National Institute for Health and Clinical Excellence

Metastatic malignant disease of unknown primary origin

Guideline Consultation Comments Table
2 December 2009 – 1 February 2010

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Birmingham Cancer Network	25.00	Full	Algorithm	17	Would suggest that algorithm should state that initial assessment needs to include assessment and documentation of baseline performance status – (would suggest ECOG) – and also assessment of any symptom control issues. My suggestion would be that any patients with poor performance status or symptom control should be referred at an early stage to hospital supportive / palliative care team and that algorithm should state this	CUP team assessment, as stated in the algorithm, includes holistic assessment. Additionally referral to palliative and supportive care is defined as an outcome in the pathway.
SH	Birmingham Cancer Network	25.01	Full	2	31	Fully agree with the recommendation of CUP nurse specialist / key worker. However my concern, from a practical perspective is that even a relatively large cancer centre at any given time will have comparatively few patients with MUP or CUP. The tendency may well be for Trusts to 'incorporate 'the CUP role into that of another CNS for example. Perhaps the role should be dedicated to CUP and time for meaningful audit (and research) should be part of the job description. Diluting the CUP role will lead to it being given a lesser status in my opinion.	There was extensive discussion about workload throughout the guideline development process. Considering the CUP specialist nurse will be involved from the earliest stage with the large population of newly presenting patients with MUP, it is considered that a sufficient workload will exist. We agree that this role should not be incorporated into that of another site specialist nurse.
SH	Birmingham Cancer Network	25.02	Full	2	33	Would agree that a regional CUP MDT might be useful, especially with regards to patients with complex diagnostic issues and the fact that some resources e.g. certain imaging, may only be available in one or a limited number of locations. The concern I would have is that a number of patients we see are already subjected to MDT delay and also some are currently discussed at several MDTs also leading to significant delays for the patient. Regional CUP MDT should be available but not the norm / default option in my opinion.	We entirely agree that management of these patients should take place in real time and it is the express function of the CUP team to achieve this. We envisage using the CUP network MDT for those patients who present with difficult diagnostic issues or prior to chemotherapy, along similar lines to conventional MDT functioning.
SH	British Association of Dermatologists	35.00	Full	Epidemiology	19	The definition of CUP is inconsistent. Even on page 19 two definitions are used within a paragraph or two. It needs to be clearly stated whether the definition is "Cancer' of UP or	Carcinoma of unknown primary will be used throughout.

						'Carcinoma' of UP.	
SH	British Association of Dermatologists	35.01	Full	Epidemiology	19	The statement: 'CUP… is the third most common cause of cancer death in England and Wales' seems unbelievable, given the large numbers of deaths from know cancers such as breast, lung, and GI, and considering less that 10,000 new cases of CUP were registered in 2006.	**Figure 7** on p25 demonstrates that there were ~11,000 deaths annually attributed to CUP. This is the same number of deaths as occur due to breast cancer which is recognised as the third most common cause of cancer death (after lung and colorectal cancer).
SH	British Association of Dermatologists	35.02	Full	2	32 -33	The CUP team structure seems appropriate with oncologist, palliative care physician and CNS. Rather than try to set up a CUP MDT would patients not be better served by having CUP cases added to the upper GI MDT – since most cases are likely to be GI or lung.	The GDG discussed this a great length and concluded patients would be best served if CUP was regarded as 'site specific disease' in its own right.
SH	British Association of Dermatologists	35.03	Full	2	33	With the relatively low number of patients and the fact that they are usually of advanced age, making the MDT 'specialist' and 'regional' level might disadvantage patients and delay investigation and treatment. Why can these MDTs not be at local level, added to an established site specialist MDT as stated above? The small number shold not interfere with the site specific MDT too much.	The 'specialist' CUP MDT will reside at network level and it is anticipated that sufficient patients exist for meetings of this MDT to occur weekly.
SH	British Association of Dermatologists	35.04	Full	3	37	*" We were ...??NOT… told the implications…'.* This quote from a patient/carer looks as if it should have the 'not' in the first sentence.	We have made this change
SH	British Association of Dermatologists	35.05	Full	3	39	The comprehensive history and physical examination should include thorough examination of the skin: 1. A comprehensive physical examination of the skin, to include the buccal and genital mucosa is absolutely essential and ideally should be performed by a dermatologist. This is not mentioned in the guidance. While not in the remit of the British Association Dermatologists (BAD), where biopsy of the secondary suggests that the primary may be of malignant melanoma origin, then an ophthalmologist should also examine the ocular system, and in females a gynaecologist should examine the vaginal mucosa. Given how easy these screening investigations can be carried out at low cost, it is surprising they have not been considered as essential practice.	We agree that thorough examination of the skin is important and consider the first bullet point now mandates this since we have amended it to specifically mention the skin. The constraints of the guideline development process mean that very explicit and detailed instructions on specific clinical matters cannot be included.

						2. The BAD is surprised that invasive and low-yield procedures such as endoscopy are considered, whereas a low cost, non-invasive and quite high yield skin examination is not specifically mentioned. 3. The BAD is surprised by the lack of emphasis on a full physical examination of the skin and mucus membranes, which are not specifically mentioned as among the investigations to be offered to every patient with a CUP. This should be done in every case, and would preferably be carried out by a dermatologist. Certainly where any undiagnosed skin lesion is found, a dermatology opinion should be considered essential. 4. The skin is a relatively easy organ to screen and should be cost effective. It gives rise to many carcinomata which can metastasise to include commonly melanoma, squamous cell carcinoma as well as rarer sarcomas and merkel cell carcinoma. These can arise in sites not routinely looked at such as umbilicus, buccal mucosa, vulval skin and scalp and can also arise in apparently innocuous skin lesions such as sebaceous cysts. In examining the skin it is possible to pick up evidence both primary and metastatic tumours but also non-metastatic effects such as rashes, thickening of the skin and other changes some of which are rare but specific and may help towards diagnosis of the underlying cancer. (eg rash typical of pancreatic tumour - necrolytic migratory erythema, eruption of warts in GI cancer etc)	
SH	British Association of Otolaryngologists Head and Neck Surgeons (ENT UK)	12.00	Full	3	39	“comprehensive history and physical examination including breast, nodal areas, genital, rectal and pelvic examination”. In the case of nodal metastatic disease of unknown primary, there is much evidence that simple outpatient clinical examination by an ENT specialist can reveal a primary, asymptomatic primary tumour in the upper aerodigestive tract. If not, then examination under anaesthetic, endoscopy, blind biopsy of risk sites and even tonsillectomy will pick up many more. I accept that in	We agree about the importance of rapid ENT assessment of every appropriate patient. We feel the specialist ENT assessment should be highlighted in the group of patients most likely to benefit, and hence feel this is adequately covered in section 1.4.1.1.

						1.4.1.1 you do suggest later that such neck nodes should go to a head and neck MDT. I do wonder however if that comment should actually have gone here, as it would carry greater emphasis.	
SH	British Association of Otolaryngologists Head and Neck Surgeons (ENT UK)	12.01	Full	General	General	A very interesting and useful document	Thank you
SH	British Nuclear Medicine Society	29.00	Full	3	44-45	Would be in agreement with the two recommendations made ie - Offer 18-FDG PET-CT to patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on panendoscopy if radical treatment is considered to be an option. - Consider 18-FDG PET-CT in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team or specialist network CUP MDT. In patients falling into the second category who undergo 18-F FDG PET-CT and in whom the primary is not identified it may be worthwhile repeating the PET-CT after a time interval on the basis that very small lesions may with an increase in size and metabolic activity become detectable. I note that the quality of the research evidence for use of PET-CT is moderate to poor but that the pooled data suggests relatively high sensitivity and specificity. A coordinated national strategy should be considered to utilize data which may already be available and prospectively collect data.	We believe the key research recommendation regarding PET-CT adequately covers this point.
SH	British Nuclear Medicine Society	29.01	Full	General		Would point out that strictly speaking we should refer to 18-F FDG not 18-FDG.	This change has been made
SH	Cancer of Unknown Primary Foundation	11.00	Full	General	General	We are very encouraged by the (draft) Guidelines which promise to be of great practical benefit to those managing and treating patients, and the patients themselves when fully implemented; reducing *ad hoc* treatment in favour of evidence-based approaches while stimulating a much needed research approach to the CUP phenomenon.	Thank you
SH	Cancer of Unknown Primary Foundation	11.01	Full	1	4	The logic of the first key priority would be improved by a statement that starts with the recommendation (captured on page 32) that *Trusts should establish a CUP team consisting of an oncologist, a palliative care physician and*	We agree that establishing a CUP team should form one of the key priorities and have amended the text accordingly.

						a CUP specialist nurse/key worker as a minimum before giving the responsibilities of the lead clinician. Apart from maintaining the logic, this would give significance to the establishment of the CUP Team which is to be a fundamental component of the future management and treatment of CUP patients.	
SH	Cancer of Unknown Primary Foundation	11.02	Full	2	32	It is a *sine qua non* that establishing effective multidisciplinary CUP teams to deliver all aspects of care for CUP patients is a function of fully resourcing this recommendation. We trust that the recommendations included in the Guideline in this respect are undiluted.	Thank you
SH	Cancer of Unknown Primary Foundation	11.03	Full	1	6	The best long term hope for this group of patients is research, of all kinds, into CUP. We therefore support fully the establishment of an NCRI Clinical Studies Group for CUP at the earliest opportunity.	Thank you
SH	Cancer of Unknown Primary Foundation	11.04	Full	4	6	We support particularly trials that demonstrate improved outcomes through using gene-expression-based profiling and other diagnostic approaches. Molecular profiling may lead to an understanding of CUP biology as well as more individually-targeted therapies. Trials may also give hope to patients that their involvement in a trial may contribute to improvements for future patients.	Thank you
SH	Department of Health	24.00	Full	3	39	There is reference to CT of the chest or abdomen or pelvis. We think that this should read “and/or to enable CT scanning to include all three body areas when appropriate”. Otherwise, we are happy with the imaging elements of this..	Changes have been made to this text.
SH	Department of Health	24.01	Full	3	39	Patients in this setting will often have had a CXR early. If they have not already had a CXR, and whole body CT is planned, there is no need to have a CXR as well. Could you please consider amending 'CT chest or abdo or pelvis' to read 'CT chest AND abdo AND pelvis'.	We feel that clinical judgement will result in chest X-rays only being performed when a CT scan of the chest is not available. This is implied by the phrase ‘as clinically appropriate’
SH	Department of Health	24.02	Full	3	44	The PET-CT indications are fair. There appear to be no estimates of numbers for England on NICE figures and cancer of unknown primary origin was not included in the likely demand report of the PETCT board to the Department of Health, February 2009. http://www.bnms.org.uk/images/stories/downloads/docume	The needs assessment chapter in the full guideline will give an estimate of CUP incidence in England and Wales if it can be calculated. Although the Waltonen et al 2009 paper was published in October it didn't get indexed in the main

