Full	74	4	We should aim to complete optimal staging in those patients with low risk rather than discussion with the patient. Or even better to perform adequate staging in the first place.	We agree
SH	Royal College of Obstetricians and Gynaecologists	14.07	Short version	74	4-5	Section 1.3.2.2 need to recommend 6 cycles of adjuvant carboplatin and paclitaxel for those women with suboptimal staging and stage 1 disease	The GDG is not aware of any evidence to support this treatment regimen which relates to advanced disease and not early stage disease.
SH	NHS Improvement	22.23	Full	74	6	Delegates abstained from voting on the basis that this is too prescriptive and inconsistent with the principles of staging disease optimally and then making a decision about adjuvant chemotherapy	The GDG maintain this recommendation based on the discussion and evidence assessed.
SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.09	Full	74	6	This is far too prescriptive and inconsistent with the principles of staging optimally and then making a decision on adjuvant treatment.	The GDG maintain this recommendation based on the discussion and evidence assessed.
SH	NCRI/RCP/RCR/ACP/JCCO	30.57	Full	74	6	The available trials have been unable to show any PFS or OS advantage for optimally staged patients. Without evidence adjuvant chemotherapy should be discussed with patients who have been optimally staged.	The GDG recognise that this is a difficult area, given that, on the one hand, the evidence available suggests that adequately staged women with stage 1 disease do not derive survival benefit from adjuvant chemotherapy, but on the other hand, published data on the long term survival benefit in

							this group is still awaited. Given the reservations implicit in the concept on optimal staging (SRL v lymph node sampling), the lack of a prospective RCT that explores this, and the apparent benefit of adjuvant chemotherapy in patients with stage 1 disease, the GDG were reluctant to recommend that adjuvant therapy be withheld in all adequately staged stage 1 cases. The recommendation was therefore based on the consideration of best available data by the GDG and in the light of current practise.
SH	British Gynaecological Cancer Society 2	34.23	Full	74	6	Delegates abstained from voting on the basis that this is too prescriptive and inconsistent with the principles of staging disease optimally and then making a decision about adjuvant chemotherapy	The GDG maintain this recommendation based on the discussion and evidence assessed.
SH	Guys and St Thomas NHS Foundation Trust	36.07	Full	74	6	The available trials have been unable to show any PFS or OS advantage for optimally staged patients. Without evidence adjuvant chemotherapy should be discussed with patients who have been optimally staged.	The GDG recognise that this is a difficult area, given that, on the one hand, the evidence available suggests that adequately staged women with stage 1 disease do not derive survival benefit from adjuvant chemotherapy, but on the other hand, published data on the long term survival benefit in this group is still awaited. Given the reservations implicit in the concept on optimal staging (SRL v lymph node sampling), the lack of a prospective RCT that explores this, and the apparent benefit of adjuvant chemotherapy in patients with stage 1 disease, the GDG were reluctant to recommend that adjuvant therapy be withheld in all adequately staged stage 1 cases. The recommendation was therefore based on the consideration of best available data by the GDG and in the light of current practise.
SH	NCRI/RCP/RCR/ACP/JCCO	30.83	NICE	74	6-10	There is no evidence for 1.3.2.3 and 1.3.2.4	Evidence to support 1.3.2.3 comes from ICON1. Recommendation 1.3.2.4 has been deleted.
SH	NCRI/RCP/RCR/ACP/JCCO	30.59	Full	74	7	The Bell study used to justify the use of 3 cycles of adjuvant carboplatin-paclitaxel was seriously underpowered and would only have detected an absolute difference of 10% (almost a doubling in recurrence rate) between 3 and 6 cycles. Given the retrospective analysis (Chan et al 2010) suggestive of benefit for 6 cycles in the most common subtype of ovarian cancer. We believe that too much weight has been placed on these findings.	The recommendation on p 74, lines 8-10 has been deleted

SH	Northern Ireland Cancer Network & Belfast Health and Social Care Trust	25.10	Full	74	8	There is minimal evidence to support this statement.	The recommendation on p 74, lines 8-10 has been deleted
SH	NCRI/RCP/RCR/ACP/JCCO	30.58	Full	74	8	We are uncertain of the evidence to support the practice of prescribing carboplatin & pacltaxel in stage I cases and why it is this considered as an alternative to single agent carboplatin?	The recommendation on p 74, lines 8-10 has been deleted
SH	NHS Improvement	22.24	Full	74	8-10	86% of delegates voted against this statement: • Recommendation based on just one inadequately powered study (Bell et al, Gynaecol Oncol 2006) • This illustrates the inconsistent approach throughout the guidance on the level of evidence required for recommendations	The recommendation on p 74, lines 8-10 has been deleted
SH	NCRI/RCP/RCR/ACP/JCCO	30.86	NICE Full	74 74	8-10 8-10	1.3.2.4The recommendation that 3 cycles rather than 6 should be used in patients with early stage disease is a potentially dangerous assertion based on rather old and uncertain data. The single trial used to make this statement (Bell et al Gyne Oncol 2006) was a randomised trial in which stage I patients were not sub classified into Ic and other stage I. We know that biologically these stages behave differently. Secondly carboplatin AUC 7.5 was used- not the situation in UK where Carboplatin AUC 5 is used and thirdly, only 24 % were serous tumours (which is low) and 30 % of all tumours were grade 3. Concern about a recommendation of using 3 versus 6 cycles was recently published by Chan J et al (Gyne Oncol 2010 116:301-6). Furthermore, the European data (ICON 1 and ACTION used 6 cycles of treatment). While debate continues about whether or not paclitaxel should be added to carboplatin- for late as well as early disease (NICE) it would be wrong to recommend the adoption of only 3 cycles of treatment with a lower dose of carboplatin There are no comparative data suggesting that 3 cycles of carboplatin/paclitaxel is equivalent to 6 cycles of single agent carboplatin (see pg 24 algorithm)	The recommendation on p 74, lines 8-10 has been deleted

SH	British Gynaecological Cancer Society 2	34.24	Full	74	8-10	86% of delegates voted against this statement: • Recommendation based on just one inadequately powered study (Bell et al, Gynaecol Oncol 2006) • This illustrates the inconsistent approach throughout the guidance on the level of evidence required for recommendations	The recommendation on p 74, lines 8-10 has been deleted
SH	Medical Research Council Clinical Trials Unit	21.04	Full	74	33	Again I think it should be noted that when you state "there was no evidence that combination therapy was any more effective than monotherapy in early stage disease" that platinum-taxane combinations haven't been specifically compared to single agent platinum in this population.	We have clarified this in the text
SH	Medical Research Council Clinical Trials Unit	21.05	Full	74	35	Isn't there sufficient variation in UK practice between centres using carboplatin or carboplatin-paclitaxel as their adjuvant regimen of choice such that neither can be referred to as "current standard practice"?	The recommendation on p 74, lines 8-10 has been deleted
SH	Ovacome		Full	74	37	There does not appear to be any data to support the efficacy of a 3 dose regimen, and we wonder why the GDC has come to this position with no evidence to support it.	The recommendation on p 74, lines 8-10 has been deleted
SH	Medical Research Council Clinical Trials Unit	21.06	Full	74	39	I think that it would be helpful to note that this is evidence from a single RCT. eg. "They were aware of evidence, **from a single RCT,** that 3 cycles of…"	The recommendation on p 74, lines 8-10 has been deleted
PR	NETSCC, Health Technology Assessment	5.29	Full	76		The style in parts of Chapter 5 is a little less tight and could be adjusted for consistency with the rest of the Guideline.	We have revised the background to section 5.1
SH	British Gynaecological Cancer Society	8.03	full	76		I am very concerned that no recommendation made on surgery • Section 5.1 badly written and out of date • Relevant evidence not included: *Eisenhauer et al, Gynecol Oncol 103, 2006, 1083-1090; Wimberger et al Gynecol Oncol. 2007; 106(1):69-74; Chi et al, Gynecol Oncol 114 (2009) 26–31; Bristow et al, J Clin Oncol. 2002 Mar 1;20(5):1248-590.* • *Van der Burg et al NEJM, 1995 Mar 9;332(10):629-34). is not mentioned and provides strong evidence for the impact of surgery on survival (see cohort of patients*	We have revised the background to section 5.1 Whilst the GDG acknowledge that RCT evidence in this area is limited, the evidence search identified two reviews of randomised evidence on this topic and appraised these. Because randomised evidence was available, retrospective studies were not appraised. Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question.

