Supplemental Table 4. Evidence tables

1) What are the indications for PTNB for lung lesions?

1-1) What are the conventional indications and general factors for considering PTNB?

Source of recommendation	BTS guideline on the investigation and management of pulmonary nodules	Evaluation of individuals with pulmonary nodules When is it lung cancer	Guidelines for management of incidental pulmonary nodules detected on CT images From the Fleischner Society 2017	Establishing the diagnosis of lung cancer Diagnosis and management of lung cancer
Year	2015	2013	2017	2013
K-Agree II score	85	83	54	80
Recommendation	▸ Use composite prediction models based on clinical and radiological factors to estimate the probability that a pulmonary nodule (≥8 mm or ≥300 mm3) is malignant. Grade C ▸ Use the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules (≥8 mm or ≥300 mm3) at presentation in people aged ≥50 who are smokers or former smokers. Grade C ▸Consider the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules (≥8 mm or ≥300 mm3) in all patients at presentation. Grade D ▸ Base the risk assessment of people with multiple pulmonary nodules on that of the largest nodule. Grade C ▸ Use the Brock risk prediction tool to calculate risk of malignancy in SSNs ≥5	4.1.1.1. In the individual with a solid, indeterminate nodule that measures >8 mm in diameter, we suggest that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment and/or quantitatively by using a validated model (Grade 2C). 4.2.4.1. In the individual with a solid, indeterminate nodule that measures . 8 mm in diameter and low to moderate pretest probability of malignancy (5%-65%), we suggest that functional imaging, preferably with PET, should be performed to characterize the nodule (Grade 2C) . 4.2.4.2. In the individual with a solid, indeterminate nodule that measures . 8 mm in diameter	▸ Prior imaging studies should always be reviewed whenever they are available to determine possible growth or stability (grade 1A; strong recommendation, high-quality evidence). ▸ For nodules with particularly suspicious morphology (ie, lobulated margins or cystic components), a growing solid component, or a solid component larger than 8 mm, PET/CT, biopsy, or resection are recommended (grade 1B; strong recommendation, moderate-quality evidence.) ▸For solitary solid noncalcified nodules larger than 8 mm in diameter, consider 3-month follow-up, work-up with combined positron emission	2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or medi- astinoscopy) (Grade 1C). 2.3.4. In patients suspected of having lung cancer, who have lesions in multiple distant sites suspected of metastases but in whom biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by

	mm that are unchanged at 3 months. Grade C ‣ Interpret negative lung biopsies in the context of the pre-test probability of malignancy. Grade D ‣ Consider repeating percutaneous lung biopsies where the probability of malignancy is high. Grade D ‣ Offer further diagnostic investigation (biopsy, imaging or resection) for patients with nodules showing clear growth or a VDT of <400 days (assessed after 3 months, and 1 year). Grade C	and a high pretest probability of malignancy (>65%), we suggest that functional imaging should not be performed to characterize the nodule (Grade 2C) . 4.6.2.1.1. In the individual with a solid, indeterminate nodule that measures > 8 mm in diameter, we suggest nonsurgical biopsy in the following circumstances (Grade 2C): • When clinical pretest probability and findings on imaging tests are discordant • When the probability of malignancy is low to moderate (~10% to 60%) • When a benign diagnosis requiring specific medical treatment is suspected • When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high. 6.5.1. In the individual with a nonsolid (pure ground glass) nodule measuring 5 mm in diameter, we suggest no further evaluation (Grade 2C) . 6.5.2. In the individual with a nonsolid (pure ground glass) nodule measuring . 5 mm in diameter, we suggest annual surveillance with chest CT for at least 3 years (Grade 2C) . 6.5.4. In the individual with a part-solid nodule measuring> 8 mm in diameter, we suggest repeat chest CT at 3 months followed by	tomography (PET) and CT (PET/CT), tissue sampling, or a combination thereof; any one of these options may be appropriate depending on size, morphology, comorbidity, and other factors. (grade 1A; strong recommendation, high-quality evidence). For pure ground-glass nodules smaller than 6 mm (ie, 5 mm and smaller) in diameter, no routine follow-up is recommended (grade 1B; strong recommendation, moderate-quality evidence). For pure ground-glass nodules 6 mm or larger, follow-up scanning is recommended at 6–12 months and then every 2 years there after until 5 years (grade 1B; strong recommendation, moderate-quality evidence). In patients with multiple subsolid nodules smaller than 6 mm, one must consider infectious causes. If lesions remain persistent after an initial follow-up scan at 3–6 months, consider follow-up at approximately 2 and 4 years to confirm stability, depending on the clinical setting (grade 1C; strong recommendation, low- or very-low-quality evidence).	the least invasive method (Grade 1C). 2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy (via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C).

		further evaluation with PET, nonsurgical biopsy, and/or surgical resection for nodules that persist (Grade 2C).		
Supporting text	As with any diagnostic test, the post-test probability of malignancy (after a non-malignant CT biopsy) will depend on the pre-test probability and the negative likelihood ratio (calculated here as 0.10, 95% CI 0.08 to 0.12). The effect of a negative (ie, non-malignant) biopsy on the post-test probability of cancer is shown in figure 10. Where the pre-test probability is high (eg, 90%) there is still approximately a 50% chance of malignancy even after a non-malignant biopsy (exact value 47.0%, 95% CI 41.9% to 51.9%). This has recently been confirmed in the largest retrospective series, where there was a 90% prevalence of malignancy. However, in this series half of the lesions were outside the definition of pulmonary nodules as they were greater than 30 mm. The authors emphasised the importance of considering repeat biopsies as they showed that repeat biopsies usually confirm the diagnosis of malignancy. However, if the pre-test probability of cancer is only 50%, then the chance of malignancy drops to about 10% after a non-malignant biopsy (exact value 9.0%, 95% CI 7.4% to 10.7%). The impact of CT-guided biopsy findings on clinical decision making was investigated by Baldwin et al. Clinicians were presented with 114 patient scenarios with and without the results of CT-guided biopsy of pulmonary nodules, and asked	We further distinguish small, subcentimeter nodules from larger nodules because nodules that measure 8mm in diameter are much less likely to be malignant, typically defy accurate characterization by imaging tests, and often are difficult to approach by nonsurgical biopsy. Early follow-up at 3 months may be indicated for nonsolid nodules measuring > 10 mm (followed by nonsurgical biopsy and/or surgical resection for nodules that persist). Part-solid nodules measuring >15 mm in diameter should proceed directly to further evaluation with PET, nonsurgical biopsy, and/or surgical resection.	As a general rule, transthoracic needle biopsy is an effective approach in experienced hands, but it has important limitations for very small nodules and ground-glass lesions due to potential problems with inadequate sampling and false-negative results.	▸ The sensitivity of TTNA is excellent for malignant disease, but TTNA has a higher rate of pneumothorax than do bronchoscopic modalities. ▸ FB is the most useful test for central lesions, whereas in the case of peripheral lesions, the sensitivity of navigational bronchoscopy, R-EBUS, and TTNA is greater than that of conventional bronchoscopy. ▸ CT scan-guided TTNB is preferred for nodules located in proximity to the chest wall or for deeper lesions provided that fissures do not need to be traversed and there is no surrounding emphysema. Bronchoscopic techniques are favored for nodules located in proximity to a patent bronchus and in individuals who are at high risk for pneumothorax following TTNB. ▸ The type of biopsy should be selected based on nodule size, location, and relation to a patent airway; the risk of complications in the individual patient; and available expertise.