						nts/pet-ct_indications_likely_demand_table_2009.pdf The following reference may be useful: J. D. Waltonen, E. Ozer, N. C. Hall, D. E. Schuller, and A. Agrawal Metastatic Carcinoma of the Neck of Unknown Primary Origin: Evolution and Efficacy of the Modern Workup Arch Otolaryngol Head Neck Surg, October 1, 2009; 135(10): 1024 – 1029. Primary tumor location was identified in 84 patients (45.9%). Pre-operative imaging (computed tomography [CT], magnetic resonance imaging, positron emission tomography [PET], and/or PET-CT fusion scan) identified sites suggestive of primary tumor location in 69 patients. Subsequent directed biopsy of these sites yielded positive results in 42 cases (60.9%). The rate of successful identification of a primary tumor for each of the imaging modalities was as follows: CT scan of the neck, 14 of 146 patients (9.6%); magnetic resonance imaging of the neck, 0 of 13 patients (0%); whole-body PET scan, 6 of 41 patients (14.6%); and PET-CT fusion study, 23 of 52 patients (44.2%) (P = .001). The highest yield in identifying primary tumor sites was obtained in patients who had undergone PET-CT plus panendoscopy with directed biopsies with or without tonsillectomy: 31 of 52 patients (59.6%). In Appendix 1 1 "What is the expected value of perfect information in reducing uncertainty surrounding the cost-effectiveness of systemic treatment in patients with confirmed carcinoma of unknown primary and no clinical features fitting a recognised syndrome?" Table 11: Unit cost of supportive care resource use **Resource** Unit cost (£)	databases until two months later. Both Medline and Embase have entry dates as mid December 2009. So in terms of our searching, it was published after our cut-off date of October 9th 2009. It will probably be included when the guideline is updated.

						Source for unit cost Hospital inpatient day 249 PSSRU 2008 Outpatient visit (follow-up) 71 PSSRU 2008 Radiotherapy fraction 96 Ref Cost 2007-2008 MRI scan 262 Ref Cost 2007-2008 CT scan 135 Ref Cost 2007-2008 Hospice inpatient visit 395 Ref Cost 2007-2008	
						This does not include the costs for PETCT, but we believe that the modelling would be strengthened if it were to be included.	PET-CT is not used for routine monitoring of response to treatment nor in the follow up of untreated

							patients. Therefore the costs of this have not been included in the economic analysis We accept that implementation of this guideline may not be cost neutral
						The recommendation that another MDT is convened carries no costings for the imaging (and pathology) resources to support them, for example, a weekly one-hour MDT, including a cross sectional and PETCT radiologist with preparation, would be 150 clinical hours per annum.	
SH	Department of Health	24.03	Full	General		Could you please consider indicating the number of patients seen annually, for the MDT to be functional. It may be that not all trusts see enough cases to justify an independent MDT, and that it may be beneficial if they were to link to a regional meeting.	We feel that the recommendation of a network MDT will avoid problems of too few patients and fulfils your suggestion of a link to a regional meeting.
SH	Department of Health	24.04	Full	3	37	PETCT has the potential to bypass a bevy of diagnostic tests and achieve much earlier diagnosis, some rather unpleasant (such as endoscopy) in patients who are in most cases close to end of life. We feel that it should be given greater prominence, unless symptoms are very suggestive of a particular primary site. This is akin to early application of VATS in exudative pleural effusion - a fairly invasive or expensive test, but one that cuts out weeks of fiddling with repeated aspirations, percutaneous biopsy etc.	We entirely agree that PETCT has the potential to shorten the diagnostic pathway, but regrettably no evidence exists for this. By making this one of our key research recommendations we have given PETCT the prominence that you and we feel is important.
SH	East Midlands Cancer Network	10.00	Full	2	30	It is going to be difficult to justify a specialist team for the numbers. Should this not come in to 'acute oncology' as per NCAG?	The final NCAG report contains very little about patients newly presenting with previously undiagnosed cancer. The precise arrangements for implementation of both 'acute oncology' and the NICE CUP guideline are currently under discussion.
SH	East Midlands Cancer Network	10.01	Full	2	35	To suggest a CUP NSSG is ridiculous. It betrays a totals lack of understanding of the real world and discredits the document.	Putting CUP on the same basis as other 'site specific' cancers is entirely logical and achievable. This will fulfil the aim of the guideline to improve management for this group of patients.
SH	East Midlands Cancer Network	10.02	Full	3	37	Diagnostic profiles very helpful	Thank you

SH	Leeds Teaching Hospital NHS Trust	31.00	Full	2	32	As a minimum a member of the Specialist palliative care team (SPCT) might be more appropriate for the CUP team than a palliative care physician specifically. Many Trusts will find that a palliative care physician is the most appropriate member of the SPCT for this role, but if the pathway is guideline/protocol based it may not always be necessary.	The GDG felt strongly that a palliative care physician should be a core member of the CUP team and be involved in decision making regarding suitability of further investigations and treatment. This is specifically not protocol driven and hence medical input is essential in every case.
SH	Leeds Teaching Hospital NHS Trust	31.01	Full	2	32	Does 'cover for all members of the CUP team at all times' mean that there should be out of hours cover? This may be achievable for oncologists and palliative care physician via the hospital and citywide medical on call rotas but CNS cover is unlikely to be possible.	We have amended the text to clarify that this is an advisory service on a 9-5 basis.
SH	Leeds Teaching Hospital NHS Trust	31.02	Full	2	32	Who 'refers patients'?	Any clinician who manages these patients.
SH	Leeds Teaching Hospital NHS Trust	31.03	Full	2	32	Whilst it is essential that a management plan is in place for all patients with malignancy of undefined primary origin within the time frames specified, it is not essential that all patients are 'seen' by the CUP team within the specified time frame. However, as this will be essential for some patients, such a service must exist. For many patients, the implementation of a diagnostic algorithm agreed between the admitting team and the CUP team, with results pro-actively reviewed by the CUP team would ensure a diagnosis is established as efficiently as possible and that patients are referred to the appropriate team for ongoing management as quickly as possible. This has the advantage of avoiding patients being seen and managed by multiple teams. Patients should be provided with appropriate information and have access to the CUP team at any point during the diagnostic pathway if requested. With increasing tumour site specialisation, for patients where a diagnosis is established, it is essential that patients are reviewed by the relevant site specific oncologists to facilitate decision making about treatment options and potential benefits. It is not appropriate for the CUP team to be making these decisions.	The wording has been changed from 'see' to 'assess'. Thank you It is appropriate for the CUP team to ensure that patients are referred to the relevant site specific team as efficiently as possible, and this is stated throughout the guideline.

						Likewise, the members of the CUP team are not interchangeable, and it might be worth defining the differing roles more clearly - Palliative care is only an appropriate first port of call if a decision-making framework is in place which has excluded the need for an oncology opinion.	We agree that through the process of team discussion, decisions will not be based on the opinion of a sole clinician and this is covered in chapter 4 of the guideline.
SH	Leeds Teaching Hospital NHS Trust	31.04	Full	2	33	Most but not all patients will fulfil the referral criteria for specialist palliative care – reference should be made to the NICE Supportive and Palliative Care Guidance 2004. Therefore the second bullet point should read: • Referred for specialist palliative care, or • Appropriate supportive/palliative care plan in place Follow-up by GP/DN is often appropriate for patients with very advanced disease who are not undergoing specific oncological treatment. Representatives of the Primary Care team were not on the Guideline Development group, and a primary care opinion would be valuable.	This section refers to ensuring active supervision by the CUP team orchestrating care. We agree that this group of patients may well be appropriately managed by palliative care services and arrangements for prompt referral for this are included on p32 of the full guideline. There was primary care representation on the GDG - please see Appendix 6.1 of the full guideline.
SH	Leeds Teaching Hospital NHS Trust	31.05	Full	4	54	This section describes when investigations should be considered and therefore should precede the section describing the investigations (Section 1.2)	The GDG considered the order of sections and favoured the current order, particularly since giving guidance about choice of tests was difficult if those tests had not been previously specified.
SH	Leeds Teaching Hospital NHS Trust	31.06	Full	5	63	This section suggests referring patients to a Bone MDT. Most Trusts do not have a bone MDT	The use of the term 'appropriate' MDT means that patients with bone tumours will be referred to a sarcoma MDT.
SH	Leeds Teaching Hospital NHS Trust	31.07	Full	6	68	What is a 'specific syndrome'?	This refers to the potentially treatable conditions listed in paragraph 3 on p 68. This recommendations has been clarified by amending the text to read 'specific treatable syndrome'
SH	Merseyside & Cheshire Cancer Network	33.00	Full	General	General	The guidance is welcome and presents a well balanced review given the complexicity of the problem and a majority of poor performance status patients.	Thank you
SH	Merseyside & Cheshire Cancer Network	33.01	Full	General	General	There are two things that a patient in this situation needs: 1) A clear explanation of what the situation is, and why this is likely to cause difficulties in treatment, and 2) assurance that any further tests and/or treatment proposed	We feel that the CUP team as currently formulated would fulfil this role.

						is based on solid evidence and is not just "suck it and see". In particular the patient needs to be told of any possible side-effects of any proposed intervention. The patient has to have confidence in the people treating them, since much of what they are told has to be taken on trust. We think this could be achieved by giving each patient an advocate who is medically trained and aware of the case details, but is not part of the treatment team. Think your proposals include people whose job it is to make sure that the patient's interests are represented, but it is not clear if these people would be independent of the treatment team.	
SH	Merseyside & Cheshire Cancer Network	33.02	Full	4	54	Have is some concern over the statement that investigations should be performed if the patient is prepared to accept treatment (1.3.1.2). There are situations when it may be difficult to advise properly on treatment options without having done some investigations. We thought that this section may cause some confusion and be open to interpretation.	It is unacceptable to perform unneccessary tests. By definition this means tests should not be performed in patients for whom they will make no difference, for instance when a decision has already been made that treatment will not be accepted. The recommendations in the guideline have been worded accordingly.
SH	Merseyside & Cheshire Cancer Network	33.03	Full	General	General	Pleased that the document recognises the importance of the family and carers of patients as well as the Key Worker Policy. It is crucial that the policy and the proposed interfaces and discussions with the patient and their representatives are meticulously followed. The NHS often hides behind consent, or lack of it, when refusing to consider a patients position with family and known third parties. This can be harrowing especially when a patient is unable to communicate effectively, or even consider decisions that are being made on their behalf. We're of the strong opinion that consent forms should be initiated at the beginning of processes rather tackling the trauma nearer the end. Whilst we realise that this is a Draft Guideline, and one that seems to have an age to get to this stage, we're horrified at the degree and extent of known problems identified on Page 5. What thought has been given to the timeframe for addressing these issues, some of which may	We agree that there is a need to implement these guidelines promptly, given the major shortcomings in the management of patients with CUP.