						who had biopsy only up front) • Key issues not addressed • Surgery after neoadjuvant treatment not mentioned	We believe that the revised background and analysis does address the key issues and considers surgery after neoadjuvant therapy
SH	Central South Coast Cancer Network	24.05	Full	76		**Management of advanced ovarian cancer** This group of patients represents the majority of ovarian cancer patients however the space within the guideline dedicated to this area is surprisingly small.	This reflects the paucity of evidence available to address the clinical questions posed
SH	Central South Coast Cancer Network	24.06	Full	76		In section 5.1 (the value of primary surgery) the guideline recognises the lack of prospective randomised evidence. This reflects the reality that prospective randomised trial data in surgery is very difficult if not sometimes impossible to achieve. The guideline mentions many studies showing a negative association between the '*amount of residual disease after surgery and outcome*'. One paper that has not been mentioned (Crawford[1] et al 2005) is a prospective observational study within a carefully controlled double blind randomised chemotherapy trial; SCOTROC 1. In this study, which included over 1000 patients who were carefully defined, all having CT scans throughout their treatment and having similar chemotherapy, there was a clear biological gradient supporting the idea that effectiveness of surgery diminishes in relation to how advanced the disease was at the outset, irrespective of the 'success' of primary debulking. The guideline completely omits to discuss the trade off between radicality of surgery and benefit. I accept that the evidence here is somewhat incomplete however there will be wide variations throughout the country in this respect. The guideline does not address delayed primary surgery following primary chemotherapy as opposed	Thank you for your comments. We agree that the Crawford 2005 paper is relevant to the debate concerning post-operative residuum being a prognostic factor. However the background is meant to highlight the uncertainty/variation in practice which resulted in the guideline needing to investigate this topic. It is not intended as an exhaustive review of the available literature. Therefore this paper has not been specically cited. This has been mentioned in the revised background. This is addressed as the Vergote 2010 paper is now included in the evidence review The Verote

						to primary surgery. In particular it does not include data from the prospective randomised trial EORTC-55971 that has been presented at the IGCS in 2008 (Vergote, I. 2008)[2]. As this work may not yet been published at least a holding statement should be considered in this respect. In practice many units in the UK as well as internationally are moving their clinical practice in this direction for patients in whom complete surgical debulking is not feasible. Thank you for allowing comments on this guideline. Crawford S.C. *et al* (2005) '*Does aggressive surgery only benefit patients with less aggressive ovarian cancer? Results from an international comparison within the SCOTROC-1 trial*'. JCO 34, 8802-11 [2] Vergote I. 'Eortc-gcg/ncic-ctg randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage iiic-iv ovarian, fallopian tube and peritoneal cancer (ovca) International Gynaecological Cancer Society, Bangkok 2008, abstract number 1767.	2008 presentation was not included as we do not use unpublished data. .
SH	NCRI/RCP/RCR/ACP/JCCO	30.80	Full	76		This section seems to be rather confused. Does surgery matter? YES. But does it matter when it is done? Some believe that in the up front management (ie the first 6-12 months after diagnosis), achieving no residual disease is better than optimal debulking is better than sub-optimal debulking. What is the evidence that it matters when surgery is done? Is there any? – except for the 2010 Vergote paper. Using neoadjuvant chemotherapy for bulking Stage III/IV doesn't seem to disadvantage patients, and having one large operation (interval debulking) may well be better than an open and close initially to be followed by another operation as IDS. The EORTC study (Vergote NEJM 2010) should	The GDG agrees that is this is a confusing area with a paucity of adequate evidence to address the issues raised. We have revised the background to this topic to state the issues more clearly. As detailed in the guideline, there is no adequate evidence concerning the timing of primary surgery The GDG agrees that this issue should be discussed in the background. We have revised the background to this topic to

						encourage more use of the neoadjuvant context and the translational research that can go with it – especially the possibility of using new drugs up front for the first time in ovarian cancer. Surgeons should be persuaded to be more aggressive particularly in terms of dissection of diaphragmatic disease. The evidence certainly shows best outcomes for those with no residual disease.	state the issues more clearly. We have revised the background to this topic to state the issues more clearly.
SH	NCRI/RCP/RCR/ACP/JCCO	30.60	Full	76	1	We would suggest stage II disease is separated from stage III/IV. Cure is a realistic prospect in stage II disease whereas in stage III/IV it is unlikely. The management should be attuned to that possibility. This separation is also appropriate because the subsequent discussion focuses on the number of operations and timing of surgery. In a woman with stage II disease the patient should undergo surgery followed by chemotherapy. The EORTC NEJM (2010) study recruited patients with stage III/IV disease and the van der Burg NEJM paper that looked at the value of second operation in the middle of chemotherapy following initial surgery also recruited patients with stage III/IV disease.	The GDG agrees that the implications for surgery are potentially different in women with Stage II disease compared to stage III/IV. However there is insufficient evidence to make definitive recommendations
SH	NCRI/RCP/RCR/ACP/JCCO	30.63	Full	76	1	The recently published paper on timing of primary surgery needs to be discussed fully and its implications absorbed. This paper by Vergote et al (New Eng J Medicine, 2010; 363: 943-53) indicates that primary treatment with platinum based chemotherapy followed by surgery after 3 cycles of chemo is non inferior to primary surgery, and for less fit women and those in whom the prospect of debulking is low, is probably preferable. The guidance needs to tackle the issue of surgery for advanced disease, which exercises MDTs week in week out. Unless it does so, this guidance will not take the management forward.	The Vergote paper has now been included in the evidence review
SH	NCRI/RCP/RCR/ACP/JCCO	30.62	Full	76	4	A recommendation regarding surgical requirements in advanced disease as well as the role of neoadjuvant chemotherapy should be included.	We have inserted a recommendation
SH	Guys and St Thomas NHS Foundation Trust	36.08	Full	76	4	A recommendation regarding surgical requirements in advanced disease as well as the role of neoadjuvant chemotherapy should be included.	We have inserted a recommendation
SH	Central South Coast Cancer Network	24.03	Full	76	37-44	The guideline states that, "*given that women with stage 1 ovarian cancer have significantly less disease*	We note your comment. However the statement is a valid hypothesis, which can have arguments for