	to specify management. The proportion of successful decisions (against known outcomes) was assessed. Agreement between clinicians on the need for surgery increased with biopsy result information compared with CT findings alone (κ value 0.57 vs 0.44, respectively). The major benefit of knowing the CT-guided biopsy result was a reduction in unnecessary surgery, especially when the clinical perception of pre-test probability of malignancy was intermediate (31–70%).			
Grades of recommendation	Above column	Above column	Not applicable	Above column
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Yes	Yes	Yes
Similarity of value and preference	No	Yes	Yes	Yes
Similarity of benefit by recommendation	No	Yes	Yes	Yes
Generally, acceptable	No	Yes	Yes	Yes
Applicability				
Applicability of intervention/instrument	No	Yes	Yes	Yes
Applicability of essential technique	No	Yes	Yes	Yes
No legal and institutional barriers	Yes	Yes	Yes	Yes
Generally, applicable	No	Yes	Yes	Yes

Source of recommendation	**Guidelines for radiologically guided lung biopsy**	**Special Treatment Issues in Non-small Cell Lung Cancer**	**Executive Summary Diagnosis and Management of Lung Cancer**	**Lung cancer (CG121) NICE**

		Diagnosis and Management of Lung Cancer		
Year	2003	2013	2013	2011
K-Agree II score	63	71	52	67
Recommendation	‣ New or enlarging solitary nodule or mass on the chest radiograph which is not amenable to diagnosis by bronchoscopy or CT shows it is unlikely to be accessible by bronchoscopy [B] ‣Patients with lesions on the chest radiograph should be discussed in a multidisciplinary meeting with a respiratory physician and radiologist at a minimum. [C] ‣Multiple nodules in a patient not known to have malignancy or who has had a prolonged remission or more than one primary malignancy [B] ‣Persistent focal infiltrates, either single or multiple, for which no diagnosis has been made by sputum or blood culture, serology, or bronchoscopy. ‣There are relative contraindications to PTLB and the balance of benefit against risk for the procedure should be assessed at a multidisciplinary meeting. [C]	Not applicable	4.5.1.3. In the individual with a solid, indeterminate nodule that shows clear evidence of malignant growth on serial imaging, we recommend nonsurgical biopsy and/or surgical resection unless specifically contraindicated (Grade 1C). 2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or medi- astinoscopy) (Grade 1C). 2.3.4. In patients suspected of having lung cancer, who have lesions in multiple distant sites suspected of metastases but in whom biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by the least invasive method (Grade 1C). 2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy (via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C).	Transthoracic needle biopsy is used to obtain diagnostic samples from lesions that are not accessible via the bronchial tree and where there is no obvious lymph node involvement.
Supporting text	Not applicable	Not applicable	Not applicable	Not applicable

Grades of recommendation	Above column	Not applicable	Above column	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Yes	Yes	Not applicable
Similarity of value and preference	Yes	Yes	Yes	Not applicable
Similarity of benefit by recommendation	Yes	Yes	Yes	Not applicable
Generally, acceptable	Yes	Yes	Yes	Not applicable
Applicability				
Applicability of intervention/instrument	Yes	Yes	Yes	Not applicable
Applicability of essential technique	Yes	Yes	Yes	Not applicable
No legal and institutional barriers	Yes	Yes	Yes	Not applicable
Generally, applicable	Yes	Yes	Yes	Not applicable

Source of recommendation	**Management of lung cacner (Scottish Intercollegiate Guidelines Network)**	**Metastatic Non-Small-Cell Lung Cancer, ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**	**Invasive Staging**
Year	2014	2018	2003
K-Agree II score	83	50	58
Recommendation	Percutaneous FNA biopsy should be considered as the preferred diagnostic technique in patients with peripheral lesions. (B) In patients being considered for active therapy, pleural effusion should be investigated with pleural aspiration and/or pleural biopsy using image guided or thoracoscopic biopsy. (D)	• Transthoracic fine needle aspiration and/or core biopsy, passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in case of mid to peripheral lesions	Not applicable
Supporting text	Percutaneous FNA biopsy is a highly sensitive technique for diagnosing lung cancer (sensitivity of 88–92%). Fine needle		Not applicable

	aspirations can be done as blind percutaneous biopsy or guided by fluoroscopy, ultrasound, CT or magnetic resonance imaging (MRI). Larger cutting needles can also be used to obtain biopsy cores of intact tissue for histology. Sensitivity is greater for peripheral lung lesions than fibre optic bronchoscopy. There is a high false negative rate (25%) resulting in limited ability to confirm a benign diagnosis. This may be improved by using core biopsies for histology rather than aspirates for cytology. Potential complications include bleeding and pneumothorax (chest drain 10%, haemoptysis 3%, mortality 0.04%). A pleural biopsy should be undertaken in patients with negative fluid cytology. Some patients may require VATS biopsy to confirm pleural malignancy as aspiration and pleural biopsy alone may be insufficient.		
Grades of recommendation	Recommendation B to D; Evidence level 2++, 2+	Not applicable	Not applicable
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Yes	No	Not applicable
Similarity of value and preference	No	No	Not applicable
Similarity of benefit by recommendation	Yes	Yes	Not applicable
Generally, acceptable	Yes	No	Not applicable
Applicability			
Applicability of intervention/instrument	Yes	Yes	Not applicable
Applicability of essential technique	Yes	Yes	Not applicable
No legal and institutional barriers	Yes	Yes	Not applicable
Generally, applicable	Yes	No	Not applicable

1-2) What are the upcoming indications for PTNB in the era of personalized medicine?