						take an eternity to resolve and ultimately result in a very patch service across Networks	
SH	Merseyside & Cheshire Cancer Network	33.04	Full	4	54	Only comment would concern the statement that patients not fit for treatment shouldn't have further investigations or biopsy. Had many patients whom are not fit for treatment but still want to know the diagnosis; hence performed the biopsy. It is also good practice to confirm cancer with a biopsy in patients whom is is safe to do so, as there are many instances where cancer is presumed from imaging, but the patient doesn't die as expected and it turns out it wasn't cancer after all. There are many patients who are not fit for treatment but are fit for biopsy. These are usually the peripheral lesions which are not near vascular structures.	The question whether it is beneficial to investigate to end uncertainty, when there is little likelihood of clinical benefit, was carefully considered by the GDG. It was the opinion of the whole GDG, including patient/carer members, that in this situation testing should be limited rather than exhaustive.
SH	Merseyside & Cheshire Cancer Network	33.05	Full	3	48	This section appears to use the words 'probable metastatic origin' as a 'cover all' statement which belies the complexity of the situation. Solitary and multiple intrapulmonary nodules are a very common finding on CT scans and as scanner images improve are becoming an even more frequent finding. Moreover, whether solitary or multiple, these nodules are very rarely malignant the incidence at our large Trust being 3% when this was last audited a few years ago (multiple hundred cases were assessed). We are currently repeating this audit to update our figures. In addition CT scans with multiple nodules are often reported as showing '"multiple metastases" when reported by non-specialist radiologists but when discussed at the lung MDT we do not agree. Hence, would suggest that a couple of other brief statements be added. First there should be some acknowledgement that solitary and multiple pulmonary nodules are both very common and very rarely malignant. Second there should be a statement that all pulmonary nodules should be discussed at a specialist lung MDT, where the clinicians have extensive experience of managing this situation. In addition chest physicians would agree that a bronchoscopy with brushings and washings is appropriate but many would not agree that 'blind' biopsies should be taken at bronchoscopy. The additional pick up in this	We have amended the text to clarify the fact that only some lung nodules need to be investigated as possibly malignant. We are of the opinion that more direct ways of obtaining a respiratory opinion, where necessary, should be employed rather than referral to an MDT meeting. Blind biopsies are not explicitly recommended in the guideline

						specific situation is small and this has to be balanced against the increased risks associated with taking blind biopsies. I would suggest this should be +/- biopsy based on clinician discretion.	
SH	Merseyside & Cheshire Cancer Network	33.06	Full	5	63	Not clear what this section is trying to state with respect to the lung. If it is a lone metastasis from certain known primary tumours (bowel, sarcoma etc) we would certainly offer surgery where appropriate but this isn't CUP. If it is a solitary lesion with no known primary or other site(s) of metastasis we would treat this as a primary lung tumour anyway.	We agree that solitary lesions in the lung would be managed as you suggest. The current wording of the recommendation does not contradict this.
SH	Merseyside & Cheshire Cancer Network	33.07	Full	4	54	1.3.1.4, is insufficient in the Guidance, Section 1.3.2 is selecting optimal treatment, for some patients - a significant number, Palliative Care may well be the optimal treatment and this should be a separate section in 1.3.2 and should reference the NICE Guidance for the Support of Palliative Care.	Throughout the GDG process great efforts were made to ensure that 'active' treatment eg chemotherapy was not the default management for patients with CUP. Similarly every opportunity was taken to promote palliative care input at every relevant stage. 1.3.2.1 though not specifically mentioning palliative care does make it quite clear that chemotherapy is not for all patients. Where relevant the issue of palliative care has been further highlighted by additions to qualifying statements.
SH	Merseyside & Cheshire Cancer Network	33.08	Full	General	General	Think that NICE need to do better than this to avoid disrupting existing pathways to the detriment of patients.	We recognise your concerns that a new system may be more complex than the existing system, but felt that the status quo was suboptimal. The guideline was written to complement existing pathways and care was taken to avoid any possibility of confusion and duplication.
SH	Merseyside & Cheshire Cancer Network	33.09	Full	General	General	This guideline provides a clear description of, and commentary, on the issues of relevance to the management of patients with carcinomas of unknown primary site. The attempt to provide clarity to the patients' pathways is welcomed but concerned that the proposed guidance cuts across other guidance and might interfere with existing pathways that work well. The overall approach will arguably increase the level of complexity of the system and introduce delays (for some patients) rather	We recognise your concerns that a new system may be more complex than the existing system, but felt that the status quo was suboptimal. The guideline was written to complement existing pathways and care was taken to avoid any possibility of confusion and duplication.

						than simplifying the system; complex systems are generally more likely to be ineffective.	
SH	Merseyside & Cheshire Cancer Network	33.10	Full	General	General	Main problem with the guidance is the lack of clarity, in places, between investigation and management of malignancies of undefined primary type and carcinomas of unknown primary. The definitions are fine but the patient algorithm (page 17), for example, suggests that the guidance covers MUP not just CUP – elsewhere the focus is on CUP.	We consider that patient management includes investigation. The process of managing CUP patients is a continuum from presentation through to treatment. The gross heterogeneity of CUP patients means that definitions and pathways are inevitably imprecise. We have reviewed the use of MUP and CUP in the algorithm and are happy that this reflects the clinical reality.
SH	Merseyside & Cheshire Cancer Network	33.11	Full	General	General	The proposed research questions usefully highlight some of the key areas of uncertainty and should be prioritised for funding.	Thank you
SH	Merseyside & Cheshire Cancer Network	33.12	Full	General	General	The inclusion of emotional patient and physician anecdotes distracts and detracts from the systematic evidence base of the rest of the document; would suggest that the anecdotes are deleted. The suspicion needs to be refuted that the anecdotes are there to hide a lack of systematic evidence of the postulated shortcomings of the current service (no evidence is referenced in this regard).	We can confirm that inclusion of patient comments are intended to complement the evidence. The GDG was keen to highlight the problems that patients experience at the present time.
SH	Merseyside & Cheshire Cancer Network	33.13	Full	General	General	The value and importance of fine needle aspiration cytology in the initial investigation and triage of patients with MUP receives little, if any, mention.	The GDG felt that although FNA cytology was a straightforward way to diagnose malignancy, there are often limitations in the amount of information provided by cytology about tissue of origin. Since many cases inevitably require more information that can only be obtained from immunohistochemistry of solid tissue biopsy samples, they decided to recommend histology instead of FNA cytology, thereby also reducing the need for two procedures.
SH	Merseyside & Cheshire Cancer Network	33.14	Full	Introduction	17	The patient pathway lacks flexibility and has an unclear clinical entry point in so far as it is unclear how much evidence is required to define a patient as having a malignancy of undefined primary. If malignancy has been defined at this point why is there a need for a “non-malignant diagnosis” exit point?	The process of managing CUP patients is a continuum from presentation through to treatment. The gross heterogeneity of CUP patients means that definitions and pathways are inevitably imprecise. We have

						Patients may arrive at a diagnosis of MUP or CUP by a variety of entirely appropriate routes including referral from GPs and from other hospital-based specialists – the route of entry is likely to determine the extent of investigations at entry and the need for subsequent investigations. Current referral pathways from GPs may be varied and in many patients will be based on either the site of metastasis (e.g. back pain) or the presumed site of primary (e.g. neck lump) – existing site-specific teams will already have protocols for the rapid investigation of neck lumps, axillary lumps etc – these do not need interference from the CUP clinical team member at this stage. Site-specific teams will often be the best ones to guide investigations (according to protocols) and will often be the team that is asked to deal with the local effects of metastasis (e.g. bone destruction, brain compression). The CUP team should be able to delegate the responsibility for dealing with these patients throughout the pathway (those avoiding the replication of existing resources in other teams). Would suggest that the prime role of the CUP team in a hospital should be to monitor the pathways of patients with MUP; many of these patients can be managed by site-specific teams but some patients may need more direct management by the CUP team. Site specific teams should ensure good communication with the CUP team so that bi-directional advice can be obtained easily. In some situations the CUP team could provide rapid triage to site-specific teams (without seeing the patients). The CUP team do not need to review the clinical details and pathology of patients who are already being appropriately managed by other teams. Referral forms could be modified by having a supplementary MUP or CUP tick box – this would notify the CUP team but the main referral route to a site-specific team would be unhindered. The patient pathway algorithm should be modified to allow detailed interactions between site-specific and CUP teams at different points.	reviewed the use of MUP and CUP in the algorithm and are happy that this reflects the clinical reality. We recognise your concerns that a new system may be more complex than the existing system, but felt that the status quo was suboptimal. The guideline was written to complement existing pathways and care was taken to avoid any possibility of confusion and duplication. We concur with your valuable suggestions on the interaction between CUP team and site specific teams.
SH	Merseyside & Cheshire Cancer Network	33.15	Full	Introduction	18	The pathology pathway is over-simplistic and does not reflect the subtleties of the later text. The importance of fine needle aspiration cytology in the	We disagree and feel that the algorithm is clear.

						initial triage of patients is totally ignored and the important cautionary notes (in the later text) about inappropriate biopsies are absent. The phase 1 and 2 immunocytochemistry panels will often be combined to provide a rapid diagnosis, depending on the original H&E morphology. To suggest that these are sequential exercises is unhelpful.	Fine needle aspiration cytology may provide sufficient tissue to allow immunohistochemistry but often it gives only a diagnosis of malignancy requiring a follow up biopsy to provide enough tissue to further characterise the tumour. Thus a tissue sample is preferred for definitive diagnosis and to save time in having one rather than two procedures. We agree that phase one and two immunocytochemistry panels may be combined but there is little point in a panel of epithelial markers if the tumour is a lymphoma. The time saved by combining one and two is 24 hours at most but there is a cost saving by the two stage procedure. The recommendations are not prescriptive- a pathologist may use 30+ antibodies immediately if he/she wishes.
SH	Merseyside & Cheshire Cancer Network	33.16	Full	1	28	Definitions – please note that the term biopsy should encompass fine needle aspiration cytology and needle core biopsies in specific circumstances (neck, axilla, inguinal). Open surgical biopsy should be strongly discouraged unless other investigations are inconclusive.	We have amended the text to include FNA where appropriate.
SH	Merseyside & Cheshire Cancer Network	33.17	Full	2	30-31,34	It is questionable as to whether processes that are appropriate for highly focussed tumour site-specific pathways are entirely relevant to CUP. This seems to be acknowledged on page 34 but, even so, the document persists in using existing structures as a model (probably inappropriately). A modified model as suggested in comment #6 should be considered.	Please refer to previous response. The GDG is keen for a new, generic diagnostic triage role to be developed.
SH	Merseyside & Cheshire Cancer Network	33.18	Full	2	30	The current deficiencies section notes a range of issues that may be relevant in some situations. There is an implication that (1) there are shortcomings in the investigation and management of most CUP patients (no evidence) and that this **can** be attributed to a number of factors. It would be more honest to state that **"for patients who experience shortcomings in their investigation**	We consider the existing text to be accurate as it refers to shortcomings in the strategies not the management of every individual patient.

