Appendix I – Health Economics Evidence Tables

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect		Conclusions	Uncertainty
Navani et al. (2015) Patients who had undergone a CT scan and had suspected stage I to IIIA lung cancer. Study conducted in the UK. **Partially applicable [a, c]** **Potentially serious limitations [b, d, e]**	**Treatment effects** Taken from the LUNG-BOOST, an open-label, multicentre, pragmatic, randomised controlled trial (NCT00652769). N=133. N=66 to EBUS-TBN and n=67 to conventional diagnosis and staging (CDS, (from which one later withdrew consent). **Costs and resource use** Unit costs were obtained from NHS reference costs, NICE 2011 lung cancer guideline, and a published study; these were multiplied by the resource use and summed across all resource items. Price year 2010-2011. **Utility**	The primary endpoint was the time from first outpatient appointment with the respiratory specialist to treatment decision by the multidisciplinary team, after completion of the diagnosis and staging procedures. Analysis took a UK NHS perspective.	**Conventional diagnosis and staging (n=66)** 2,348 £GBP (192.20) **Endobronchial ultrasound-guided transbronchial needle aspiration** 2,407 £GBP (180.50) The median time to treatment decision was shorter with EBUS-TBNA (14 days; 95% CI 14–15) than with CDS (29 days; 23–35) resulting in a hazard ratio of 1·98, (1·39–2·82, p<0·0001).			"The results of the cost analysis suggested that use of EBUS-TBNA as an initial investigation after a CT scan was not more expensive than CDS. Because patients in the EBUS group of the trial had an earlier treatment decision (the primary outcome), we can conclude that EBUS-TBNA was more effective for the same cost, and was therefore cost-effective."	No sensitivity analysis was conducted.

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Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect		Conclusions	Uncertainty
	Utility not measured or expressed in terms of QALYs.						

a) QALYs as per the NICE reference case were not used to measure effectiveness.
b) An incremental cost-effectiveness analysis could not be conducted in line with the NICE reference case.
c) The population was not necessarily comprised of people with an 'intermediate' probability of mediastinal malignancy as per the review protocol for this question
d) No analysis exploring uncertainty in the cost conclusions was conducted
e) No longer term cost consequences were reported

Study, population, country and quality	Data sources	Other comments	Cost (95% CI)	Effect (95% CI)		Conclusions	Uncertainty
Sharples et al. (2012) Patients requiring mediastinal staging of lung cancer. Patients had known or suspected NSCLC with suspected	**Treatment effects** Take from the ASTER, a prospective randomised controlled trial. (n=241). Surgical staging n=118. Endosonography n=123. Mean age was 64.5 years (SD 8.9). **Costs and resource use**	Analysis took a UK NHS perspective. 6-month time horizon post randomisation. Discounting not relevant.	Endosonography followed by Surgical Staging			Because of the very small QALY difference, the authors concluded that an ICER could not be estimated but 63% of bootstrapped samples showed endosonography dominated surgical	The probabilistic sensitivity analysis, showed that 63% of bootstrapped samples showed endosonography dominated (which means it was less expensive and
			10,808 £GBP (9,843 to 11,764)	0.348 QALYs (0.321 to 0.373)			
			Surgical Staging Alone				
			11,735 £GBP (10,843 to 12-647)	0.342 QALYs (0.316 to 0.367)			

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Study, population, country and quality	Data sources	Other comments	Cost (95% CI)	Effect (95% CI)		Conclusions	Uncertainty
mediastinal lymph node N2 or N3 involvement. Study population from the ASTER RCT. Study conducted in the UK, The Netherlands, Belgium	Resource use was collected in terms of numbers of procedures done, (surgical, radiotherapy, chemotherapy) treatments administered, hospital and hospice stays. Costs were taken from the Department of Health (DoH) NHS reference costs 2008-2009. Estimates of endosonography was estimated by Papworth Hospital finance department. Price year 2008-2009.	Funded by the NIHR HTA programme. Analysis also partly reported in Rintoul et al. (2013)	**Incremental cost (95% CI)**	**Incremental effect (95% CI)**	**ICER**	staging and endosonography was cost-effective at a threshold of £30,000/QALY in 99.9% of samples.	produced more benefit compared to) surgical staging and endosonography was cost-effective at a threshold of £30,000/QALY in 99.9% of samples.
			Endosonography followed by Surgical Staging vs Surgical Staging Alone				
			-927 £GBP (-2246 to 394)	0.00652 QALYs (-0.0298 to 0.0418)	Endosonography followed by Surgical Staging **Dominant**		
Directly applicable							
Potentially serious limitations [a, b, c]	**Utility** Measured using the EQ-5D, in line with the NICE reference case. Utility measured at baseline, end of staging, 2 months and 6 months.						

a) The costs related to combined endosonography as calculated by Papworth hospital appears to be lower than the cost of EBUS-TBNA alone as per the NICE lung cancer 2011 guidelines. The committee were unsure of the justification for this.
b) The analysis had a short time horizon so is potentially missing relevant longer term costs and QALYs
c) Complete cost and QALY information was only available for 47% of patients in each arm