Source of recommendation	BTS guideline on the investigation and management of pulmonary nodules	Evaluation of individuals with pulmonary nodules When is it lung cancer	Guidelines for management of incidental pulmonary nodules detected on CT images From the Fleischner Society 2017	Establishing the diagnosis of lung cancer Diagnosis and management of lung cancer
Year	2015	2013	2017	2013
K-Agree II score	85	83	54	80
Recommendation	Not applicable	4.6.2.1.1. In the individual with a solid, indeterminate nodule that measures . 8 mm in diameter, we suggest nonsurgical biopsy in the following circumstances (Grade 2C) - When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high. (Grade 2C).	Not applicable	In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable.
Supporting text	Not applicable	For individuals who desire treatment but either refuse or cannot tolerate surgery (even limited resection), surgical diagnosis is precluded. And nonsurgical biopsy can be an option.	Decisions regarding choice of procedure in any given case are best made in the context of a multidisciplinary conference, where the merits and limitations of each approach can be discussed	If specimens are not adequate for histologic and molecular characterization then obtaining a second biopsy is acceptable given the importance of accurate tumor characterization. The physician evaluating the patient with suspected lung cancer must understand that obtaining adequate amounts of tissue at the time of diagnosis is essential if accurate histologic differentiation (squamous cell vs adenocarcinoma) is to be achieved and, when applicable, the tissue can then be evaluated for driver mutations (K- ras, EGFR, EML4-ALK, and c-ros oncogene 1[ROS1] translocations). Ideally, one would like to obtain core or surgical biopsy specimens in patients with lung cancer to accurately define histology and obtain molecular analysis; however, the majority of patients with NSCLC present with unresectable advanced disease, which means that small biopsy specimens

				or cytologic specimens are the primary means of diagnosis. In the case of TTNA, it is recommended that core needle biopsies be performed when feasible. Furthermore, it is likely that the ability to fully characterize lung cancers from limited specimens depends not only on the amount of tissue but also on the systems in place to handle and prepare the specimen.
Grades of recommendation	Not applicable	Grade 2C	Not applicable	Grade 1B
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Not applicable	Yes	Yes	Yes
Similarity of value and preference	Not applicable	Yes	No	Yes
Similarity of benefit by recommendation	Not applicable	Yes	No	Yes
Generally, acceptable	Not applicable	Yes	Yes	Yes
Applicability				
Applicability of intervention/instrument	Not applicable	Yes	Yes	Yes
Applicability of essential technique	Not applicable	Yes	Yes	Yes
No legal and institutional barriers	Not applicable	Yes	Yes	Yes
Generally, applicable	Not applicable	Yes	Yes	Yes

Source of recommendation	**Guidelines for radiologically guided lung biopsy**	**Special Treatment Issues in Non-small Cell Lung Cancer Diagnosis and Management of Lung Cancer**	**Executive Summary Diagnosis and Management of Lung Cancer**	**Lung cancer (CG121) NICE**
Year	2003	2013	2013	2011
K-Agree II score	63	71	52	67

Recommendation	Not applicable	Not applicable	In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fluid) is reliable. However, it is recommended that adequate tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable	Ensure adequate samples are taken without unacceptable risk to the patient to permit pathological diagnosis including tumour sub-typing and measurement of predictive markers. [NEW 2011]
Supporting text	As an aid to diagnosis, immunocytochemistry may be undertaken in a minority of cases. Using a panel of antibodies can assist in identifying metastatic lesions and confirming a pulmonary origin for some adenocarcinomas. Immunocytochemistry of FNA samples can deliver comparable results to those obtained from biopsy material, although it is rarely feasible to perform more than a small panel of immunostains on an FNA sample. Liquid-based cytology has much to recommend it, even for the preparation of FNA samples.Instead of, or as well as, making smears, the sample is washed into a preservative solution. Good fixation is ensured and it is simple to make multiple preparations for immunocytochemistry. It is at least as accurate as smear preparations and, by removal of red cells, debris and inflammatory cells, the slides are quicker and easier to read. It does, however, involve extra technical work and cost.	Not applicable	If specimens are not adequate for histologic and molecular characterization then obtaining a second biopsy is acceptable given the importance of accurate tumor characterization.	
Grades of recommendation	Not applicable	Not applicable	Grade 1B	Not applicable
Acceptability				

Similarity of population (prevalence, incidence, etc.)	Yes	Not applicable	Yes	Yes
Similarity of value and preference	Yes	Not applicable	Yes	Yes
Similarity of benefit by recommendation	Yes	Not applicable	Yes	No
Generally, acceptable	Yes	Not applicable	Yes	Yes
Applicability				
Applicability of intervention/instrument	Yes	Not applicable	Yes	Yes
Applicability of essential technique	Yes	Not applicable	Yes	Yes
No legal and institutional barriers	Yes	Not applicable	Yes	Yes
Generally, applicable	Yes	Not applicable	Yes	Yes

Source of recommendation	**Management of lung cacner (Scottish Intercollegiate Guidelines Network)**	**Metastatic Non-Small-Cell Lung Cancer, ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**	**Invasive Staging**
Year	2014	2018	2003
K-Agree II score	83	50	58
Recommendation	Not applicable	• Transthoracic fine needle aspiration and/or core biopsy, passing a needle through the parenchyma under imaging guidance (typically CT), is indicated in case of mid to peripheral lesions • Adequate tissue material for histological diagnosis and molecular testing should be obtained to allow for individual treatment decisions. • EGFR mutation status should be systematically analysed in advanced NSCC [I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [III, B]. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [I, A] • The availability of TKIs effective against T790M-mutant recurrent disease makes T790M testing on disease relapse mandatory [I, A] • Testing for ALK rearrangement should be systematically carried out in advanced non-	Not applicable