						and management this may be attributed to one or more of the factors".	
SH	Merseyside & Cheshire Cancer Network	33.19	Full	3	37-38	Diagnosis – patient's expectations need to be managed. Doctors know that it is never going to be possible to find the primary site for all metastatic cancers (tumour regression, primary too small for detection when metastasis is diagnosed, etc). Patients should be aware of this and should be pleasantly surprised when a primary site is found quickly. This is picked up in the recommendation on page 53 but could be emphasised earlier.	We feel this issue is adequately covered in the introduction to the Diagnosis chapter.
SH	Merseyside & Cheshire Cancer Network	33.20	Full	3	39	There is no mention of early fine needle aspiration cytology to confirm malignancy (rather than inflammation, for example.) There is a good evidence base for FNAC rapid diagnosis clinics in a range of areas, but particularly in the initial investigation of lumps and bumps of uncertain nature.	The GDG felt that although FNA cytology was a straightforward way to diagnose malignancy, there are often limitations in the amount of information provided by cytology about tissue of origin. Since many cases inevitably require more information that can only be obtained from immunohistochemistry of solid tissue biopsy samples, they decided to recommend histology instead of FNA cytology, thereby also reducing the need for two procedures.
SH	Merseyside & Cheshire Cancer Network	33.21	Full	3	45	Appreciate the need to simplify the complexities of pathological diagnostic process but, in order to avoid misleading general readers, the comments on immunocytochemical panels should be modulated. CK7 and CK20 are really only of value for adenocarcinomas (not all carcinomas – this is noted in the recommendation on page 46), TTF-1 increases or reduces the probability of a lung primary (does not "confirm or exclude"). These comments are supported by the evidence presented on page 46.	This text has been amended
SH	Merseyside & Cheshire Cancer Network	33.22	Full	3	45	It would be useful to debate the value of more rapid diagnosis by having a broader antibody panel as compared to a slower diagnosis by the use of successive smaller panels of antibodies. The point of balance suggested seems unnecessarily restrictive.	Expert opinion governed the recommendation made
SH	Merseyside & Cheshire Cancer Network	33.23	Full	3	37	There is no mention in this section of the role of a network specialist MDT in the diagnostic pathway. In a proportion of patients, the correct diagnosis is reached by discussion	We feel this has adequately been covered by the recommendations on the CUP network MDT in chapter 2.

						by a panel of site-specific expert pathologists who can each offer views on the likely tumour type. This concentration of expert pathologists is likely to be in the Network hub. It would be useful to include a recommendation that once initial investigations have been completed the pathology (and imaging) are reviewed centrally so that further investigations are targeted. It my common experience that such tertiary referral cases where diagnosis is difficult often have a lot of wasted investigations (and hence wasted biopsy tissue and time) in peripheral hospitals before they are referred on. Early central referral (analogous to the haematological malignancies system) would be advantageous and would provide a valuable element of quality control for the process.	
SH	Merseyside & Cheshire Cancer Network	33.24	Full	2	34	The role of the Network should be expanded to ensure the provision of a specialist clinical, imaging and pathology service (in the Network hub) to support rapid, early review of patients.	It is implied in recommendation (p32, lines 53-54) that there will be a properly constituted CUP network MDT. This would include a nominated specialist radiologist and pathologist.
SH	Merseyside & Cheshire Cancer Network	33.25	Full	5	60	Open neck node biopsy should be strongly discouraged as it worsens prognosis in patients with metastatic squamous cell carcinoma. FNAC is the optimal investigation in this situation.	Open neck node biopsy is not proposed and our recommendation, to refer patients to a head and neck MDT for evaluation, should ensure optimal management
SH	National Public Health Service for Wales	7				This organisation responded and said they had no comments to make	Thank you
PR	NETSCC (Ref 1)	30.01	Full	General	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)** In my view the work fulfils the declared intentions of the NICE guideline.	Thank you
PR	NETSCC (Ref 1)	30.02	Full	General	General	No comments. In my opinion the declared intentions are fulfilled.	Thank you
PR	NETSCC (Ref 1)	30.05	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).**	Thank you

						The methods used are clearly described and appear to comply with the NICE guidelines.	
PR	NETSCC (Ref 1)	30.08	Full	General	General	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** In general there are no statistical issues of concern.	Thank you
PR	NETSCC (Ref 1)	30.09	Full	6	69	The methods applied to the health economic evaluation of systemic treatment seems sound. It is unclear what constitutes best supportive care? There is obviously a lot of uncertainty involved highlighting the need for future research to fill in the gaps.	Categories of relevant resource use that constitute best supportive care were defined after reviewing the existing literature for treatment of malignancies with similar severity (such as metastatic non-small cell lung cancer and pancreatic cancer) (Billingham et al 2002, Maslove et al, 2005).
PR	NETSCC (Ref 1)	30.15	Full	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?** Given the nature of CUP and the heterogeneity of cases it is not an easy task to develop guidelines and make specific recommendations. In many cases the evidence is sparse and further research is required to clarify and strengthen many of the recommendations.	Thank you
PR	NETSCC (Ref 1)	30.16	Full	3	44	I wonder if PET should be used as standard. The following opinion was obtained from a clinician working in a local PET centre. Suffice to say that most CUPs are very FDG avid reflecting their biologically-aggressive phenotype and therefore FDG PET is usually more sensitive than conventional imaging for finding the primary and if it doesn't most other subsequent tests also fail. There is a considerable variation in the rate of true positive primary detections, which probably relates to the rigour of pre-PET evaluation, but most series are still less than 50% sensitivity, possibly reflecting spontaneous regression of the primary. Often the challenge is differentiating the primary from multiple sites of metastasis. Generally PET finds more mets also than CI. I believe that FDG PET is most useful to define the pattern of metastasis which can, in combination with histology and tissue IHC identify the most likely culprit.	The formal evidence review does not support any stronger statements on the use of PET-CT than those currently included in the guideline

PR	NETSCC (Ref 1)	30.20	Full	General		**3.2 Are any important limitations of the evidence clearly described and discussed?** Yes in general limitations in evidence are openly discussed and clearly described.	Thank you
PR	NETSCC (Ref 1)	30.23	Full	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.** Overall the guideline is well written and comprehensive. For clarity I would probably like to see subsections within the main sections numbered. For example, in section 3 (Diagnosis) we would have 3.1 (Introduction), 3.2 (Initial diagnostic phase), 3.3 (special tests), 3.3.1 (Tumour markers), etc.	We have introduced numbers for subsections
PR	NETSCC (Ref 1)	30.24	Full	General		The evidence behind the recommendations is clearly described. However in many cases evidence from the literature and clinical practice is lacking which makes it difficult to confidently make evidence based recommendations. It is clear that more prospective clinical research is needed in the future in order to enhance the recommendations.	We agree
PR	NETSCC (Ref 1)	30.25	Full	2	32	Do CUP specialist nurses exist in practice? If not how will they be identified and trained?	This is a new specialist nurse role, for a newly identified 'site specialty'. Recruitment, training and other functions will be identical to that of other existing specialist nurses.
PR	NETSCC (Ref 1)	30.28	Full	General		**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** Most of the research recommendations are quite general. I am not sure whether some of them individually are viable. Would it be more useful to recommend one or two specific trials that should take place which would perhaps be able to answer many of the research questions being posed?	The aim of the research recommendations was to give a general steer to the clinical and research community dealing with this previously neglected area. Very specific recommendations were made for high priority areas.
PR	NETSCC (Ref 1)	30.29	Full	3	43	Is it likely that such a specific prospective study evaluating the effectiveness of mammograms in CUP would realistically happen?	It was felt that once robust definitions were applied to patients with unknown primary cancer, a discrete subgroup could be identified for whom mammography may contribute usefully. A prospective study of the test in this situation would be feasible

							and worthwhile.
PR	NETSCC (Ref 1)	30.30	Full	3	45	As comment in 3.1 Given the nature of CUP and the heterogeneity of cases it is not an easy task to develop guidelines and make specific recommendations. In many cases the evidence is sparse and further research is required to clarify and strengthen many of the recommendations.	Thank you. We have recommended research in a variety of areas
PR	NETSCC (Ref 1)	30.31	Full	6	69	This recommendation is very general. Should more specific recommendations be given about the possible treatment arms that should be included in any randomized trials?	The GDG did not consider it possible or appropriate to propose specific treatment arms for trials since many factors would need to be considered by those undertaking this research, in this rapidly changing field.
PR	NETSCC (Ref 1)	30.35	Full	General	General	**5. 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.** Interesting guideline to read and there is obviously a lot of scope for future prospective research in order to strengthen the guidelines. I would be interested in seeing more detail about proposed future clinical trials and laboratory research aimed at answering many of the questions posed in the guideline. No other comments.	The aim of the research recommendations was to give a general steer to the clinical and research community dealing with this previously neglected area. Very specific recommendations were made for high priority areas.
PR	NETSCC (Ref 2)	30.03	Full	General	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 fulfils the intentions of the guideline. I note the absence of a recommendation on complementary and alternative medicine. This absence is appropriate.	Thank you
PR	NETSCC (Ref 2)	30.06	Full	Methodology	8-16	**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).** Methodology - The authors make reference to the NICE Guidelines Manual in their account of methods used, and as far as I can tell, their application of methods complies scrupulously with the Manual. I am particularly impressed	Thank you