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Study, population, country and quality	Data sources	Other comments	Model Results	Conclusions	Uncertainty
Luque et al. (2016) Patients who require staging for suspected lung cancer. Model created for a Spanish health care setting. **Partially applicable** [b, c] **Very serious limitations** [a, d]	**Effects** Sensitivity and specificity for +ve CT scan; TBNA – Silvestri et al. (2013) PET – Gould et al. (2003) EBUS – Admas et al. (2009) EUS – Micames et al. (2007) MED – Silvestri et al. (2013) Sensitivity and specificity for -ve CT scan; TBNA – Disdier et al. (2001) PET – Gould et al. (2003) EBUS – Herth et al. (2008) MED– Silvestri et al. (2013)	This was a model based analysis, using an influence diagram (ID) that represents the possible tests, their costs, and their outcomes. This model is equivalent to a decision tree containing millions of branches. In the first evaluation, the authors only took into account the clinical outcomes (effectiveness). In the second, the authors used a willingness-to-pay of €30,000 per quality adjusted life year (QALY) to convert economic costs into effectiveness.	"Two strategies were obtained using two different criteria. When considering only effectiveness, a positive computed tomography (CT) scan must be followed by a transbronchial needle aspiration (TBNA), an endobronchial ultrasound (EBUS), and an endoscopic ultrasound (EUS). When the CT scan is negative, a positron emission tomography (PET), EBUS, and EUS are performed. If the TBNA or the PET is positive, then a mediastinoscopy is performed only if the EBUS and EUS are negative. If the TBNA or the PET is negative, then a mediastinoscopy is performed only if the EBUS and the EUS give contradictory results. When taking into account economic costs, a positive CT scan is followed by a TBNA; an EBUS is done only when the CT scan or the TBNA is negative. This recommendation of performing a TBNA in certain cases should be discussed by the pneumology community because TBNA is a cheap technique that could avoid an EBUS, an expensive test, for many patients."	"We have determined the optimal sequence of tests for the mediastinal staging of NSCLC by considering sensitivity, specificity, and the economic cost of each test. The main novelty of our study is the recommendation of performing TBNA whenever the CT scan is positive. Our model is publicly available so that different experts can populate it with their own parameters and re-examine its conclusions. It is therefore proposed	The model incorporated first order uncertainty (examined the random variability in outcomes between identical patients) and second order uncertainty (examined the uncertainty in estimation of the parameter of interest). Although the authors did not provide numerical value for the results, they concluded that the main finding of these analyses is that the resulting strategy is robust to the uncertainty of the numerical

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Study, population, country and quality	Data sources	Other comments	Model Results	Conclusions	Uncertainty
	Costs and resource use Costs of tests were taken from ORDEN (2013), Gómez León (2014), Castelao Naval (2013), Kunst (2008), Navani (2009). Costs were expressed in Euros€. **Utility** Morbidities were express in QALYs. Taken from Holty (2005), Von Bartheld (2014), Silvestri (2013)			as an evidence-based instrument for reaching a consensus."	parameters because only the specificity of the EBUS when the CT scan is negative had a significant impact on the optimal strategy.

a) Costs and QALYs associated with each alternate recommended pathway are not given in the results section of the paper and sensitivity analysis are not presented in the conventional sense. It is therefore difficult to assess the face validity of the results, given the new and highly complex modelling method used in this study.
b) Costs for each of the diagnostic tests do not appear to be broadly in line with costs obtained for the UK NHS from other sources.
c) The study setting is the Spanish healthcare system, which is somewhat different from the English setting.
d) The model only has 3 treatment states, thoracotomy, chemoradiotherapy and no treatment and it is unclear whether these were appropriate and whether the costs and QALYs were taken from a relevant health system to the UK.

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Study, population, country and quality	Data sources	Other comments	Model Results	Conclusions	Uncertainty
NICE Lung Cancer Guideline 2011 **Directly applicable** **Very serious limitations** [a, b, c]	Prevalence of NM stages – committee assumptions Sensitivity/Specificity of Diagnostic Tests – committee assumptions Treatment options received – NCLA registry data Overall survival – NCLA registry data Utility losses from procedures – committee assumptions Long term utility estimates – Sources from NICE TA162, TA181, TA184 Costs – EBUS micro costed, other tests from relevant UK HRG codes, treatment costs from HRGs, BNF and NICE TA181.	The economic model built for the 2011 NICE guideline examined a number of sequential testing strategies for 3 populations; those with a low, intermediate and high probability of mediastinal malignancy. Only the intermediate population is of relevance for this update.	For the intermediate population the model concludes that the most cost effective strategy is PET-CT followed by conventional TBNA, the second most cost effective strategy is neck ultrasound followed by PET-CT and conventional TBNA.	The committee noted a number of limitations with the model. Importantly, more accurate testing strategies did not lead to better outcomes for patients because false negatives were modelled to have the same outcomes as true negatives. They noted that many of the important parameters were based on assumptions but agreed it provided useful evidence in building a diagnostic pathway.	The model was robust to one way sensitivity analysis on a number of important parameters but no sensitivity analysis was conducted on the assumed diagnostic accuracy data and no probabilistic sensitivity analysis was conducted.

a) The cost differential between conventional TBNA and EBUS (£162 vs £1,365) was far larger than has been suggested by the costs analysis conducted for this guideline (see appendix J). Given that the results of the model appear highly influenced by the costs of the tests, this is an important limitation.
b) A number of crucial parameters, including the diagnostic accuracy of the tests were based on committee assumptions.
c) The modelled consequences for false negative patients may have been highly unrealistic as greater accuracy did not lead to an increase in QALYs.

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