						it is possible that less chemotherapy will be required for cure." I disagree with this statement. We do not currently titrate the dosage and number of cycles of chemotherapy with tumour volume and I am not aware of any evidence that this is the case. The statement is weak and diminishes the credibility of the guidance.	and against.
SH	North East London Cancer Network	29.03	Full	76	43	• Section 5.1 badly written and out of date • Relevant evidence not included: *Eisenhauer et al, Gynecol Oncol 103, 2006, 1083-1090; Wimberger et al Gynecol Oncol. 2007; 106(1):69-74; Chi et al, Gynecol Oncol 114 (2009) 26–31; Bristow et al, J Clin Oncol. 2002 Mar 1;20(5):1248-590.* • *Van der Burg et al NEJM, 1995 Mar 9;332(10):629-34). is not mentioned and provides strong evidence for the impact of surgery on survival (see cohort of patients who had biopsy only up front)* • Key issues not addressed • Surgery after neoadjuvant treatment not mentioned • This guidance not supportive of optimal surgery and is counter to the views and evolving practice of the british and international gynaecological oncology community, and could potentially restrict the development of ovarian cancer management in the UK. • Level of evidence accepted by NICE GDG intermittently insufficient (eg 1 underpowered trial to support 3 cycles chemo vs 6), biased (trials relevant in surgery not even considered: see references above), contradictory (systematic lymphadenectomy is not indicated but optimal staging may be) and already out of date • Complete cytoreduction to no visible disease is increasingly the goal in other surgical specialties and 100% consensus amongst delegates that optimal debulking to no visible disease is the standard of care in	We have revised the background to section 5.1 Whilst the GDG acknowledge that RCT evidence in this area is limited, the evidence search identified two reviews of randomised evidence on this topic and appraised these. Because randomised evidence was available, retrospective studies were not appraised. Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. We believe that the revised background and analysis does address the key issues and considers surgery after neoadjuvant therapy The background has been extended to cover the role of surgery in advanced disease. We have also clarified in the recommendations that lymph node assessment should be performed. The recommendation to consider 3 cycles of adjuvant carboplatin plus paclitaxel has been deleted. We agree

						advanced ovarian cancer (consistent with GCIG definition) • This section of the guidance explicitly condones suboptial practice	We disagree. This question investigated the value of surgery in advanced disease when complete extirpation of disease is not possible
SH	NCRI/RCP/RCR/ACP/JCCO	30.61	Full	76	43	Section 5.1 would benefit from a redraft for clarity. It is also out of date in places Relevant evidence that should be included: *Eisenhauer et al, Gynecol Oncol 103, 2006, 1083-1090; Wimberger et al Gynecol Oncol. 2007; 106(1):69-74; Chi et al, Gynecol Oncol 114 (2009) 26–31; Bristow et al, J Clin Oncol. 2002 Mar 1;20(5):1248-590.* *Van der Burg et al NEJM, 1995 Mar 9;332(10):629-34). is not mentioned and provides strong evidence for the impact of surgery on survival (see cohort of patients who had biopsy only up front)* Many key issues are not addressed. These include: Surgery after neoadjuvant treatment should be mentioned The summary here is at variance with the international community and standards of surgery for ovarian cancer. The NICE guideline appears to summarise a minority view The standard of evidence required to validate surgery as therapy for ovarian cancer as summarised in this document is at odds with that for early detection in primary care This section will potentially compromise care of women in the UK, reflect badly on quality of care as compared internationally and reflects a view not held by the majority of our experts who treat women with ovarian cancer	We have revised the background to section 5.1 Whilst the GDG acknowledge that RCT evidence in this area is limited, the evidence search identified two reviews of randomised evidence on this topic and appraised these. Because randomised evidence was available, retrospective studies were not appraised. Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. We believe that the revised background and analysis does address the key issues and considers surgery after neoadjuvant therapy We have made a recommendation on surgery

						Optimal debulking to no visible disease is the standard of care in advanced ovarian cancer (consistent with GCIG definition) This section of the guidance explicitly condones suboptimal practice	We agree We disagree. This question investigated the value of surgery in advanced disease when complete extirpation of disease is not possible
SH	NHS Improvement	22.25	Full	76 to 77		**D**elegates very concerned that no recommendation made on surgery • Section 5.1 badly written and out of date • Relevant evidence not included: *Eisenhauer et al, Gynecol Oncol 103, 2006, 1083-1090; Wimberger et al Gynecol Oncol. 2007; 106(1):69-74; Chi et al, Gynecol Oncol 114 (2009) 26–31; Bristow et al, J Clin Oncol. 2002 Mar 1;20(5):1248-590.* • *Van der Burg et al NEJM, 1995 Mar 9;332(10):629-34). is not mentioned and provides strong evidence for the impact of surgery on survival (see cohort of patients who had biopsy only up front)* • Key issues not addressed • Surgery after neoadjuvant treatment not mentioned (*Vergote et al NEJM, 2010; 363:943-53*) • Although it is understood that a recommendation cannot be made without evidence, the levels of evidence accepted by NICE GDG intermittently insufficient (eg 1 underpowered trial to support 3 cycles chemo vs 6), biased (trials relevant in surgery not even considered: see references above), contradictory (systematic lymphadenectomy is not indicated but optimal staging may be) and already out of date (*Vergote et al NEJM, 2010; 363:943-53*) • Surgery does not lend itself to prospective randomised controlled trials. Nonetheless, the merits of the evidence available was not presented or discussed in these 2 pages. • Complete cytoreduction to no visible disease is increasingly the goal in other surgical specialties and 100% consensus amongst	We have revised the background to section 5.1 Whilst the GDG acknowledge that RCT evidence in this area is limited, the evidence search identified two reviews of randomised evidence on this topic and appraised these. Because randomised evidence was available, retrospective studies were not appraised. Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. We believe that the revised background and analysis does address the key issues and considers surgery after neoadjuvant therapy The background has been extended to cover the role of surgery in advanced disease. We have also clarified in the recommendations that lymph node assessment should be performed. The recommendation to consider 3 cycles of adjuvant carboplatin plus paclitaxel has been deleted. We feel this issue has be addressed by the revisions made to this section We agree

						delegates that optimal debulking to no visible disease is the standard of care in advanced ovarian cancer (consistent with GCIG definition) • This section of the guidance explicitly condones suboptimal practice All involved in the meeting and subsequent consultation process support the following statement: **This guidance is not supportive of optimal surgery and is counter to the views and evolving practice of the British and international gynaecological oncology community, and could potentially restrict the development of ovarian cancer management in the UK.**	We disagree. This question investigated the value of surgery in advanced disease when complete extirpation of disease is not possible We have inserted a new recommendation which is supportive of optimal surgery and reflects evolving practice of the International Gynaecological Oncology community.
SH	British Gynaecological Cancer Society 2	34.26	Full	76 to 77		**D**elegates very concerned that no recommendation made on surgery • Section 5.1 badly written and out of date • Relevant evidence not included: *Eisenhauer et al, Gynecol Oncol 103, 2006, 1083-1090; Wimberger et al Gynecol Oncol. 2007; 106(1):69-74; Chi et al, Gynecol Oncol 114 (2009) 26–31; Bristow et al, J Clin Oncol. 2002 Mar 1;20(5):1248-590.* • *Van der Burg et al NEJM, 1995 Mar 9;332(10):629-34). is not mentioned and provides strong evidence for the impact of surgery on survival (see cohort of patients who had biopsy only up front)* • Key issues not addressed • Surgery after neoadjuvant treatment not mentioned (*Vergote et al NEJM, 2010; 363:943-53*) • Although it is understood that a recommendation cannot be made without evidence, the levels of evidence accepted by NICE GDG intermittently insufficient (eg 1 underpowered trial to support 3 cycles chemo vs 6), biased (trials relevant in surgery not even considered: see references above), contradictory (systematic lymphadenectomy is not indicated but optimal staging may be) and already out of	We have revised the background to section 5.1 Whilst the GDG acknowledge that RCT evidence in this area is limited, the evidence search identified two reviews of randomised evidence on this topic and appraised these. Because randomised evidence was available, retrospective studies were not appraised. Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. We believe that the revised background and analysis does address the key issues and considers surgery after neoadjuvant therapy The background has been extended to cover the role of surgery in advanced disease. We have also clarified in the recommendations that lymph node assessment should be performed. The recommendation to consider 3 cycles of adjuvant carboplatin plus paclitaxel has been deleted.