						with their attention to the review of clinical literature.	
PR	NETSCC (Ref 2)	30.10	Full	6	69	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Health Economic Analysis - It is reasonable to restrict the health economic analysis to patients with confirmed CUP who do not fall into one of the recognised "treatable syndromes" -- if I had to choose one topic to cover, this would be it. The analysis' conclusions may seem quite nihilistic to clinicians accustomed to offering more complex chemotherapy to this group. In this regard I would favour a more positive definition of the population, to better describe, for example, the kind of patients reported by Golfinopoulos et al 2009.	The economic analysis itself cannot be used to define the patient population, but clearly should be consistent with the definition used everywhere else in the guideline. To this end, throughout the EVPI analysis (and in particular for the purposes of expert elicitation to inform the model), emphasis was given to consistent use of terminology and alignment with the definition of the patient population that was also used for the systematic search of the clinical literature.
PR	NETSCC (Ref 2)	30.11	Full	6	69	I think that before they agree to step down to fluoropyrimidine monotherapy (which the guideline suggests is probably most cost-effective in the WTP bracket £20000-£40000), clinicians would want to be convinced that these really are the patients left over after excluding those with recognised "treatable syndromes".	The economic analysis only related to those patients with confirmed CUP who do not fall into one of the recognised "treatable syndromes". Recommendations for those patients with recognised treatable syndromes are covered elsewhere in the guideline.
PR	NETSCC (Ref 2)	30.12	Full	Appendices	75	EVPI analysis - An EVPI calculation follows readily from the stochastic methods used in the main economic analysis. It is appropriately located in the Appendix. Although these methods are still in development and have limitations (notably in the case of EVPI, that it offers only an upper bound for the value of research information), I think they merit dissemination and the clinical guideline appendix is a fair platform for this.	Thank you
PR	NETSCC (Ref 2)	30.13	Full	Epidemiology	19	Epidemiology - I note the problems with ICD nomenclature. I agree that summation of codes C77 to C80 is probably the closest that we can approach CUP statistically. I think this is therefore an entirely reasonable tool for descriptive epidemiology, within the scope of the guideline. Scientifically, I would be interested to see if the same statistics are generated using the complementary data (i.e., by subtracting the figures for all non-C77 to C80 codes, from the figures for all cancer). I don't think such a cross-checking exercise is needed for the purposes of the	We acknowledge the limitations on accurately defining the incidence of CUP.

						guideline however.	
PR	NETSCC (Ref 2)	30.17	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?** The recommendations are generally well based on the findings and appropriately justified.	Thank you
PR	NETSCC (Ref 2)	30.18	Full	6	68	Chemotherapy in patients with confirmed CUP - There is something of a mismatch between the clinical guideline conclusion about choice of chemotherapy (which reduces to "the evidence is very poor and we simply cannot tell"), and the economic analysis which ranks fluorouracil ahead of other agents in the WTP bracket £20000-£40000. I think the guideline should be more explicit about what the economists are suggesting, which is that in the absence of any better evidence, at a range of WTP usually considered by NICE, fluorouracil has the edge.	The health economic evaluation for this topic was confined to assessing the 'expected value of perfect information (EVPI)'. This is a decision analytical approach that allows us to estimate the cost of existing uncertainty and to prioritise future research by identifying areas where collection of additional data will lead to reduction in the current level of uncertainty. To put this another way, The EVPI analysis was undertaken with the objective of informing research recommendations. The results of the EVPI analysis were discussed at length by the GDG and after careful consideration, the GDG felt that an explicit recommendation to use one regimen over others would not be robustly supported by the results of the EVPI analysis alone. Factors that contributed to this decision included the limited nature of evidence on clinical effectiveness and reliance of the EVPI analysis predominantly on expert opinion for estimation of numerous parameters.
PR	NETSCC (Ref 2)	30.21	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?** Yes -- the key ones that stand out are 1) the difficulty of categorising CUP within the ICD framework, and 2) the absence of any clinically preferred chemotherapy for patients with confirmed CUP who do not fall into one of the recognised "treatable syndromes"	Thank you
PR	NETSCC (Ref 2)	30.26	Full	General	Gener	**4.1 Is the whole report readable and well presented?**	Thank you

					al	**Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The report is very readable, I particularly like the introduction to each section, which frames the clinical problem in terms of stakeholder experience with quotes. This gives immediate clinical relevance and indeed urgency to the recommendations.	
PR	NETSCC (Ref 2)	30.32	Full	General	General	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** The research recommendations are on the whole clear and justified.	Thank you
PR	NETSCC (Ref 2)	30.33	Full	3	41	Endoscopy - It seems strange that no research recommendation has been made here, given recommendations made for markers and mammography. I note the low pickup rate in (apparently) unselected patients. Surely one valid research question would be how endoscopy could be best targeted to optimise pick-up rate. The guideline presumes that clinical gastrointestinal symptoms would predict this; that presumption would seem to warrant a further look. After all the guideline itself concludes that "Any estimate of the diagnostic yield of gastrointestinal endoscopy in this subgroup of patients depends heavily on the prior probability of gastrointestinal tumours, and there was no reliable source of this information".	The GDG did not feel that trials specifically looking at the use of endoscopy were feasible, particularly in an era when new test such as PET-CT were emerging.
PR	NETSCC (Ref 2)	30.36	Full	General		**5. 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.** I think the guideline will prove to be a landmark in care for this group of patients, I am very glad to have been able to review it, and having now read it makes me want to go out and start a CUP MDT and tumour team in my own cancer network. Well done.	Thank you
PR	NETSCC (Ref 2)	30.37	Full	Key priorities	5	KPs - Shouldn't this be chest AND abdomen AND pelvis?	We have made this change
PR	NETSCC (Ref 2)	30.38	Full	General	General	chemotherapy treatment – redundancy?	We have made this change

PR	NETSCC (Ref 2)	30.39	Full	General	28	typo hetereogeneous	This has been corrected.
PR	NETSCC (Ref 2)	30.40	Full	3	37	" We were told the implications of not finding the primary site. In fact we were not even told that she was actually only receiving palliative treatment through her cancer journey"? missing "not" in first sentence?	We have made this change
PR	NETSCC (Ref 2)	30.41	Full	3	41	Tumour Markers - You may wish to explicitly specify tumour βHCG, our lab at least uses a different protocol for pregnancy testing.	We have included a statement to say 'the method used for measuring hCG must recognize both intact hCG and its free β-subunit".
PR	NETSCC (Ref 2)	30.42	Full	3	44	18-FDG-PET-CT - typo 1-8FDG-PET-CT	We have changed the text.
PR	NETSCC (Ref 2)	30.43	Full	5	61	Squamous carcinoma involving the inguinal nodes - Metastatic carcinoma in inguinal lymph nodes most commonly represents spread from melanomas ... ?? melanomas -> carcinoma ??	We agree that melanoma is the most common metastatic cancer in inguinal lymph nodes but it lies outside the scope of this guideline
SH	NHS Direct	28.00	Full	General	General	Guidance welcome by NHS Direct. No comments on content.	Thank you
SH	NHS Great Yarmouth and Waveney	34.00	Full	Key priorities	4	It may be unrealistic to have a target of referral to the specialist MDT as an inpatient by the end of the next day. Also this misses the issue of the lengthy time it often takes to identify that the patient is suffering from CUP, which happens prior to the referral being made. Careful workforce planning will be required to put in place a CNS for these patients, perhaps a combined role within the specialist oncology nursing team at the centre may work.	The GDG discussed this at length and felt that this was an appropriate timescale to work to, in keeping with the Cancer Reform Strategy. By providing a robust definition for MUP the GDG feels this problem will be overcome. We agree that implementation will need careful consideration.
SH	North East London Cancer Network	27.00	Full	General	General	**Comment from Consultant in Histopathology**: The potential benefit of autopsy in determining origin may be approriate at the very end of the guidance (either hospital or Coroner's) for many reasons including epidemiological/audit purposes.	The potential benefit of autopsy in determining origin was not a topic that was investigated by the guideline. Therefore the evidence in this area has not been appraised and the GDG did not feel it was appropriate to comment or make recommendations on this issue.
SH	North East London Cancer	27.01	Full	General	Gener	**Comment from Consultant in Histopathology**: I am not	The GDG aspired to establish CUP as

	Network				al	entirely clear whether the CUP team is a new team or whether one of the existing site-specific teams could take on this role.	a site specialty on the same basis as other organ derived cancers. The team approach to management should reflect this but will be implemented in different ways in different places.
SH	North East London Cancer Network	27.02	Full	General	General	**Comment from Chair of Skin (Dermatology) Tumour Advisory Board:** There is no mention of skin involvement either in the form of cutaneous metastases or in the form of paraneoplastic syndromes. In the last year, have personally seen 3 cases of metastatic malignant disease where the paraneoplastic syndromes (eg Bazex eg acanthosis nigricans eg dermatomyositis) gave a clue to the tumour of origin or to recurrence at a stage before the tumour was identified. We often have cutaneous metastases with unknown primary and I think this type of patient should involve some dermatology/dermatopathology input.	We agree that patients with CUP present in a multitude of different ways. The GDG felt that we shouldn't go into detail of every possible presentation. However, clear recommendations were made about the desirability of attempted radical treatment for solitary metastases. Where these involve the skin, we agree that a dermatology opinion could usefully be sought. The recommendation has been changed accordingly.
SH	North East London Cancer Network	27.03	Full	3	39	**Comment from Consultant Clinical Oncologist:** I think the document is comprehensive but agree that the addition of dermatological assessment should be included. On page 39, the details of skin examination, with particular regard to pigmented lesions, evidence of paraneoplastic dermatological manifestations should be included.	We feel that this would be covered by a comprehensive physical examination, but in addition to recommendation has now been changed to explicitly include skin.
SH	Royal College of Nursing	22.00	Full	2	32	The mention of the nominated radiologist and pathologist is discussed without any mention of guidance on this, and what this means to a team – extended membership is hinted at in later bits of the document but it is not clear about these roles and where these individuals function e.g. at 'team' level or at 'network MDT' level.	It is implied in recommendation (p32, line 53-54) that there will be a properly constituted CUP network MDT. This would include a nominated specialist radiologist and pathologist.
SH	Royal College of Nursing	22.01	Full	2	33	The levels of teams and responsibilities are a bit muddled. The use of the words such as teams, network MDTs, and network site specific group differs to the terms used by peer review and not very clear how each Trust will function and indeed if each Trust is expected to have a team..	We have reviewed the document and feel confident that there is internal consistency and that the terms are also consistent with those used at a national level.
SH	Royal College of Nursing	22.02	Full	4	54	It would be unethical to suggest that investigations should only be performed if the patient is prepared to accept treatment – a patient should be free to refuse treatment at any point in a clinical pathway. Risks can often only be conveyed once an investigation has been completed and a	It is unacceptable to perform unneccessary tests. By definition this means tests should not be performed in patients for whom they will make no difference, for instance when a