		squamous NSCLC [I, A] • Testing for ROS1 rearrangement should be systematically carried out in advanced NSCLC [III, A]. • BRAF V600 mutation status should be systematically analysed in advanced NSCLC for the prescription of BRAF/MEK inhibitors [II, A] • PD-L1 IHC should be systematically determined in advanced NSCLC [I, A] • All tumours with clinical evidence of EGFR TKI resistance, not previously treated with osimertinib, should be tested for presence of EGFR exon 20 T790M mutation [I, A] • Liquid biopsy can be used as the initial test for detection of T790M mutation, and if tested negative, re-biopsy should be attempted if feasible [II, A] • Osimertinib is the standard therapy for patients whose tumours are tested positive for T790M either in liquid biopsy or re-biopsy, if not received previously [I, A; ESMO-MCBS v1.1 score: 4] • Platinum-based doublet is the standard therapy for patients whose tumour is tested T790M negative in either re-biopsy or in liquid biopsy (only when re-biopsy is not feasible) [I, A]	
Supporting text	Molecular analysis and stratification of lung cancer is rapidly becoming a standard of care for the selection of patients for specific targeted therapy (EGFR, ALK, BRAF, KRAS). These tests are, in general, performed on pathologically validated tumour tissue following diagnosis and subtyping by standard morphology and, as required, immunohistochemistry. To support the expanding need for more detailed pathological information from lung cancer samples, it is essential that adequate tumour tissue is made available. The vast majority of cases are diagnosed solely on small biopsy or cytology samples, so tissue availability is very limited. Every effort should be made, within the constraints of patient safety, to maximize tumour yield from any invasive diagnostic procedure. The pathologist should also conserve as much material as possible, in anticipation of molecular pathology testing, by the judicious use of material for initial		Not applicable

	diagnosis and tumour subtyping. This will be greatly assisted by the provision of full clinical details accompanying samples submitted for pathological diagnosis.		
Grades of recommendation	level of evidence 4	EGFR - 1A, EGFR mutation - 1A, T790M - 1A, ALK - 1A, ROS1 - 3A, BRAF - 2A, PD-L1 - 1A	Not applicable
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Yes	Yes	Not applicable
Similarity of value and preference	Yes	Yes	Not applicable
Similarity of benefit by recommendation	Yes	Yes	Not applicable
Generally, acceptable	Yes	Yes	Not applicable
Applicability			
Applicability of intervention/instrument	Yes	Yes	Not applicable
Applicability of essential technique	Yes	Yes	Not applicable
No legal and institutional barriers	Yes	Yes	Not applicable
Generally, applicable	Yes	Yes	Not applicable

1-3) What are the contraindications for PTNB?

Source of recommendation	BTS guideline on the investigation and management of pulmonary nodules	Evaluation of individuals with pulmonary nodules When is it lung cancer	Guidelines for management of incidental pulmonary nodules detected on CT images From the Fleischner Society 2017	Establishing the diagnosis of lung cancer Diagnosis and management of lung cancer
Year	2015	2013	2017	2013
K-Agree II score	85	83	54	80
Recommendation	Not applicable	Not applicable	Not applicable	Not applicable
Supporting text	Not applicable	Not applicable	Not applicable	Not applicable
Grades of recommendation	Not applicable	Not applicable	Not applicable	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Not applicable	Not applicable	Not applicable	Not applicable
Similarity of value and preference	Not applicable	Not applicable	Not applicable	Not applicable
Similarity of benefit by recommendation	Not applicable	Not applicable	Not applicable	Not applicable
Generally, acceptable	Not applicable	Not applicable	Not applicable	Not applicable
Applicability				
Applicability of intervention/instrument	Not applicable	Not applicable	Not applicable	Not applicable
Applicability of essential technique	Not applicable	Not applicable	Not applicable	Not applicable
No legal and institutional barriers	Not applicable	Not applicable	Not applicable	Not applicable
Generally, applicable	Not applicable	Not applicable	Not applicable	Not applicable

Source of recommendation	Guidelines for radiologically guided lung biopsy	Special Treatment Issues in Non-small Cell Lung Cancer Diagnosis and Management of Lung Cancer	Executive Summary Diagnosis and Management of Lung Cancer	Lung cancer (CG121) NICE
Year	2003	2013	2013	2011
K-Agree II score	63	71	52	67
Recommendation	▸ There are relative contraindications to PTLB and the balance of benefit against risk for the procedure should be assessed at a multidisciplinary meeting. [C] ▸ Written information should be given to all patients before the procedure. [C] ▸ Informed consent should be obtained in a written form from all patients. [C]	Not applicable	Not applicable	Not applicable
Supporting text	There are several relative contraindications to PTLB. Patients should not undergo the procedure without adequate prebiopsy assessment or if they plan to fly within 6 weeks of the procedure. The risk is increased by abnormalities of lung function, respiratory failure (including mechanical ventilation), arterial and venous pulmonary hypertension, and coagulation abnormalities (see preoperative investigations). The balance of benefit against risk for the procedure shouldbe assessed at a multidisciplinary meeting. The role of needle biopsy is to establish a diagnosis to enable appropriate treatment to be given. Failure to obtain informed consent from a patient is a contraindication, and management should be reconsidered in these circumstances. Previous pneumonectomy is an exclusion criterion for needle biopsy in many series. However, if the lesion in the remaining lung is pleurally based and is accessible without traversing any lung tissue, it may not be considered an absolute contraindication as the risk of pneumothorax is low. Pulmonary arterial and venous hypertension may increase the risk of haemorrhage but there are no data to support this.	Not applicable	Not applicable	Not applicable

	If the hypertension is significant, this would be a contraindication to surgery; the risk of the diagnostic procedure needs to considered against the benefit of having an answer on patient management. Mechanical ventilation will make the process of biopsy more difficult but, if the lesion is visualised by ultrasound, it may be undertaken. Biopsy samples of intrapulmonary lesions can be taken by experienced operators under CT guidance while ventilation is controlled during the procedure, but this is difficult because of the limited space as well as access of medical and nursing staff during radiation exposure. Vascular lesions, either aneurysms or arteriovenous malformations, should have been identified by CT and should not be subjected to biopsy. This diagnosis should be considered before the biopsy procedure at a multidisciplinary meeting. Biopsy of an unsuspected vascular lesion may lead to an increased risk of haemorrhage. Pulmonary arterial and venous hypertension may increase the risk of haemorrhage but there are no data to support this. If the hypertension is significant, this would be a contraindication to surgery; the risk of the diagnostic procedure needs to considered against the benefit of having an answer on patient management. Informed consent should be obtained in writing before the biopsy procedure in accordance with individual hospital policies. Verbal and understandable written patient information before diagnostic procedures improves the patient's tolerance of the procedure, as has been shown in bronchoscopy.			
Grades of recommendation	Strong recommendation; low-quality evidence [C]	Not applicable	Not applicable	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	No	Not applicable	Not applicable	Not applicable