						date (*Vergote et al NEJM, 2010; 363:943-53*) • Surgery does not lend itself to prospective randomised controlled trials. Nonetheless, the merits of the evidence available was not presented or discussed in these 2 pages. • Complete cytoreduction to no visible disease is increasingly the goal in other surgical specialties and 100% consensus amongst delegates that optimal debulking to no visible disease is the standard of care in advanced ovarian cancer (consistent with GCIG definition) • This section of the guidance explicitly condones suboptimal practice All involved in the meeting and subsequent consultation process support the following statement: **This guidance is not supportive of optimal surgery and is counter to the views and evolving practice of the British and international gynaecological oncology community, and could potentially restrict the development of ovarian cancer management in the UK.**	We feel this issue has be addressed by the revisions made to this section We agree We disagree. This question investigated the value of surgery in advanced disease when complete extirpation of disease is not possible We have inserted a new recommendation which is supportive of optimal surgery and reflects evolving practice of the International Gynaecological Oncology community.
SH	NCRI/RCP/RCR/ACP/JCCO	30.65	Full	77	14	The implications of the van der Burg publication (NEJM, 1995) needs more consideration within the guidelines. This publication showed that women who had received inadequate primary surgery gained a survival benefit by undergoing an adequate procedure after 3 cycles of chemotherapy. This randomised controlled trial by any definition should be classed as strong evidence in support of cytoreductive surgery. The text describes “marginal survival benefit” and then quotes a relative risk of 0.68! The evidence provided in the systematic review by Tangitjamol is of significantly stronger value than other evidence referenced elsewhere in the document on which many of the recommendations have been based. We believe that the draft guideline inappropriately	Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. Bristow et al 2007 was not selected for inclusion since all the randomised studies within it were already included in the systematic review by Tangjitgamol. The remainder of the studies in Bristow were non-randomised. We agree that in these guidelines different recommendations are made on varying qualities of evidence, reflecting the context of the issue being discussed. For surgery, a consensus already exists that surgery should be performed as part of primary management, that its objective is to achieve optimal cytoreduction wherever possible and that it should be performed in cancer centres. Simply restating these statements, on the basis of

						makes some recommendations based on weak retrospective studies and ignores stronger retrospective and prospective studies in relation to surgery in advanced disease. It is unclear on what basis certain retrospective studies have been included in the document and which retrospective studies have been excluded. It does not appear to reflect the quality of the retrospective study. The meta-analysis by Bristow et al (2007, JCO) has to be classed as good retrospective evidence and should be included in the document.	insufficient evidence, serves no purpose. The areas of debate which these guidelines might have addressed is what actually is optimal cytoreduction, what is the optimal way of achieving optimal cytoreduction and do patients in whom optimal cytoreduction is not possible derive any benefit or are they harmed by surgery? We believe that these questions are not yet answerable on the basis of current evidence , which is not sufficient to change the practice of some some surgeons one way or the other
SH	NCRI/RCP/RCR/ACP/JCCO	30.64	Full	77	23	There appears to be confusion relating to the relevance of 2nd look laparotomy performed as a second procedure after primary laparotomy and completion of chemotherapy. Whilst accepting that there is no value in performing this second procedure in women who have completed primary treatment consisting of a combination of primary laparotomy and chemotherapy, it is inappropriate to then make assertions about the lack of value of the primary laparotomy simply because there is evidence to support lack of benefit for a second operation performed as a second-look procedure. The arguments on this page are not clear. No one would consider 'second-look' surgery as originally defined as 21st century practice. Referring back to papers on from the 1980s is irrelevant and confusing and the text misses out the clear level 1 evidence that interval debulking surgery in patients having subpotimal surgery at the outset improves survival (van der Burg NEJM 19965)	Van der Burg is included in systematic review of Tangjitgamol (2009) which was appraised for this clinical question. The clinical question investigated the value of surgery in the primary management of ovarian cancer so it was appropriate to review the evidence relating to second look laparotomy as it was part of primary management. The accepted fact now is that surgery in this context had no therapeutic value . There is a parallel with primary surgery in that up until this evidence was available there was a professional consensus that second look laparotomy was useful. This was based on retrospective evidence that indicated that the amount of post-operative disease after second look laparotomy has prognostic significance. It is not irrelevant to refer back to older papers, if they have a value. The van der Burg 1995 paper is included in the meta-analysis mentioned in the evidence, which has been extended slightly to address the issue that you have raised
PR	NETSCC, Health Technology Assessment	5.18	Full	78		Table 5.2 is valuable in identifying previously non-translated non-English language trials having questionable treatment allocation. A valuable critical review of the literature.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.66	Full	80-81		All studies of patients with advanced disease show that optimal debulking is the strongest prognostic	The Vergote paper has now been added to the evidence review

						factor. The effect is very large. The trials of 'neodajuvant' and interval debulking relate to particular situations where optimal debulking has been deemed impossible or has not been feasible. The latest data (Vergote et al NEJM 2010) is a trial of patients where the possibility of obtaining optimal debulking was in doubt. It is not a trial of all-comers with Stage 3. This is apparent from careful scrutiny of the Appendices that accompany Vergote's NEJM paper and from comments made by investigators at the IGCS 2010 in Prague.	
SH	Airedale NHS Foundation Trust	16.10	Full	81	1	We strongly support the recommendation to investigate properly the effectiveness of primary surgery in this clinical situation	Thank you
SH	Central South Coast Cancer Network	24.15	Full	81	1	Recommendation that research should be undertaken to determine the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised – not supported by evidence	We hope that the revisions made to this section now make the need for this research recommendation more clear.
SH	NCRI/RCP/RCR/ACP/JCCO	30.67	Full	81	1	Prospective trials of surgery versus no surgery are important but it would be better to start with primary peritoneal cancer. The document recommends research in tumours that cannot be fully excised. This statement fails to appreciate that cytoreduction rates vary considerably between one surgeon and another. Whilst some surgeons have cytoreduction rates of 90%, others have cytoreduction rates in the single figures. It is thought that this variation is due to a lack of surgical effort, skill and desire in performing cytoreduction rather than the fact that the tumour is not cytoreducable.	We agree that this would be an appropriate group in that there will be widespread disease that cannot be fully extirpated by surgery. It is suggested though that that patients with IIIc-IV ovarian (and fallopian cancer) could usefully be included Reported cytoreduction rates are variable and are, in part, a function of selection. Whilst accepting the point that cytoreduction rates are infludence by surgical factors, widespread peritoneal involvement, particularly of small bowel serosa, is not going to be completely surgically removable. This subset of patients is not insignficant numerically and the question of what to do in situation remains.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.12	NICE guidelin e	81	1-3	It is unlikely this study will get ethics approval/ recruit.	We disagree
PR	NETSCC, Health Technology Assessment	5.33	Full	81	1-3	"5. Research should be undertaken to determine the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised. This would be a prospective randomised clinical trial recruiting women who have biopsy-proven advanced	Thank you

						ovarian cancer and who are fit enough to receive surgery and chemotherapy…" Agreed.	
SH	NHS Improvement	22.26	Full	81	1-3	Although all present support research in this area the following comments were made: • This guidance is not supportive of a trial of conventional v ultra-radical surgery and is out of date • Inconsistent with recent developments in surgery • Research indicated on determining the impact of radical surgery on survival and on quality of life • Research indicated to optimise selection for optimal debulking surgery. • Necessity of establishing standards of surgical competence emphasised.	The recommendation was aimed at those patients who are not candidates for optimal cytoreduction by whatever surgical approach.
SH	British Gynaecological Cancer Society 2	34.27	Full	81	1-3	Although all present support research in this area the following comments were made: • This guidance is not supportive of a trial of conventional v ultra-radical surgery and is out of date • Inconsistent with recent developments in surgery • Research indicated on determining the impact of radical surgery on survival and on quality of life • Research indicated to optimise selection for optimal debulking surgery. • Necessity of establishing standards of surgical competence emphasised.	The recommendation was aimed at those patients who are not candidates for optimal cytoreduction by whatever surgical approach.
SH	Guys and St Thomas NHS Foundation Trust	36.09	Full	81	2	Not all of us would be supportive of that research.	We have noted your comments
SH	NCRI/RCP/RCR/ACP/JCCO	30.68	Full	81		Whilst there is uncertainty about the best way of delivering intraperitoneal therapy and many 'doubters', the evidence from randomised trials suggests there is an effect on survival. The presence of increased toxicity alone – which tends to diminish with experience should not negate the statistically significant results. Clearly more research is needed but a dogmatic statement stating that IP therapy	The GDG placed a high value on improving the outcomes of disease-free and overall survival, both of which were shown to benefit from the use of intra-peritoneal chemotherapy compared to standard intravenous chemotherapy. However, the GDG recognised that intra-peritoneal chemotherapy was associated with more