						patient should have the right to assess their personal risk once all information is available.	decision has already been made that treatment will not be accepted. The recommendations in the guideline have been worded accordingly.
SH	Royal College of Paediatrics and Child Health	6				This organisation responded and said they had no comments to make	Thank you
SH	Royal College of Pathologists	26.00	Full	3	39	The statement about "biopsy and standard histological examination" is concise but some important aims of the initial diagnostic CUP biopsy are omitted. Further accuracy and clarity could be achieved by editing this statement to read: " – biopsy and standard histological examination, *with immunohistochemistry if required,* to distinguish carcinoma from other malignant diagnoses, *and to sub-type the carcinoma and where possible predict the likely primary site."* For more detail see also comment #3 below (NICE p17).	'Standard' in this context is meant to discriminate between commonly performed tests and more complex or rarely used tests. We would expect a Histopathologist to apply a preliminary immunohistochemistry screen initially. However we have inserted the wording "with immunohistochemistry if required" into the text for clarity.
SH	Royal College of Pathologists	26.01	Full	2	32	"Malignancy of undefined primary origin" as described constitutes a very large number of patients within the hospital system (potentially up to some 10-15% of all patients presenting with cancer if regarded as equivalent to "cancer of initially unknown origin"). Referral to the CUP team of all of these patients and their assessment within two days would constitute a huge workload. Clarification of how far along the initial assessment pathways (e.g. of the individual common presentations described in sections 3 & 5 of the Full Guideline) these patients should be before referral to the CUP team would be welcomed: otherwise it is very likely that significant variations in practice will develop. This echoes comments #8 & #14 below.	We accept that a large number of patients may initially fall into the MUP category. We anticipate that as the acute oncology service and the CUP service evolve in parallel, systems will be developed for efficiently handling this work.
SH	Royal College of Pathologists	26.02	Full	3	39	See also comment #1 above (NICE p10). The statement about "biopsy and standard histological examination" is concise but some important aims of the initial diagnostic CUP biopsy are omitted. Further accuracy and clarity could be achieved by editing this statement to read: " – biopsy and standard histological examination, *with immunohistochemistry if required,* to distinguish carcinoma from other malignant diagnoses, *and to sub-type the carcinoma and where possible predict the likely primary site."* More for the Full Guideline than the NICE document, two	'Standard' in this context is meant to discriminate between commonly performed tests and more complex or rarely used tests. We would expect a Histopathologist to apply a preliminary immunohistochemistry screen initially. However we have inserted the wording "with immunohistochemistry if required" into the text for clarity.

						further comments may be of use with regard to the purpose of biopsy in CUP. First, the main aims are: (1) to diagnose malignancy; (2) to identify the cancer type and thus, in this context, exclude non-epithelial cancers; (3) for the epithelial cancers to sub-type the tumour into neuro-endocrine, squamous, adenocarcinoma etc; and (4) where possible, to predict the likely primary site(s) for adenocarcinomas (and if necessary, well-differentiated neuroendocrine carcinomas). Second, this can be achieved through routine histology with immunohistochemistry where required. (See also Oien KA, Semin Oncol, 2009 and many others.)	
SH	Royal College of Pathologists	26.03	Full	3	46	See detailed comments above and below about IHC in CUP in general and about the specific panel described: comments #3 & #41.	Thank you
SH	Royal College of Pathologists	26.04	Full	3	49	Suggested edit: "Obtain a *cell or* tissue sample…" See also comments #34 & #42 below.	We have not made this change, please see response to comment #34
SH	Royal College of Pathologists	26.05	Full	Algorithm	18	In the algorithm, the terms "Tumour characterised sufficiently…" and "Incompletely characterised tumour" are perhaps slightly open to interpretation. A little further detail or clarity would be helpful to avoid significant variations in practice. Likewise, as per comments #1 & #3 above, amplification of the aims of the pathological examination of the diagnostic biopsy in CUP may be helpful.	We consider that given that specific requirement that clinical evidence is also considered, the wording of the algorithm is clear and doesn't require any changes.
SH	Royal College of Pathologists	26.06	Full	General	General	This guideline provides a clear description of, and commentary, on the issues of relevance to the management of patients with carcinomas of unknown primary site. The attempt to provide clarity to the patients' pathways is welcomed but concerns have been raised that the proposed guidance cuts across other guidance and might interfere with existing pathways that work well. The overall approach will arguably increase the level of complexity of the system and introduce delays (for some patients) rather than simplifying the system; complex systems are generally more likely to be ineffective.	We recognise your concerns that a new system may be more complex than the existing system, but felt that the status quo was suboptimal. The guideline was written to complement existing pathways and care was taken to avoid any possibility of confusion and duplication.
SH	Royal College of Pathologists	26.07	Full	General	General	A potential significant problem with the guidance is the lack of clarity, in places, between investigation and management of malignancies of undefined primary type and carcinomas of unknown primary. The definitions are fine but the patient algorithm (page 17), for example, suggests that the guidance covers MUP not just CUP – elsewhere the focus is on CUP. (See also comment #2	We consider that patient management includes investigation. The process of managing CUP patients is a continuum from presentation through to treatment. The gross heterogeneity of CUP patients means that definitions and pathways are inevitably

						above and comments #14 & #41 below on the possible confusion in this area in terms of the IHC described.)	imprecise. We have reviewed the use of MUP and CUP in the algorithm and are happy that this reflects the clinical reality.
SH	Royal College of Pathologists	26.08	Full	General	General	The proposed research questions usefully highlight some of the key areas of uncertainty and should be prioritised for funding.	Thank you
SH	Royal College of Pathologists	26.09	Full	General	General	The inclusion of emotional patient and physician anecdotes may distract and detract from the systematic evidence base of the rest of the document; it has been suggested that the anecdotes are deleted. The suspicion needs to be refuted that the anecdotes are there to hide a lack of systematic evidence of the postulated shortcomings of the current service (no evidence is referenced in this regard).	We can confirm that inclusion of patient comments are intended to complement the evidence. The GDG was keen to highlight the problems that patients experience at the present time.
SH	Royal College of Pathologists	26.10	Full	General	General	The value and importance of fine needle aspiration cytology in the initial investigation and triage of patients with MUP receives little, if any, mention.	The GDG felt that although FNA cytology was a straightforward way to diagnose malignancy, there are often limitations in the amount of information provided by cytology about tissue of origin. Since many cases inevitably require more information that can only be obtained from immunohistochemistry of solid tissue biopsy samples, they decided to recommend histology instead of FNA cytology, thereby also reducing the need for two procedures.
SH	Royal College of Pathologists	26.11	Full	Key priorities	5	As per comments #1 & #3 above (NICE p10 & p17).	See response to comments #1 and #3
SH	Royal College of Pathologists	26.12	Full	Research recommendation	6	See detailed comments #32 & #35 below about gene-expression based profiling (GEBP) and IHC. To summarise… Optimally performed histopathology including immunohistochemistry is of great value in CUP. Any trials of GEBP need to be compared with such optimal pathology and other investigations. It is likely that GEBP will be of additional value in a (small but important) minority of patients.	See response to comments #32 & #35
SH	Royal College of Pathologists	26.13	Full	Introduction	17	The patient pathway lacks flexibility and has an unclear clinical entry point in so far as it is unclear how much evidence is required to define a patient as having a malignancy of undefined primary. If malignancy has been	The process of managing CUP patients is a continuum from presentation through to treatment. The gross heterogeneity of CUP patients

						defined at this point, why is there a need for a "non-malignant diagnosis" exit point? Patients may arrive at a diagnosis of MUP or CUP by a variety of entirely appropriate routes including referral from GPs and from other hospital-based specialists – the route of entry is likely to determine the extent of investigations at entry and the need for subsequent investigations. Current referral pathways from GPs may be varied and in many patients will be based on either the site of metastasis (e.g. back pain) or the presumed site of primary (e.g. neck lump) – existing site-specific teams will already have protocols for the rapid investigation of neck lumps, axillary lumps etc – these do not need interference from the CUP clinical team member at this stage. Site-specific teams will often be the best ones to guide investigations (according to protocols) and will often be the team that is asked to deal with the local effects of metastasis (e.g. bone destruction, brain compression). The CUP team should be able to delegate the responsibility for dealing with these patients throughout the pathway (those avoiding the replication of existing resources in other teams). We would suggest that the prime role of the CUP team in a hospital should be to monitor the pathways of patients with MUP; many of these patients can be managed by site-specific teams but some patients may need more direct management by the CUP team. Site specific teams should ensure good communication with the CUP team so that bi-directional advice can be obtained easily. In some situations the CUP team could provide rapid triage to site-specific teams (without seeing the patients). The CUP team do not need to review the clinical details and pathology of patients who are already being appropriately managed by other teams. Referral forms could be modified by having a supplementary MUP or CUP tick box – this would notify the CUP team but the main referral route to a site-specific team would be unhindered. The patient pathway algorithm should be modified to allow detailed interactions between site-specific and CUP teams at different points. See also comments #2 & #8.	means that definitions and pathways are inevitably imprecise. We have reviewed the use of MUP and CUP in the algorithm and are happy that this reflects the clinical reality. We recognise your concerns that a new system may be more complex than the existing system, but felt that the status quo was suboptimal. The guideline was written to complement existing pathways and care was taken to avoid any possibility of confusion and duplication. We concur with your valuable suggestions on the interaction between CUP team and site specific teams.