Similarity of value and preference	Yes	Not applicable	Not applicable	Not applicable
Similarity of benefit by recommendation	Yes	Not applicable	Not applicable	Not applicable
Generally, acceptable	Yes	Not applicable	Not applicable	Not applicable
Applicability				
Applicability of intervention/instrument	Yes	Not applicable	Not applicable	Not applicable
Applicability of essential technique	Yes	Not applicable	Not applicable	Not applicable
No legal and institutional barriers	Yes	Not applicable	Not applicable	Not applicable
Generally, applicable	Yes	Not applicable	Not applicable	Not applicable

Source of recommendation	**Management of lung cacner (Scottish Intercollegiate Guidelines Network)**	**Metastatic Non-Small-Cell Lung Cancer, ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**	**Invasive Staging**
Year	2014	2018	2003
K-Agree II score	83	50	58
Recommendation	Not applicable	Not applicable	Not applicable
Supporting text	Not applicable	Not applicable	Not applicable
Grades of recommendation	Not applicable	Not applicable	Not applicable
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Not applicable	Not applicable	Not applicable
Similarity of value and preference	Not applicable	Not applicable	Not applicable
Similarity of benefit by recommendation	Not applicable	Not applicable	Not applicable
Generally, acceptable	Not applicable	Not applicable	Not applicable
Applicability			

Applicability of intervention/instrument	Not applicable	Not applicable	Not applicable
Applicability of essential technique	Not applicable	Not applicable	Not applicable
No legal and institutional barriers	Not applicable	Not applicable	Not applicable
Generally, applicable	Not applicable	Not applicable	Not applicable

2) Which laboratory and imaging evaluations are appropriate for patients before PTNB?

2-1) What kinds of laboratory tests are required prior to PTNB?

Source of recommendation	**Guidelines for radiologically guided lung biopsy**
Year	2003
K-Agree II score	63
Recommendation	Prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count should be checked before percutaneous lung biopsy. Oral anticoagulants should be stopped before a percutaneous lung biopsy in accordance with the published guidelines on perioperative anticoagulation. PT, APTT, platelet count, and pulmonary function tests are desirable before needle biopsy. In patients with risk factors for bleeding, PT, APTT and platelet count are required.
Supporting text	Not applicable
Grades of recommendation	Strong recommendation; low-quality evidence [C]
Acceptability	
Similarity of population (prevalence, incidence, etc.)	No
Similarity of value and preference	Yes
Similarity of benefit by recommendation	Yes
Generally, acceptable	Yes
Applicability	
Applicability of intervention/instrument	Yes
Applicability of essential technique	Yes
No legal and institutional barriers	Yes

Generally, applicable	Yes

2-2) Should a pulmonary function test be performed prior to PTNB?

Source of recommendation	**Guidelines for radiologically guided lung biopsy**
Year	2003
K-Agree II score	63
Recommendation	The balance of benefit against risk for PTLB should be assessed by a multidisciplinary team with a respiratory physician and radiologist as a minimum. All patients should have recent pulmonary function tests (spirometry) before needle biopsy. Patients with FEV1 ,35% predicted should not undergo needle biopsy without further assessment by the multidisciplinary team.
Supporting text	Not applicable
Grades of recommendation	Strong recommendation; low-quality evidence [C]
Acceptability	
Similarity of population (prevalence, incidence, etc.)	No
Similarity of value and preference	Yes
Similarity of benefit by recommendation	Yes
Generally, acceptable	Yes
Applicability	
Applicability of intervention/instrument	Yes
Applicability of essential technique	Yes
No legal and institutional barriers	Yes

Generally, applicable	Yes

2-3) Which imaging examinations should be performed prior to PTNB?

Source of recommendation	**Guidelines for radiologically guided lung biopsy**	**Evaluation of individuals with pulmonary nodules: When is it lung cancer**
Year	2003	2013
K-Agree II score	63	83
Recommendation	All patients should have a diagnostic CT scan of the chest before a biopsy procedure. [B] Recent chest radiographs and CT scans and all previous radiological investigations should be reviewed to decide if a biopsy is appropriate and must be available to the radiologist at the time of the biopsy. [C] Repeat imaging should be performed if there has been significant change in the patient's clinical condition, if there has been significant delay before the biopsy is performed, or if the localising CT scan at the time of the biopsy shows significant change. [C]	Not applicable
Supporting text		As a metabolic biopsy tool, PET scan can identify which lesions or portions of lesions are metabolically active and most likely to yield a definitive tissue result.
Grades of recommendation	Strong recommendation; medium to low -quality evidence [B to C]	Not applicable
Acceptability		
Similarity of population (prevalence, incidence, etc.)	Yes	Yes
Similarity of value and preference	Yes	Yes
Similarity of benefit by recommendation	Yes	Yes

Generally, acceptable	Yes	Yes
Applicability		
Applicability of intervention/instrument	Yes	Yes
Applicability of essential technique	Yes	Yes
No legal and institutional barriers	Yes	Yes
Generally, applicable	Yes	Yes

3) What are the appropriate techniques for PTNB of lung lesions?

3-1) How accurate should PTNB be?