						should only be part of clinical trials ignores positive data and the recommendations from the National Cancer Institute, USA. All practicing specialists in Gynaecological Cancer would support further trials but on the basis of level 1 evidence it would be wrong not to allow a discussion about IP therapy with the patient and the use of professional judgement (something repeatedly lacking from this document)	toxicity/adverse events than standard intravenous 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. Although there was high-quality evidence (assessed according to GRADE analysis) on the use of intra-peritoneal chemotherapy, the GDG noted that the studies investigated historical drug regimens and did not investigate intra-peritoneal administration of drugs given intra-venously in current standard UK regimens. There was also a lot of heterogeneity in the studies making it difficult to draw robust conclusions from the evidence. In addition, only one study presented quality of life data and so it was difficult to know if these data were representative. Based on this the GDG did not feel able to recommend the use of intra-peritoneal chemotherapy outside of clinical trials. NICE guidelines do not replace clinical judgement as there will always be situations when the recommendations are not appropriate for a particular patient.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.08	NICE guideline	89	1-3	The evidence for IP therapy is strong – part of the reason for poor uptake in the UK is the change to a new delivery approach – if a multidisciplinary team set up the appropriate pathway then this could be part of service improvement rather than a trial. This would only be for cases with optimal debulking	Service improvement should be based on evidence. The balance of risk and benefit in the use of IP chemotherapy is not defined to the extent that service improvement can be recommended.
SH	Royal College of Obstetricians and Gynaecologists	14.08	Short version	89	1-3	Section 1.4 needs a statement on the role of laparoscopy in determining whether a case with advanced disease (stage 2 -4) is operable. It also needs a statement on the role of neoadjuvant chemotherapy (NACT) followed by delayed primary surgery for cases with stage 3 and 4 disease where it will not be possible to achieve optimal cytoreduction at surgery. Data from an EORTC study has been published this year and it demonstrates that NACT followed by delayed primary surgery is a valid	Laparoscopy is discussed as a method of obtaining tissue diagnosis within the patient pathway of care but the role of laparoscopy as a means of predicting optimal cytoreduction was out the scope of these guidelines The guidance was not designed as a complete manual of ovarian cancer management. The section on primary surgery has been revised to include consideration of neoaduvant chemotherapy

						strategy	
SH	NHS Improvement	22.27	Full	89	1-3	95% voted against this guidance • Level 1 evidence strong of benefits of this type of treatment • Importance of considering patient's choice. • Since *Armstrong et al* published 4 years ago, great experience has accrued to minimise morbidity • Option should be available but offered only in special centres organised and resourced properly and competent to minimise toxicity and co-morbidities – • The PETROC study inclusion criteria (women who had neoadjuvant chemotherapy and interval debulking surgery) exclude a significant proportion of patients from this study.	The GDG placed a high value on improving the outcomes of disease-free and overall survival, both of which were shown to benefit from the use of intra-peritoneal chemotherapy compared to standard intravenous chemotherapy. However, the GDG recognised that intra-peritoneal chemotherapy was associated with more toxicity/adverse events than standard intravenous 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. Although there was high-quality evidence (assessed according to GRADE analysis) on the use of intra-peritoneal chemotherapy, the GDG noted that the studies investigated historical drug regimens and did not investigate intra-peritoneal administration of drugs given intra-venously in current standard UK regimens. There was also a lot of heterogeneity in the studies making it difficult to draw robust conclusions from the evidence. In addition, only one study presented quality of life data and so it was difficult to know if these data were representative. Based on this the GDG did not feel able to recommend the use of intra-peritoneal chemotherapy outside of clinical trials.
SH	British Gynaecological Cancer Society 2	34.28	Full	89	1-3	95% voted against this guidance • Level 1 evidence strong of benefits of this type of treatment • Importance of considering patient's choice. • Since *Armstrong et al* published 4 years ago, great experience has accrued to minimise morbidity • Option should be available but offered only in special centres organised and resourced properly and competent to minimise toxicity and co-morbidities –	The GDG placed a high value on improving the outcomes of disease-free and overall survival, both of which were shown to benefit from the use of intra-peritoneal chemotherapy compared to standard intravenous chemotherapy. However, the GDG recognised that intra-peritoneal chemotherapy was associated with more toxicity/adverse events than standard intravenous chemotherapy and that one study had shown health-related quality of life to be adversely affected by intra-peritoneal chemotherapy in the

						• The PETROC study inclusion criteria (women who had neoadjuvant chemotherapy and interval debulking surgery) exclude a significant proportion of patients from this study.	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. Although there was high-quality evidence (assessed according to GRADE analysis) on the use of intra-peritoneal chemotherapy, the GDG noted that the studies investigated historical drug regimens and did not investigate intra-peritoneal administration of drugs given intra-venously in current standard UK regimens. There was also a lot of heterogeneity in the studies making it difficult to draw robust conclusions from the evidence. In addition, only one study presented quality of life data and so it was difficult to know if these data were representative. Based on this the GDG did not feel able to recommend the use of intra-peritoneal chemotherapy outside of clinical trials.
SH	Target Ovarian Cancer	33.27	Full	89	2	We welcome the fact that IP therapy has been considered as part of this guidance. It is nearly 5 years since the US advised that women with advanced stage, but with effective debulking, should be treated using IP therapy. The trials have shown that on average survival in women with advanced ovarian cancer is extended by about a year. This represents a potentially extremely important opportunity to improve survival for women in the UK. Whilst we accept that UK chemotherapy regimens may differ, it is of absolute importance, given the benefit seen in the range of IP trials, that this method of delivery is trialled as quickly as possible in the UK, covering as wide a range of participants as possible. All women who meet the criteria should be offered access to clinical trials, and the number of participating centres increased. From the Pathfinder Study we know that over 60% did not have clinical trials discussed with them. To ensure the UK improves its survival rates it must take a much more pragmatic and proactive approach. Otherwise we will always risk being the last adopter of new techniques, with potentially devastating impact on those women	The GDG accept that further research needs to be carried out in this area as the evidence in terms of risk and benefit was not clear, hence the need for a recommendation for further research. If the NCRI feel that the PETROC trial is insufficient for the purpose of identifying practice for UK patients then it is their remit to advocate such a trial.