SH	Royal College of Pathologists	26.14	Full	Introduction	18	The pathology pathway is over-simplistic and does not reflect the subtleties of the later text. The importance of fine needle aspiration cytology in the initial triage of patients is totally ignored and the important cautionary notes (in the later text) about inappropriate biopsies are absent. The phase 1 and 2 immunocytochemistry panels will often be combined to provide a rapid diagnosis, depending on the original H&E morphology. To suggest that these are sequential exercises is unhelpful. See also comment #6 (NICE, p33) for more detailed comment on the algorithm.	We have reviewed the algorithm in light of your comment but do not agree that further changes are needed. Fine needle aspiration cytology may provide sufficient tissue to allow immunohistochemistry but often it gives only a diagnosis of malignancy requiring a follow up biopsy to provide enough tissue to further characterise the tumour. Thus a tissue sample is preferred for definitive diagnosis and to save time in having one rather than two procedures. We agree that phase one and two immunocytochemistry panels may be combined but there is little point in a panel of epithelial markers if the tumour is a lymphoma. The time saved by combining one and two is 24 hours at most but there is a cost saving by the two stage procedure. The recommendations are not prescriptive- a pathologist may use 30+ antibodies immediately if he/she wishes.
SH	Royal College of Pathologists	26.15	Full	1	28	Definitions – please note that the term biopsy should encompass fine needle aspiration cytology and needle core biopsies in specific circumstances (neck, axilla, inguinal). Open surgical biopsy should be strongly discouraged unless other investigations are inconclusive.	We have amended the text to include FNA where appropriate.
SH	Royal College of Pathologists	26.16	Full	1	29	Correction: "*suspected*" not "supected"	This change has been made
SH	Royal College of Pathologists	26.17	Full	2	30	Is the quote correct? i.e. "…now having an ultrasound confirmed *?missing word* taking up most of my upper abdomen…"	Thank you
SH	Royal College of Pathologists	26.18	Full	2	30-31,34	It is questionable as to whether processes that are appropriate for highly focussed tumour site-specific pathways are entirely relevant to CUP. This seems to be acknowledged on page 34 but, even so, the document persists in using existing structures as a model (probably inappropriately). A modified model as suggested in	Please refer to previous response. The GDG is keen for a new, generic diagnostic triage role to be developed.

						comment #14 (Full, Introduction, p17) should be considered.	
SH	Royal College of Pathologists	26.19	Full	2	30	The current deficiencies section notes a range of issues that may be relevant in some situations. There is an implication that (1) there are shortcomings in the investigation and management of most CUP patients (no evidence) and that this **can** be attributed to a number of factors. It would be more honest to state that **"for patients who experience shortcomings in their investigation and management this may be attributed to one or more of the factors".**	We consider the existing text to be accurate as it refers to shortcomings in the strategies not the management of every individual patient.
SH	Royal College of Pathologists	26.20	Full	2	31	Correction "*was*" not "were"	This change has been made.
SH	Royal College of Pathologists	26.21	Full	2	34	The role of the Network should be expanded to ensure the provision of a specialist clinical, imaging and pathology service (in the Network hub) to support rapid, early review of patients.	It is implied in recommendation (p32, lines 53-54) that there will be a properly constituted CUP network MDT. This would include a nominated specialist radiologist and pathologist.
SH	Royal College of Pathologists	26.22	Full	3	37-52	There is no mention in this section (Diagnosis) of the role of a network specialist MDT in the diagnostic pathway. In a proportion of patients, the correct diagnosis is reached by discussion by a panel of site-specific expert pathologists who can each offer views on the likely tumour type. This concentration of expert pathologists is likely to be in the Network hub. It would be useful to include a recommendation that once initial investigations have been completed the pathology (and imaging) are reviewed centrally so that further investigations are targeted. It is a common experience that such tertiary referral cases where diagnosis is difficult often have a lot of wasted investigations (and hence wasted biopsy tissue and time) in peripheral hospitals before they are referred on. Early central referral (analogous to the haematological malignancies system) would be advantageous and would provide a valuable element of quality control for the process.	We feel this has adequately been covered by the recommendations on the CUP network MDT in chapter 2.
SH	Royal College of Pathologists	26.23	Full	3	37	Is the quote correct? i.e. should it be "…we were *not* told…"	We have made this change
SH	Royal College of Pathologists	26.24	Full	3	37	Not quite sure why metastatic thyroid carcinoma is split from all other epithelial and neuro-endocrine malignancies: should it not be grouped either with or beside them? (The split does not make pathological sense.)	We have deleted this as it is included in bullet 6
SH	Royal College of Pathologists	26.25	Full	3	37-38	Diagnosis – patient's expectations need to be managed.	We feel this issue is adequately

						Doctors know that it is never going to be possible to find the primary site for all metastatic cancers (tumour regression, primary too small for detection when metastasis is diagnosed, etc). Patients should be aware of this and should be pleasantly surprised when a primary site is found quickly. This is picked up in the recommendation on page 53 but could be emphasised earlier.	covered in the introduction to the Diagnosis chapter.
SH	Royal College of Pathologists	26.26	Full	3	39	There is no mention of early fine needle aspiration cytology to confirm malignancy (rather than inflammation, for example.) There is a good evidence base for FNAC rapid diagnosis clinics in a range of areas, but particularly in the initial investigation of lumps and bumps of uncertain nature.	The GDG felt that although FNA cytology was a straightforward way to diagnose malignancy, there are often limitations in the amount of information provided by cytology about tissue of origin. Since many cases inevitably require more information that can only be obtained from immunohistochemistry of solid tissue biopsy samples, they decided to recommend histology instead of FNA cytology, thereby also reducing the need for two procedures.
SH	Royal College of Pathologists	26.27	Full	3	39	Again see comments #1 & #3 above.	Thank you
SH	Royal College of Pathologists	26.28	Full	3	45	IHC Lines 40-54: again see comments #1 & #3 above.	Thank you
SH	Royal College of Pathologists	26.29	Full	3	45	The need to simplify the complexities of pathological diagnostic process is appreciated but, in order to avoid misleading general readers, the comments on immunocytochemical panels should be modulated. CK7 and CK20 are really only of value for adenocarcinomas (not all carcinomas – this is noted in the recommendation on page 46), TTF-1 increases or reduces the probability of a lung primary (does not “confirm or exclude”). These comments are supported by the evidence presented on page 46.	This text has been amended
SH	Royal College of Pathologists	26.30	Full	3	45	It would be useful to debate the value of more rapid diagnosis by having a broader antibody panel as compared to a slower diagnosis by the use of successive smaller panels of antibodies. The point of balance suggested seems unnecessarily restrictive.	Expert opinion governed the recommendation made
SH	Royal College of Pathologists	26.31	Full	3	45-47	IHC & expression-based gene profiling (EBGP). IHC and EBGP for CUP share many features: both involve assessing the level of expression of different tissue-specific genes. The main differences are (a) that IHC	We feel that the text is clear as is and does not need to be changed

						assess protein and EBGP assesses mRNA and (b) EBGP tends to assess more genes at a time. However, the fundamental approach is similar. This is not obvious from the descriptions given in the guideline which tend to come across as suggesting that EBGP is an entirely new approach and intrinsically likely to perform better. In fact, although there have been no formal studies yet comparing IHC and EBGP, when studies of either are compared their performance appears similar: there is as yet no evidence to suggest that EBGP is better than optimal histopathology. It seems to us to be more important meantime, as well as recommending future research on EBGP in CUP, that we emphasise the important contribution which well-performed histopathology, incorporating optimal IHC, which will often be beyond (or may not include) the "initial CUP screening" antibodies mentioned in the guideline, can make to CUP management. (It is likely that GEBP will be of additional value in a (small but important) minority of patients.)	
SH	Royal College of Pathologists	26.32	Full	3	49	Investigation of malignant peritoneal disease, Line 11. Suggested edit: "*effusion* cytology" not "*FNA* cytology".	We have made this change
SH	Royal College of Pathologists	26.33	Full	3	49	Investigation of malignant peritoneal disease, Line 34. The evidence for preferring an additional tissue sample as opposed to effusion cytology alone in patients with malignant ascites is not convincing. This recommendation may best be omitted; or it could be stated simply that histology+IHC may be of value if cytology+IHC is not of sufficient help. See also comment #42 below (Evidence p161 & 163).	Expert opinion supported the recommendation that histology was superior to cytology and hence this was the basis for our recommendation, particularly bearing in mind delays that arise from sequential testing if cytology proves unhelpful.
SH	Royal College of Pathologists	26.34	Full	4	56-57	(IHC &) Expression-based gene profiling (EBGP). See comments #1, #3 & especially #32 above. Also, the quotation provided is not relevant to current EBGP for CUP. The quote relates to candidate prognostic and more importantly predictive biomarkers for cancer. Currently, CUP profiling, whether at the IHC or EBGP levels, aims to identify the likely tumour type, sub-type and, if appropriate, primary site. No predictive biomarkers are currently available for CUP *per se*.	The quotation has been edited to be more relevant to this section and it no longer explicitly suggests a predictive role for GEBP.
SH	Royal College of Pathologists	26.35	Full	5	60	Open neck node biopsy should be strongly discouraged as it worsens prognosis in patients with metastatic squamous cell carcinoma. FNAC is the optimal investigation in this	Open neck node biopsy is not proposed and our recommendation, to refer patients to a head and neck MDT

						situation.	for evaluation, should ensure optimal management
SH	Royal College of Pathologists	26.36	Full	5	63	Radical treatment for solitary metastases. Line 18. Add “isolated” or “solitary” before “liver metastases”. Patients and their relatives may read this and become concerned about liver biopsy hampering subsequent treatment even when the disease is obviously more widespread and biopsy is important (we have encountered this and have had to dispel this concern).	We believe that multiple liver metastases may be resected and therefore the current wording is appropriate.
SH	Royal College of Pathologists	26.37	Full	Appendices	115	Appendix 6.4, Line 13. Suggested edit: *Dr* Karin Oien	We have made this change
SH	Royal College of Pathologists	26.38	Evidence	4	24	4. Initial tests for metastases of undiagnosed primary. Correction (multiple times throughout at least the Evidence document): “*CD7*” and “*CD20*” should be changed to “*CK7*” and “*CK20*”. (These are quite different genes/proteins.) e.g. in the sentence “biopsy and standard histological examination including “basic” IHC panel (*CK20, CK7*) plus other IHC as appropriate.	This change has been made
SH	Royal College of Pathologists	26.39	Evidence	10	123	10. IHC for adenocarcinoma of unknown primary. As correction in comment #39 above (Evidence p24).	This change has been made
SH	Royal College of Pathologists	26.40	Evidence	10	123	10. IHC for adenocarcinoma of unknown primary. For the “index tests” described, it is appreciated that simplicity is of value. However, it is not made clear on what grounds the index panel of CK7, CK20, PSA, TTF1, PLAP (and EGFR and PR) were initially selected. That is, there is abundant evidence presented as to why the five first listed antibodies are of value in assessing CUP. But there is no description given as to why these particular antibodies, and this particular number of antibodies, were selected for study at the start of the evidence-gathering. They are undoubtedly a most valuable initial panel of antibodies. But other (or, more likely, additional) antibodies may also be of use. Also, the index tests are of use mainly for the prediction of primary site in adenocarcinoma, as stated in the section heading. For the overall assessment of CUP biopsies, much additional IHC i.e. different or additional antibodies may be required or desired, during the step-wise process of assessment (see comments #1 & #3 above (NICE p10)). As already stated, the guideline tends to switch	For practical reasons we had to restrict the number of IHC markers to a manageable number to allow us to thoroughly review the evidence for each one. The group selected the seven markers through consensus, as the most likely to be useful in an initial panel of markers for adenocarcinoma of unknown primary. The pathology algorithm in the full guideline acknowledges that other markers are of use, suggesting “additional immunohistochemistry guided by the clinical picture if the tumour is not completely characterised by the index panel of markers.”