Source of recommendation	**Establishing the Diagnosis of Lung Cancer, Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**Lung cancer (CG121)**	**Guidelines for radiologically guided lung biopsy**	**Management of lung cacner (Scottish Intercollegiate Guidelines Network)**
Year	**2013**	**2011**	**2003**	**2014**
K-Agree II score	**80**	**67**	**63**	**83**
Recommendation	3.5.2.1. In patients suspected of having lung cancer who have a peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is diagnostic option. However, it is recommended that further testing be performed if TTNA results are non-diagnostic and suspicion of lung cancer remains (Grade 1B) . 3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fl uid) is reliable. However, it is recommended that adequate	Peripheral primary tumour • Offer CT- or ultrasound-guided transthoracic needle biopsy to patients with peripheral lung lesions when treatment can be planned on the basis of this test.	Expected accuracy of sampling False positives should be less than 1%. Adequacy of sample should be over 90%. Sensitivity for malignancy should be within the range of 85–90% in lesions over 2 cm. Standards should be set and outcomes audited.	Percutaneous FNA biopsy should be considered as the preferred diagnostic technique in patients with peripheral lesions.

	tissue be obtained to accurately define the histologic type and to perform molecular analysis when applicable (Grade 1B) .			
Supporting text	The pooled sensitivity of TTNA for the diagnosis of peripheral bronchogenic carcinoma was 90% (95% CI, 88%-91%). Individual study estimates ranged from 62% to 99%. There was little difference in specificity for any group of studies analyzed. Furthermore, given the false-positive rate of 1% to 2%, a positive TTNA for cancer is reliable. On the other hand, the FN rate of TTNA is high (in the range of 20%-30%). The amount of tissue needed to accurately diagnose the lung cancer histologic type and assess molecular markers has not been studied formally. In the case of TTNA, it is recommended that core needle biopsies be performed when feasible. Furthermore, it is likely that the ability to fully characterize lung cancers from limited specimens depends not only on the amount of tissue but also on the systems in place to handle and prepare the specimen. The physician evaluating the patient with suspected lung cancer must remember that limited tissue acquisition contributes to the difficulty of accurate molecular and histologic subtyping.	TTNA sensitivity range, 85.5-94.3, specificity range, 41.67-100 in Table 4.1a	Several large studies of the accuracy of lung FNA have been reported and sensitivity, specificity, and adequacy of over 90% are achievable. The false positive rate is usually less than 1%, and the false negative rate is generally under 10%. Diagnostic accuracy is dependent on the size and site of the lesion, operator experience, needle type, choice of biopsy technique, and availability of cytopathology expertise. Larger lesions are more likely to enable a positive diagnosis of malignancy, although some operators have reported no significant difference in lesions more or less than 2 cm. The reports from lung cancer screening programmes also support the ability to achieve an accurate diagnosis in lesions of less than 1 cm. Accuracy may be further improved by reducing the number of inadequate samples by using new techniques. Some authors expound on the value of on-site technical assistance with smear preparation	Percutaneous FNA biopsy is a highly sensitive technique for diagnosing lung cancer (sensitivity of 88–92%). Fine needle aspirations can be done as blind percutaneous biopsy or guided by fluoroscopy, ultrasound, CT or magnetic resonance imagin+D6+B7:E7+A7:E7+B7:E7

			and immediate reporting to enhance the adequacy rate.	
Grades of recommendation	Grade 1B	Not applicable	Strong recommencdation; low-quality evidence [C]	Grade of recommendation B; level of evidence 2++
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Yes	Yes	Yes
Similarity of value and preference	Yes	Yes	Yes	Yes
Similarity of benefit by recommendation	Yes	Yes	Yes	Yes
Generally, acceptable	Yes	Yes	Yes	Yes
Applicability				
Applicability of intervention/instrument	Yes	Yes	Yes	Yes
Applicability of essential technique	Yes	Yes	Yes	Yes
No legal and institutional barriers	Yes	Yes	Yes	Yes
Generally, applicable	Yes	Yes	Yes	Yes

Source of recommendation	**Executive Summary Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**BTS Guidelines for the Investigation and Management of Pulmonary Nodules**	**Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**
Year	**2013**	**2015**	**2013**
K-Agree II score	**52**	**85**	**83**

Recommendation	3.5.2.1. In patients suspected of having lung cancer who have a peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is diagnostic option. However, it is recommended that further testing be performed if TTNA results are non-diagnostic and suspicion of lung cancer remains (Grade 1B) . 3.6.2.1. In patients suspected of having lung cancer, the diagnosis of non-small cell lung cancer made on cytology (sputum, TTNA, bronchoscopic specimens, or pleural fl uid) is reliable. However, it is recommended that adequate tissue be obtained to accurately defi ne the histologic type and to perform molecular analysis when applicable (Grade 1B)	▸ The diagnostic yield from CT-guided biopsy of pulmonary nodules decreases with decreasing size of the lesion. Evidence level 2+ ▸ The post-test probability of malignancy after a negative lung. Evidence level 3 biopsy depends on the pre-test probability. Evidence level 3 ▸ Repeating biopsies in patients with nodules with a high probability of malignancy showed a high confirmation rate of malignancy. Evidence level 3 ▸ Offer percutaneous lung biopsy in cases where the result will alter the management plan. Grade C ▸ Interpret negative lung biopsies in the context of the pre-test probability of malignancy. Grade D ▸ Consider repeating percutaneous lung biopsies where the probability of malignancy is high. Grade D	4.6.2.1.1. In the individual with a solid, indeterminate nodule that measures . 8 mm in diameter, we suggest nonsurgical biopsy in the following circumstances (Grade 2C): • When clinical pretest probability and findings on imaging tests are discordant • When the probability of malignancy is low to moderate (~10% to 60%) • When a benign diagnosis requiring specific medical treatment is suspected • When a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.
Supporting text	If a bronchoscopic or needle-based biopsy is selected, the possibility of a false-negative result must be kept in mind.	Whilst there is clear heterogeneity in the studies considered together in table, the pooled data gives an overall assessment of the performance of CT-guided biopsy in reported clinical practice. Overall sensitivity is 90.7% (95% CI 88.8% to 92.4%), specificity 93.9% (95% CI 91.1% to 96.0%), PPV 97.4% (95% CI 96.2% to 98.3%) and NPV 79.9% (95% CI 76.0% to 83.4%). The negative predictive value is of particular importance, as clinicians often have to make a decision about management of a non-malignant biopsy result, mindful of the possibility of a false-negative result.	TTNB of the pulmonary nodule usually is performed under CT scan guidance. In general, the sensitivity of TTNB depends on the size of the nodule, the size of the needle (especially for identifying lymphoma or benign disease), the number of needle passes, and the presence of onsite cytopathologic examination. In our previous review, 39 we identifi ed 11 studies of TTNB performed between 1998 and 2003. In these studies, the prevalence of malignancy was high (median, 75%; range, 63%-85%). Nondiagnostic results were seen in 4% to 41% of cases (median, 20.5%), but specifi c benign or malignant results were nearly always correct (although not all malignant diagnoses were confirmed surgically). Our updated literature search identifi ed 11 additional studies of TTNB for pulmonary nodule diagnosis performed between 2005 and 2011 (Tables S10-S13). Once again, the prevalence of malignancy was high (median, 68%; range, 46%-83%), and the frequency of nondiagnostic results was highly variable, ranging from , 1% to 55%, although the median value was lower than what we found previously (6%). In