						who miss out. If IP can only be offered as part of a clinical trial then we would urge a research recommendation to widen the number of participating centres, and/or consider what additional trials would be pertinent.	
SH	Janssen-Cilag Ltd	9.00	Full	89	31	It is stated that 'These recommendations refer to both early and advanced disease and should be read in conjunction with chapter 4.' We request that the statement is amended by incorporating the reference of the NICE technology appraisal guidance 91 (NICE, 2005) for clarification purposes as chapter 4 links only to early disease and not to advanced disease.	TA91 covers second-line treatment. The scope of this guideline is restricted to the recognition and initial management of ovarian cancer and recurrent ovarian cancer is therefore outside of the scope.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.09	NICE guidelin e	89	38-42	Remove usually after surgery – the alternative of Neo adjuvant CT is perfectly acceptable	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.71	Full	89-90		The statement that you must never re-treat with paclitaxel is not borne out by the literature that shows clinically useful responses for re-treatment in certain circumstances. This is particularly so with the data that has emerged over the last 5 years on the utility of weekly paclitaxel schedules. That is not to say it is the preferred option in second-line, it isn't but it may be for 3rd or 4th line platinum-sensitive relapses or in patients with liposomal doxorubicin sensitivity\cardiac problems\some dermatological conditions. The statement 'Paclitaxel is not recommended as second-line (or subsequent) therapy in women with ovarian cancer who have received the drug as part of their first-line' should be removed. In addition, the term 'rechallenge' is being wrongly used in the 3rd bullet point	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead. Because these recommendations come from a technology appraisal we are not able to edit their wording.
	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.10	NICE guidelin e	90	3-8	This is not relevant – the scope is for the initial management so relapse is not relevant	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NHS Improvement	22.28	Full	90	3-8	Consensus amongst delegates that this guidance is not relevant to "initial management" and should be removed	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.88	NICE Full	90	3-8 8-13	1.4.2.3- 1.4.2.4 All references to second line therapy should be removed. It is not part of the *recognition and initial management of ovarian cance*r, the	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.

						guidelines (NICE) for 2nd and subsequent treatments are very out of date. Hence, mention of second line therapies will cause confusion	
SH	British Gynaecological Cancer Society 2	34.29	Full	90	3-8	Consensus amongst delegates that this guidance is not relevant to “initial management” and should be removed	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.89	NICE	90	8-13	1.4.2.4. There is unanimity about the use of carboplatin and paclitaxel in recurrences greater than a year out in patients who had received previous carboplatin and paclitaxel. This point further supports the removal of any discussion about 2nd line treatment which is beyond the scope of the guideline development group. Cross referencing to NICE guidance which is more than 5 years old should not occur.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.69	Full	90	9	Second line management is out of the scope of this guideline and this sentence should be deleted. It is also incorrect, as Paclitaxel in combination with Carboplatin is effective in platinum sensitive relapse and weekly Paclitaxel is effective in patients with platinum resistant disease including those that have received the drug previously.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.70	Full	90	9	The recommendation that paclitaxel cannot be used again if used initially is completely wrong and must be deleted. There are large reasons why this is wrong, one of which is that ICON4 demonstrated a survival advantage, and this included patients previously treated with paclitaxel.. (see also: multiple comments pointing out that management of recurrent disease has nothing to do with the “the recognition and initial management of ovarian cancer’.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI/RCP/RCR/ACP/JCCO	30.72	Full	90	9	The exclusion of paclitaxel from the second-line therapy of women who have received this drug in the first-line setting is completely inappropriate and contradicts the findings of ICON4 and other studies supporting the use of doublet chemotherapy over single agent platinum in platinum-sensitive relapsed disease. Indeed the discussion of the management of relapsed ovarian cancer is both superficial and beyond the scope of this guideline.	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	Guys and St Thomas NHS Foundation Trust	36.10	Full	90	9	Second line management is out of the scope of this guideline and this sentence should be deleted. It is	These recommendations have been removed from the guideline and a cross reference to TA55

						also incorrect, as Paclitaxel in combination with Carboplatin is effective in platinum sensitive relapse and weekly Paclitaxel is effective in patients with platinum resistant disease including those that have received the drug previously.	inserted instead.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.11	NICE guideline	90	9-13	This is not relevant – the scope is for the initial management	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NCRI Gynaecology Group	12.00	NICE guidelines	90	9-13	Delete this paragraph. Management of relapsed disease needs more detailed discussion and certainly would include paclitaxel as part of second line treatment	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	NHS Improvement	22.29	Full	90	9-13	Consensus amongst delegates that this guidance is not relevant to “initial management” and should be removed	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	British Gynaecological Cancer Society 2	34.30	Full	90	9-13	Consensus amongst delegates that this guidance is not relevant to “initial management” and should be removed	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead.
SH	Janssen-Cilag Ltd	9.01	Full	90	13	It is stated that ‘For women who have not received paclitaxel as part of first-line treatment, it should be considered as one option alongside other drugs licensed for second-line treatment of ovarian cancer.’ We request for clarity purposes the amendment of the statement by adding the underlined at the end of the sentence: (recommendation on second-line or subsequent treatment can be found in NICE technology appraisal 91 (NICE, 2005)).	These recommendations have been removed from the guideline and a cross reference to TA55 inserted instead. TA91 covers second-line treatment. The scope of this guideline is restricted to the recognition and initial management of ovarian cancer and recurrent ovarian cancer is therefore outside of the scope.
SH	Janssen-Cilag Ltd	9.02	Full	90	16	We request the inclusion of NICE technology appraisal guidance 91 (NICE, 2005) in the ‘Linking evidence to recommendations’ section	TA91 covers second-line treatment. The scope of this guideline is restricted to the recognition and initial management of ovarian cancer and recurrent ovarian cancer is therefore outside of the scope.
SH	Janssen-Cilag Ltd	9.03	Full	90	49	Given the comments above, we request the inclusion of the citation of NICE technology appraisal guidance 91 (NICE, 2005) in the ‘Reference’ section by adding the following citation: National Institute for Health and Clinical Excellence (2005) Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. NICE technology appraisal guidance 91. London: National Institute for Health and Clinical Excellence	TA91 covers second-line treatment. The scope of this guideline is restricted to the recognition and initial management of ovarian cancer and recurrent ovarian cancer is therefore outside of the scope.

SH	Airedale NHS Foundation Trust	16.11	Full	92	1	We strongly concur with this section.	Thank you
SH	Target Ovarian Cancer	33.28	Full	92	1	We welcome the inclusion of this recommendation. However as per comment 8 we would like to see it earlier in the document. As per comment 19 we also believe women should be routinely given information about the tests undergo, initiated in primary care. Data from the Target Ovarian Cancer Pathfinder Study (overseen by a multidisciplinary panel of experts) was as follows with regard to who gave support, and who was most valuable. Clinical Nurse Specialist (44%, 26% cited most helpful) Support Group (30%, 9%) GP (23%, 9%) Counsellor/psychotherapist (11%, 3%) Telephone helpline (6%, 1%) Pscyhologist (4%, 1%)	Thank you. The GDG were unanimous in their support for the flow of the guideline including where the chapters were sited. Therefore we do not think any changes are needed. Please see our response to comment 19.
SH	Royal College of Nursing	39.03	Full	92	16	Nothing was mentioned about women from ethnic backgrounds, particularly those for whom English is not their first language and communications/ information needs can be difficult to be met.	Unfortunately we are not able to change the content of documents which have already been published by other organisations.
PR	NETSCC, Health Technology Assessment	5.05	Full	93	27-44	There is very limited evidence to support any of the recommendations on page 93.	The GDG's decision making process when making these recommendations is made explicit in the LETR paragraph which accompanies the recommendations.
SH	National Forum of Gynaecological Oncology Nurses	20.00	Full	93	27-44	**1.5: Support needs for women with newly diagnosed ovarian cancer** There is general consensus between patients and the manual of cancer services ***that*** highlight the vital role that Clinical Nurse Specialist (CNS) have in ensuring high standards of patients experience within cancer care. The Contribution of the Clinical Nurse Specialist in Cancer Care document (2010) highlights that CNS's play a vital role in delivering high quality of compassionate care for cancer patients and the implementation of initiatives to improve cancer services.	We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis, rather than who should deliver this information so we are not able to recommend who should do this.