						between cancer of unknown primary, carcinoma of unknown primary and adenocarcinoma of unknown primary: the IHC required for their assessment is different but only IHC for prediction of primary site in adenocarcinoma of unknown primary (i.e. once that diagnosis is itself established) is described in detail in the guideline. For clarity, either this limitation should be stated more explicitly (in this section and elsewhere in the document) or further guidance could be given on IHC to be used during the step-wise assessment. (See also Oien KA, Semin Oncol, 2009 and many others.)	
SH	Royal College of Pathologists	26.41	Evidence	12	161 & 163	12. Cytological examination of ascitic fluid. See also comment #34 above (Full, p49). The evidence for preferring an additional tissue sample as opposed to effusion cytology alone in patients with malignant ascites is not convincing. The evidence presented on peritoneal histology+IHC comes from two papers from a single gynaecological oncology unit and thus describes a very particular patient cohort which cannot be generalised to the CUP population as a whole. The quoted diagnostic accuracy of 97% in histology+IHC may be partly because the study authors used the histology as their definitive diagnosis. It is widely recognised in general pathological (cytological) practice that effusion cytology+IHC is of value in characterising the malignant cells and aiding the prediction of primary site, although because this is now so generally accepted, there are relatively few primary publications on the topic (more in post-graduate textbooks instead). This recommendation may best be omitted; or it could be stated simply that histology+IHC may be of value if cytology+IHC is not of sufficient help.	Whilst it is correct that cytology and IHC is of value in characterising malignant cells, a tissue biopsy and IHC is likely to give a higher yield of definitive diagnoses. Therefore where a tissue diagnosis is obtainable with relative ease this is preferred to reduce the number of procedures to which the patient is submitted. One procedure will also save time.
SH	Royal College of Physicians London	21.00	Full	General	General	The Royal College of Physicians is grateful for opportunity to comment on this draft guideline.	Thank you
SH	Royal College of Physicians London	21.01	Full	General	General	By putting Unknown Primary Cancer onto the same footing as "site-specific" cancers (e.g. breast, prostate etc) it will help to ensure that modern, site-specific approaches to management (i.e. specialist oncologists, multi-disciplinary teams, specialist nurses etc) can be applied to this large, neglected group. It is vital that efforts to establish fully	Thank you

						functioning and resourced multidisciplinary teams to deliver all aspects of care for unknown primary cancer patients are not diluted in any way. We fully support this important principle.	
SH	Royal College of Physicians London	21.02	Full	General	General	The establishment of an NCRI Clinical Studies Group for Unknown Primary Cancer is the top research recommendation of the Guideline Development Group. We support this and hope that such a Clinical Studies Group could be efficiently and rapidly developed.	Thank you
SH	Royal College of Physicians London	21.03	Full	General	General	The possible need for the endoscopic evaluation of the patient for diagnosis of cancer of unknown primary site is an important consideration. **Endoscopic evaluation:** The guidelines do not recommend further research for the role of endoscopic evaluation of these patients. They also suggest that "panendoscopy" (term not defined) is required in patients with cervical lymphadenopathy arising from an unknown primary site. In other patients, endoscopy is recommended only if so directed by "symptoms". The report admits that there is "no reliable source" to support the yield of occult GI tumours found after endoscopic evaluation in asymptomatic or symptomatic patients. **The report also suggests:** Mortality after upper GI endoscopy : 1 in 12,000 Morbidity after upper GI endoscopy: 1in 500 Mortality after lower GI endoscopy: 1;5000 Morbidity after lower GI endoscopy: 1in 420 **Interpretation:** While these guidelines downplay the requirement for endoscopic evaluation of these patients, it is likely that there will continue to be significant pressure, especially in centres where patients are entered into trials of chemotherapy, for endoscopists to perform urgent endoscopies to evaluate such patients in breach of the guidelines if they come into force in their current format. There is also increasing use of PET scanning in these	

						patients in Oncology centres. The rise in referrals for endoscopy following PET scanning, which shows abnormal uptake within the GI tract is also rising rapidly. What such abnormal uptake means is unknown, but frequently, endoscopic assessment is normal. The guidelines suggest that "panendoscopy" is performed before PET scans are requested. Following a negative endoscopy, a positive PET scans in this situation are likely to lead to a rise in requests for a repeat "check" endoscopy to ensure that the "tumour" was not missed on the first endoscopy. **It is the view of our experts that:** • The morbidity and mortality figures quoted should be reconsidered. • That "panendoscopy" should be defined (does it enclude enteroscopy / capsule endoscopy?) • NICE should recommend research to evaluate the timing of endoscopy in relationship to the PET scan. Before or after? • NICE should recommend further research to evaluate the usefulness of endoscopic assessment in patients with unknown primary tumours and specifically suggest that this research should be undertaken in three groups of patients: a. those with signs/ symptoms possibly suggestive of GI primary b. those without any symptoms but in whom there may be an occult primary tumour. c. Those in whom a PET scan suggests	We appreciate that the figures quoted are from an old study but our literature search did not find more recent studies to be appraised. The GDG felt it was important to quote data from this study to illustrate the risks associated with endoscopy The term panendoscopy is used in the commonly accepted ENT sense to include examination of the upper part of the aerodigestive tract. This has been clarified in the text by inserting ENT and adding a definition of panendoscopy to the glossary. In the absence of robust evidence, clinical judgement, the need to expedite care and the need for optimal use of facilities can all reasonably be factors in the choice of the order of tests. The GDG have recommended research into the timing of PET-CT in the CUP management pathway, but do not feel they are able to make this more specific. It may well be the case that when pathways for the management of CUP have been

						abnormal uptake in the GI tract, and what this means clinically	established (as a result of this guideline), the timing of endoscopy in relation to PET scan could be the subject of future research.
SH	Royal Pharmaceutical Society of Great Britain	9				This organisation responded and said they had no comments to make	Thank you
SH	Salisbury NHS Foundation Trust	8	Full	3	39	Do not consider that measurement of serum immunoglobulins alone are sufficient if there is a possibility of multiple myeloma in a patient with solitary or multiple lytic lesions. An early morning urine sample for Bence-Jones protein should be analysed, and consideration should be given to measuring serum free light chains to maximise the chance of picking up a non-secretory plasma cell dyscrasia.	We have amended this text to say 'myeloma screen' to ensure the maximum chance of picking up a non-secretory plasma cell dyscrasia.
SH	Weston Area Health Trust	32.00	Full	4	53	re Factors influencing management decisions, when to stop investigations - though this is very clear in black and white family members can see this as a 'cop-out' where their loved one is not deemed important enough (due to age etc) to investigate further.	We hope that an even handed assessment has been conveyed to ensure optimal patient care.
SH	Weston Area Health Trust	32.01	Full	2	30	There needs to be excellent communication pathways between the network MDTs (CUP and neuro-oncology) mentioned and the teams in the local hospital to ensure that pts are not left sitting in a bed waiting for a decision. Recently at a lung MDT, a pt with brain mets has been passed from them to us and back again, with no proper ownership of the pt.	We agree, thank you.
SH	Weston Area Health Trust	32.02	Full	2	32	These seem sensible. Need to ensure we have the resources to promise a next day service with cover from a clinician and nurse.	Thank you
SH	Weston Area Health Trust	32.03	Full	General	General	It would be sensible to combine with the acute oncology service, which we are developing.	This is a matter for the implementation phase
SH	Weston Area Health Trust	32.04	Full	General	General	The guidance is comprehensive. Experience of 'malignant disease of unknown primary origin' is that it is a very confusing situation for both the patient and their family members. Though oncology health professionals have a good understanding of the condition, the public struggle with not knowing where the primary is.	Thank you
SH	Weston Area Health Trust	32.05	Full	General	General	Family members have said that if the primary condition had a genetic link to it then should the family not know that so they can become more aware of their health needs i.e. screening.	Screening was not one of the topics considered by the guideline. Therefore the evidence in this area has not been appraised nor recommendations developed on screening.

Organisations that did not respond:

Abbott Laboratories Limited
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 the British Pharmaceuticals Industry (ABPI)
Barnsley Hospital NHS Foundation Trust
BASO ~ The Association for Cancer Surgery
BMJ
Boehringer Ingelheim Ltd
Bolton Council
Bolton PCT
Breakthrough Breast Cancer
Breast Cancer Campaign
British Association for Counselling and Psychotherapy
British Dietetic Association
British Gynaecological Cancer Society
British Liver Trust
British National Formulary (BNF)
British Orthopaedic Association
British Society for Human Genetics
British Thoracic Society
Calderdale PCT
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Cancer Care Cymru
Cancer Research UK
Care Quality Commission (CQC)
Central South Coast Cancer Network
Commission for Social Care Inspection
Connecting for Health
Croydon PCT
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
GE Healthcare

Get A-Head Charitable Trust
Greater Midlands Cancer Network
Grunenthal UK Ltd
Harrogate and District NHS Foundation Trust
Heart of England NHS Foundation Trust
Humber and Yorkshire Coast Cancer Network
Imaging Equipment Limited
Imperial College Healthcare NHS Trust
Institute of biomedical Science
Johnson & Johnson Medical
Leeds PCT
Lilly UK
Macmillan Cancer Support
Marie Curie Cancer Care
Medicines and Healthcare Products Regulatory Agency (MHRA)
Ministry of Defence (MoD)
Mouth Cancer Foundation
National Cancer Network Clinical Directors Group
National Council for Palliative Care
National Patient Safety Agency (NPSA)
NCC - Cancer
NCC - Mental Health
NCC - National Clinical Guidance Centre (NCGC)
NCC - Women & Children
NHS Bedfordshire
NHS Bournemouth and Poole
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Improvement
NHS Kirklees
NHS Plus
NHS Quality Improvement Scotland
NHS Sefton
NHS Sheffield
North Tees and Hartlepool Acute Trust
North Tees PCT
North Trent Cancer Network
North Yorkshire and York PCT
Nottingham University Hospitals NHS Trust
Nucletron UK Ltd
Patients Council
PERIGON Healthcare Ltd
Pfizer Limited

Public Wales NHS Trust
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust - British Bone and Soft Tissue Tumour Panel
Roche Diagnostics
Royal Brompton & Harefield NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Radiologists
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine
Sandwell PCT
Sanofi-Aventis
Sarcoma UK
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Siemens Medical Solutions Diagnostics
Skin Care Campaign
Social Care Institute for Excellence (SCIE)
Society and College of Radiographers
Society for Cardiothoracic Surgery
Society of British Neurological Surgeons
South East Wales Cancer Network
Sussex Cancer Network
Thames Valley Cancer Network
University Hospital Birmingham NHS Foundation Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
West Hertfordshire PCT & East and North Hertfordshire PCT
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Wiltshire PCT
York NHS Foundation Trust
Yorkshire and the Humber Specialised Commissioning Group