			most studies, sensitivity for identifying malignancy was 90%, but it was somewhat lower (70%-82%) in three studies that analyzed results for patients with nodules measuring 15 mm in diameter. More importantly, a sensitivity of 90% in a high-prevalence population (about 70%) translates to a risk of nondiagnostic results in about 20% of individuals with malignant nodules. It is important to emphasize that a nondiagnostic needle biopsy result does not rule out the possibility of malignancy
Grades of recommendation	Grade 1B	Recommendation Grade C to D; Evidence level 2+ to 3	Grade 2C
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Yes	Yes	Yes
Similarity of value and preference	Yes	Yes	Yes
Similarity of benefit by recommendation	Yes	Yes	Yes
Generally, acceptable	Yes	Yes	Yes
Applicability			
Applicability of intervention/instrument	Yes	Yes	Yes
Applicability of essential technique	Yes	Yes	Yes
No legal and institutional barriers	Yes	Yes	Yes
Generally, applicable	Yes	Yes	Yes

3-2) How should interventionists choose the imaging guidance modality for PTNB?

Source of recommendation	Establishing the Diagnosis of Lung Cancer, Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	Lung cancer (CG121)	Guidelines for radiologically guided lung biopsy	Management of lung cacner (Scottish Intercollegiate Guidelines Network)
Year	**2013**	**2011**	**2003**	**2014**
K-Agree II score	**80**	**67**	**63**	**83**
Recommendation	Not applicable	Peripheral primary tumour • Offer CT- or ultrasound-guided transthoracic needle biopsy to patients with peripheral lung lesions when treatment can be planned on the basis of this test.	Specific recommendations for the choice of biopsy imaging depend on the operator but, when possible, ultrasound should be used [B].	Not applicable
Supporting text	TTNA of a PLL can be performed under either fluoroscopic or CT scan guidance.	CT is used to guide biopsy where lesions are in difficult to reach locations or where they are completely surrounded by aerated lung. Ultrasound is used where the lesion abuts the chest wall and is visible on ultrasound.	The decision on the most appropriate imaging modality used for biopsy is made on reviewing the pre-biopsy CT scan. Fluoroscopy, CT, and ultrasound may all be used for imaging guidance, and familiarity of the operator with all three modalities is helpful in choosing the most appropriate technique. The imaging technique chosen is dependent on the size and position of the lesion, its visibility on plain radiographs, its relation to other structures such as fissures, vessels and bullae, equipment availability, and operator preference. Whenever possible, PTLB should be performed under ultrasound guidance as this is the safest, quickest, and least expensive method. For lesions not suitable for ultrasound guided biopsy, CT is now the preferred imaging modality. Fluoroscopic guidance may also be used for larger lesions visualised on a posteroanterior and lateral chest radiograph. If the biopsy is to be performed using fluoroscopy, the best results are usually obtained with C-arm screening (or, if	Fine needle aspirations can be done as blind percutaneous biopsy or guided by fluoroscopy, ultrasound, CT or magnetic resonance imaging (MRI). (2++)

			available, bi-plane) with vertical or horizontal needle insertion. The correct depth of needle insertion may be estimated from the pre-biopsy CT scan. If using ultrasound, needle entry into the lesion should be directly visualised and biopsy sites away from identified areas of cavitation or necrosis chosen. If using CT, a needle entry site which avoids crossing fissures, bullae and large vessels should be chosen if possible to reduce the incidence of pneumothorax and haemorrhage.	
Grades of recommendation	Not applicable	Not applicable	Strong recommencdation; medium-quality evidence [B]	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Not applicable	Yes	Yes	Not applicable
Similarity of value and preference	Not applicable	Yes	Yes	Not applicable
Similarity of benefit by recommendation	Not applicable	Yes	Yes	Not applicable
Generally, acceptable	Not applicable	Yes	Yes	Not applicable
Applicability				
Applicability of intervention/instrument	Not applicable	Yes	Yes	Not applicable
Applicability of essential technique	Not applicable	Yes	Yes	Not applicable
No legal and institutional barriers	Not applicable	Yes	Yes	Not applicable
Generally, applicable	Not applicable	Yes	Yes	Not applicable

Source of recommendation	**Executive Summary Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**BTS Guidelines for the Investigation and Management of Pulmonary Nodules**	**Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest**

			Physicians Evidence-Based Clinical Practice Guidelines
Year	**2013**	**2015**	**2013**
K-Agree II score	**52**	**85**	**83**
Recommendation	2.3.6. In patients suspected of having lung cancer who have an accessible pleural effusion, if pleural fluid cytology is negative, pleural biopsy (via image-guided pleural biopsy, medical or surgical thoracoscopy) is recommended as the next step (Grade 1C) . Remark: If the CT scan of the chest shows pleural thickening or pleural nodules/ masses, image-guided needle biopsy may be considered as the first step to obtain a biopsy of the pleura.	▸ Techniques such as multiplanar reconstructed images and C-arm cone-beam CT may increase the yield. Evidence level 3 ▸ Consider the use of other imaging techniques such as C-arm cone beam CT and MPR to improve diagnostic accuracy. Grade D	Not applicable
Supporting text	Not applicable	Three case series describe results with C-arm cone beam CT (CBCT) guidance which allows real-time fluoroscopic and 3D-CT capabilities. Jin et al reported results of CBCT-guided biopsy of 71 patients with pulmonary nodules ≤30 mm diameter. Sensitivity was 97%, specificity 100% and accuracy 98.4%. Choi et al. reported a similar cohort of 161 consecutive patients undergoing CBCT-guided biopsy, with very similar outcomes (sensitivity 96.8%, specificity 100%, accuracy 98.2%). Finally, Choo et al206 reported use of a CBCT virtual navigation system in 105 consecutive patients with nodules ≤10 mm undergoing image-guided biopsy. Again almost identical performance was reported (sensitivity 96.7%, specificity 100%, accuracy 98%) despite the small size of the lesions. CBCT guidance does involve an additional radiation dose for operator and patient (radiation dose in Jin et al was 272±116 mGy). No studies compared performance of CBCTwith conventional CT guidance (neither randomised nor cohort studies), so the additional value of CBCT guidance remains unclear. However, performance particularly for smaller nodules (≤1 cm) does appear impressive.	Not applicable