						The document widely recognises that CNS's are often at the front line of cancer care and are often the main point of contact/keyworker for patients with cancer, their families and carers. The document also highlights other areas where.	
SH	NHS Improvement	22.30	Full	93	28-32	100% of delegates supported this guidance and made the following suggestions: • Information material should be easily understood, translated in various languages. and peer-reviewed. • Recommendation should comment on the quality of information required	Thank you there is guidance and support at each Cancer Network to support the introduction of appropriate material that is easily understood.
SH	British Gynaecological Cancer Society 2	34.31	Full	93	28-32	100% of delegates supported this guidance and made the following suggestions: • Information material should be easily understood, translated in various languages. and peer-reviewed. • Recommendation should comment on the quality of information required	Thank you there is guidance and support at each Cancer Network to support the introduction of appropriate material that is easily understood.
SH	Royal College of Obstetricians and Gynaecologists	14.09	Short version	93	33-44	In section 1.5.1.2 more information is needed on fertility and hormone treatment ie assisted conception techniques do not increase the risk of ovarian cancer developing. Also need some information on whether HRT can be prescribed to pre-menopausal women who have been diagnosed with ovarian cancer after surgery has been done (information required for both low risk cases and high risk stage 1 cases).	We believe that the principle of information provision and support related to ovarian cancer is crucial at every step of the pathway. There may be elements of the information needs that are more relevant at different times, for example fertility and HRT may be an issue at a particular stage. However the needs assessment and detailed provision of information should be based on individual patient preferences, following a discussion between the patient and their keyworker.
SH	NHS Improvement	22.31	Full	93	33-44	100% of delegates supported this guidance and made the following suggestions: • Peer review mandates a 3-day communication course for core members of every MDT: this recommendation should be consistent with Peer Review standards • Full family history should always be taken • Access to a Clinical Genetics service should	There is no need to add to the existing Advanced Communication Skills training as already mandated by Peer review Measures. The guidance is about information needs for the patient and not the requirement of good clinical practice to which clinicians should adhere. Access to clinical genetics advice already exists

						be available • Access to a CNS should be included in recommendations: CNS's are skilled practitioners who have knowledge of and access to much of this information, providing it as and when the patient wants it • Please include a recommendation re patients' financial and transport needs • Information should be available about the spiritual needs of patients and resources available • Remove the words "if possible" from the recommendation on written information • Clarify who is responsible for providing this information – this should not become a paper tick-box exercise for CNS's • Should be an option for patients to decline information • Should be consistent with Peer Review measures • Survivorship issues not covered	within the NHS. We agree that the CNS has a key role to play in the care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis, rather than who should deliver this information so we are not able to recommend who should do this. The spiritual, financial and transport needs of adults with cancer are all encompassed in the Supportive and Palliative Care IOG. Within this IOG a full holistic assessment of patients is required. This phrase has been removed The role of information "giver" will depend on the place on the patient pathway. This role would be identified as that of the key worker. Survivorship is already included as part of the Cancer Reform Strategy and does not need to be replicated in this guideline.
SH	British Gynaecological Cancer Society 2	34.32	Full	93	33-44	100% of delegates supported this guidance and made the following suggestions: • Peer review mandates a 3-day communication course for core members of every MDT: this recommendation should be consistent with Peer Review standards • Full family history should always be taken • Access to a Clinical Genetics service should be available • Access to a CNS should be included in recommendations: CNS's are skilled practitioners who have knowledge of and	There is no need to add to the existing Advanced Communication Skills training as already mandated by Peer review Measures. The guidance is about information needs for the patient and not the requirement of good clinical practice to which clinicians should adhere. Access to clinical genetics advice already exists within the NHS. We agree that the CNS has a key role to play in the

						access to much of this information, providing it as and when the patient wants it • Please include a recommendation re patients' financial and transport needs • Information should be available about the spiritual needs of patients and resources available • Remove the words "if possible" from the recommendation on written information • Clarify who is responsible for providing this information – this should not become a paper tick-box exercise for CNS's • Should be an option for patients to decline information • Should be consistent with Peer Review measures • Survivorship issues not covered •	care of women with ovarian cancer and have alluded to this in the background on page 92. However the clinical question which informed the recommendations in chapter 6 focussed on what information should be provided at the point of diagnosis, rather than who should deliver this information so we are not able to recommend who should do this. The spiritual, financial and transport needs of adults with cancer are all encompassed in the Supportive and Palliative Care IOG. Within this IOG a full holistic assessment of patients is required. This phrase has been removed The role of information "giver" will depend on the place on the patient pathway. This role would be identified as that of the key worker. Survivorship is already included as part of the Cancer Reform Strategy and does not need to be replicated in this guideline.
SH	A Little Wish	35.00	Full	93	38	It is recommended that fertility information should be available. This is a really important factor as the information is not being given, but also the right information and what is available in the time. A woman's fertility of the future is too often disregarded and many later ask what the point was of surviving cancer when loss of fertility hits them.	We agree, hence we have included this in the recommendation.
SH	Target Ovarian Cancer	33.29	Full	93	39	This is especially important, as our work with women shows they are extremely concerned about recurrence and have fears that they will not recognise signs and symptoms. By having information they can know when to seek help rather than worrying unnecessarily. We would also welcome information being given about practical help available (in relation to coping in the home, finance and transport). The Pathfinder Study showed women had both emotional and practical support needs (75% in each case, and four in ten mentioning finance and transport specifically).	We agree.

SH	A Little Wish	35.01	Full	93	42	It is recommended that information about support and support groups is available. Again yes this needs to be done but also the support groups need to be wide ranging and also focus on the long term implications not just whilst fighting the cancer.	This service requirement is covered within the Supportive and Palliative care IOG
SH	Target Ovarian Cancer	33.30	Full	94	36	Citation should read Target Ovarian Cancer.	Change made
SH	Royal College of Nursing	39.04	Full	94	7	More support for a holistic assessment of the patient by the clinical nurse specialist continues throughout her diagnosis/ treatment, to ensure psychosocial and psychosexual needs are addressed.	This text is part of the LETR paragraph which describes the GDGs deliberations when making the recommendations for this clinical question. It is not a recommendation
PR	NETSCC, Health Technology Assessment	5.26	Full	94	9-11	"This clinical question was not considered amenable to health economic evaluation as there was no comparative analysis." Again, economic analysis may have been prematurely neglected here. There is potential medicolegal risk when support needs in psychological and social domains are unmet – most complaints can be related to lapses in communication. This could be evaluated economically in terms of the risk of complaints to the NHS and individual clinicians.	In order to conduct de novo economic analysis there needs to be a comparator. This clinical question did not have a comparator and hence was not amenable to economic analysis

SH	Ovacome		Full	94	36	Throughout the guideline there is significant variance in the value placed on research versus its quality. It is inappropriate to include unpublished and un-peer reviewed findings. Ovacomes study of 400 women (three times more powerful) in 2006 was similarly unpublished, and for this reason was not submitted. NICE does not usually reference such grey literature, and should not do so here. Furthermore the fact that one of the group is a paid employee of this organisation has not been declared in Appendix 6.1	NICE methodology for developing guidelines is that the published literature is systematically searched for evidence that is relevant to a particular topic. This evidence is then sifted and critically appraised by an independent systematic reviewer – not a member of the GDG. NICE methodology does allow published grey literature to be included as evidence in a guideline if it is appropriate to a particular clinical question - (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp). The Pathfinder study is published (both in hardcopy and online). It was assessed as relevant to this particular clinical question and included in the evidence review. As you state in your comment, Ovacomes study is not published and unfortunately it is therefore not possible for us to include it in our evidence review The affiliation of all group members has been publicly available on the NICE website for the entire duration of guideline development. In addition the affiliation of group members was clear in the NICE version that went out for consultation. We have amended Appendix 6.1 of the full guideline to clarify all affiliations.
PR	NETSCC, Health Technology Assessment	5.22	Full	95		The construction and reporting of the economic model is okay.	Thank you
SH	NCRI/RCP/RCR/ACP/JCCO	30.74	Full	103	10	We are unclear as to why the recommendations on follow-up after primary treatment have been included. They appear to represent personal views and are not backed up by evidence. We would recommend that they be removed.	In order to model the cost-effectiveness of the different tests for ovarian cancer in primary care, it was necessary to also estimate the costs and effects of various treatments / pathways following positive or negative tests. This is standard practice within the context of an economic evaluation and is consistent with NICEs methods guides. However, not all the pathways were clearly defined in terms of what it is people do (routinely) therefore a number of assumptions were made in these circumstances. The text you refer to explains the assumptions that were made about follow-up for

							the economic model. They are not intended to be recommendations
SH	NCRI/RCP/RCR/ACP/JCCO	30.73	Full	103	22	The incorporation of colorectal cancer data here and in the following pages, together with poorly explained Markov diagrams is inappropriate, confusing and largely unhelpful.	Colorectal cancer was chosen because it represents the major differential diagnosis for a non-ovarian malignant mass. Extra text has been included in an attempt to better explain the Markov models
SH	Abbott GmbH & Co KG	26.01	Evidence Review	110		Update evidence to include Moore R et al. (2010) Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. AJOG 203:228.e1-6. ROMA achieved significantly higher sensitivity and Negative Predictive Value for identifying women with ovarian cancer than RMI. ROMA is superior to RMI.	ROMA was not investigated as an intervention in this clinical question and therefore we are unable to include papers on its use in the evidence review.
SH	NCRI/RCP/RCR/ACP/JCCO	30.75	Full	114	1	This whole section would benefit from a redraft for clarity. Some experts question its relevance. However, if it is to be retained then the multiple tables need to be well-explained as at the moment they are unclear eg table A1.18 has a title: sensitivity analysis-drug discounts but the table has nothing to do with drug treatments. The legends need to explain what each table is about.	Thank you for this comment. The titles have been amended to better reflect their intended purpose The purpose of a sensitivity analysis is to test the robustness of the results to alternative assumptions
SH	Teenagers and Young Adults with Cancer (TYAC)	38.01	Full	131	33	This guidance is an excellent comprehensive document on epithelial ovarian cancer/carcinoma, and clear about its terms of reference. However it misses an opportunity to define the approach to germ cell tumours of the ovary, which are relevant to younger patients in particular. There would be a substantial benefit in a collaborative consensus guideline on the management of ovarian germ cell tumours, drawing together professionals with expertise in this area, such as Paediatric cancer, Teenage and Young Adult cancer, adult germ cell tumours of testis and other primary sites, and adult gynaecological cancer MDTs.	Thank you. The scope of this guideline specifically excludes germ cell tumours. Therefore it is not possible for the guideline to make recommendations on this issue.
PR	NETSCC, Health Technology Assessment	5.00	Scope section	131	42	1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) I could find no part in the guideline that was specific to NHS hospice care.	None of the topics in the scope focused on hospice care therefore no recommendations were made in this area.
SH	Airedale NHS Foundation	16.12	Full	138	3	We wish to draw attention to our contribution to	Noted.

	Trust					recruitment to the stakeholders for this guideline, See Crawford & Brunskill BJOG 2008; 115:667!!	

SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes	4.00	NICE guidelin e	4		Often delay between presentation to a health care professional and start of treatment Maximisation of treatment – what does this mean? Is it the increased use of radical surgery or the increased use of specialised teams – The EORTC question whether UK surgery is very radical	We have reworded this text

These organisations were approached but did not respond:

A Little Wish
Abbott Laboratories Limited
Aberdeen Royal Infirmary
Almac Diagnostics
Anglia cancer network
Arden Cancer Network
Association for Clinical Biochemistry
Association for Palliative Medicine of Great Britain and Ireland
Association of British Insurers (ABI)
Association of Chartered Physiotherapists in Oncology and Palliative Care
Association of Chartered Physiotherapists in Oncology and Palliative Care
Association of Clinical Biochemists, The
Association of Clinical Pathologists
Association of the British Pharmaceuticals Industry (ABPI)
AstraZeneca UK Ltd
Barnsley Hospital NHS Foundation Trust
Beckman Coulter UK Ltd
Birmingham Womens NHS Trust
BMJ
Boehringer Ingelheim Ltd
Brighton and Sussex University Hospitals Trust
British Dietetic Association
British National Formulary (BNF)
British Society for Cancer Genetics
British Society for Clinical Cytology
British Society for Human Genetics
British Society of Urogynaecological Radiology
BUPA
Cancer Care Cymru
Cancer Research UK
Care Quality Commission (CQC)
Cheshire PCT

College of Emergency Medicine
Commission for Social Care Inspection DO NOT USE - Replace by CQC
Connecting for Health
Daiichi Sankyo UK
Department for Communities and Local Government
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Derby-Burton Cancer Network
Derbyshire Mental Health Services NHS Trust
Dorset Cancer Network
East Lancashire Hospitals NHS Trust
East Midlands Cancer Network
East Midlands Cancer Network
Eusapharma (Europe) Ltd
Eve Appeal, The
GE Healthcare
GlaxoSmithKline UK
Greater Manchester and Cheshire Cancer Network
Greater Manchester and Cheshire Cardiac and Stroke Network
Greater midlands cancer network
Guerbet Laboratories Ltd
Gynaecological Cancer Network Leads Group
Harrogate and District NHS Foundation Trust
Hospira UK Limited
Human Fertilisation and Embryology Authority
Humber and Yorkshire Coast Cancer Network
Imaging Equipment Limited
Insitute of Biomedical Science
James Cook University Hospital
Leeds PCT
Leeds Teaching Hospitals NHS Trust
Leicestershire Northamptonshire and Rutland Cancer Network
Liverpool Community Health
Lothian University Hospitals Trust
Luton & Dunstable Hospital NHS Foundation Trust
Lymphoedema Support Network, The
Macmillan Cancer Support
Medicines and Healthcare Products Regulatory Agency (MHRA)
Ministry of Defence (MoD)
MRC-CTU
National Council for Palliative Care
National Patient Safety Agency (NPSA)
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NCC - Cancer

NCC - Mental Health
NCC - National Clinical Guidance Centre (NCGC)
NCC - Women & Children
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Improvement
NHS Kirklees
NHS Knowsley
NHS Plus
NHS Quality Improvement Scotland
NHS Sefton
NHS Sefton
NHS Sheffield
NHS Western Cheshire
North Tees & Hartlepool NHS Foundation Trust
North Tees and Hartlepool Acute Trust
North Trent Cancer Network
North Trent Cancer Network
North West London Cancer Network
North Yorkshire and York PCT
Nottingham University Hospitals NHS Trust
Novartis Pharmaceuticals UK Ltd
Novo Nordisk
Patients Council
Pelvic Pain Support Network
PERIGON Healthcare Ltd
Pfizer Limited
Poole and Bournemouth PCT
Randox Laboratories Ltd
Roche Products Limited
Royal College of Nursing
Royal College of Physicians London
Royal College of Radiologists
Royal Cornwall Hospitals Trust
Royal Society of Medicine
Sandwell PCT
Sanofi-Aventis
Schering-Plough Ltd
Scottish Clinical Biochemistry Managed Diagnostic Network
Scottish Intercollegiate Guidelines Network (SIGN)
Sedgefield PCT
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Society and College of Radiographers
South East Wales Cancer Network

South Tees Hospitals NHS Trust
Southend University Hospitals NHS Trust
Sussex Cancer Network
Teenage Cancer Trust, The
Thames Valley Cancer Network
Thames Valley Cancer Network
The Roy Castle Lung Cancer Foundation
The Royal College of Radiologists
The Society and College of Radiographers
University Hospital Birmingham NHS Foundation Trust
Welsh Scientific Advisory Committee (WSAC)
West Hertfordshire PCT & East and North Hertfordshire PCT
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
York NHS Foundation Trust