		One retrospective cohort study assessed the utility of MPR during CT-guided biopsy of indeterminate pulmonary nodules, comparing test performance with conventional CT-guidance. Sixty-five patients underwent nodule biopsy by CT with MPR, compared with undergoing conventional biopsy. The populations were well-matched, albeit non-randomised. Diagnostic accuracy was higher in the MPR group than in conventional group both for aspiration biopsy (96.9% vs 82.4%, respectively, $p<0.05$) and cutting biopsy (97.0% vs 81.3%, respectively, $p<0.05$). The MPR technique was particularly useful for small nodules (<20 mm).	
Grades of recommendation	Not applicable	Recommendation Grade D; Evidence level 3	Not applicable
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Not applicable	Yes	Not applicable
Similarity of value and preference	Not applicable	Yes	Not applicable
Similarity of benefit by recommendation	Not applicable	Yes	Not applicable
Generally, acceptable	Not applicable	Yes	Not applicable
Applicability			
Applicability of intervention/instrument	Not applicable	Yes	Not applicable
Applicability of essential technique	Not applicable	Yes	Not applicable
No legal and institutional barriers	Not applicable	No	Not applicable
Generally, applicable	Not applicable	Yes	Not applicable

3-3) Which needle size, how many samples, and which technique (biopsy versus aspiration) should be used for PTNB?

Source of recommendation	Establishing the Diagnosis of Lung Cancer, Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	Lung cancer (CG121)	Guidelines for radiologically guided lung biopsy	Management of lung cacner (Scottish Intercollegiate Guidelines Network)
Year	**2013**	**2011**	**2003**	**2014**
K-Agree II score	**80**	**67**	**63**	**83**
Recommendation	Not applicable	Not applicable	The decision on the type of needle used will be made by the operator and will be dependent on operator experience, available cytological support, and the position of the lesion. [B] Sufficient passes should be made to obtain diagnostic material (see later). [B]	Not applicable
Supporting text	Using a random-effects model, pooled sensitivities were 92% (95% CI, 90% to 94%) and 88% (95% CI, 85% to 90%) for studies of CT scan-guided and fluoroscopy-guided TTNA, respectively. Two studies reported direct comparisons between aspiration cytology and cutting needle biopsy histologic diagnosis. Both studies found that transthoracic needle core biopsy compared with FNA showed similar sensitivity for malignancy (86% vs 92% 161 and 98% vs 98% 178) but a better ability to determine a specifi c diagnosis for nonmalignantlesions (100% vs 44% 161 and 100% vs 50%) and that transthoracic needle core biopsies are more likely to yield enough tissue for mutation analysis.	Not applicable	The number of passes needed per procedure has not been defined. Most operators perform at least two. Variables to consider are: the difficulty of the procedure, complications arising from each biopsy, the quality of the specimen obtained, the characteristics of the lesion biopsied, and the need for specimens for cytological, histological and microbiological examination. The presence of an on-site cytologist or technician may reduce the number of passes required. When deciding whether to use FNAB or a cutting needle biopsy (CNB), it is important to be aware of the accuracy of the technique as well as its complications. Ideally, the technique must not only be able to diagnose malignancy but also to make a definite diagnosis if the lesion is benign. Different populations have different ratios of benign to malignant disease and this can affect reported positive and negative predicted values. FNAB has an accuracy of up to 95% for malignant lesions but the yield for benign lesions is lower (10–50%). Cytology is reported to be less reliable than histology in determining the cell type in malignant lesions, although Stewart and Stewart were able to diagnose correctly small and large cell carcinomas in their series. There is wide variation in reported diagnostic accuracies of FNAB between different institutions, ranging	Not applicable

			from 64% to 97%. A high diagnostic accuracy is best achieved with large nodules and a cytopathologist present to evaluate the adequacy of the specimens. A cytopathologist is not available in many centres and this factor may persuade the operator to use a cutting needle, particularly for small nodules. The high diagnostic figures reported from some American studies may be achieved after repeated biopsies over a short period (2 or 3 hours) rather than a single episode. Several recent studies have advocated the use of 18 and 20 gauge cutting needles as well as coaxial techniques to improve the diagnostic yield and have achieved diagnostic accuracies for malignancy of 74–95%. Others have found the diagnostic yield for malignancy with CNB to be lower than with FNAB. Charig and Phillips found the diagnostic accuracy of CNB to be similar to FNAB with an onsite cytopathologist. Their accuracy was in line with those reported from other core biopsy studies. Using a 21 gauge CNB needle and frozen section, Stewart and Stewart achieved a specific diagnosis in 77% of benign lesions; in other studies CNB improved the diagnostic yield compared with cytology from 10% to 40%128 and from 16.7% to 81.7%.32 The reported specific diagnosis in cases of benign disease varies from 78.3%11 32 to 91%, although this may reflect the local populations. The false negative results for malignancy may be due to a variety of factors including the patient's inability to cooperate, overlying bone which may contribute to missing the lesion completely, obtaining only necrotic tissue, or sampling pneumonitis distal to an obstructing lesion. These factors are the same irrespective of the choice of needle, but the false negative rate has been shown to be significantly lower with cutting needles. False positive rates of 0.8% have been reported with FNAB but no false positive cases have been reported using CNB.	
Grades of recommendation	Not applicable	Not applicable	Strong recommencdation; medium-quality evidence [B]	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Not applicable	Not applicable	Yes	Not applicable

Similarity of value and preference	Not applicable	Not applicable	Yes	Not applicable
Similarity of benefit by recommendation	Not applicable	Not applicable	Yes	Not applicable
Generally, acceptable	Not applicable	Not applicable	Yes	Not applicable
Applicability				
Applicability of intervention/instrument	Not applicable	Not applicable	Yes	Not applicable
Applicability of essential technique	Not applicable	Not applicable	Yes	Not applicable
No legal and institutional barriers	Not applicable	Not applicable	Yes	Not applicable
Generally, applicable	Not applicable	Not applicable	Yes	Not applicable

Source of recommendation	**Executive Summary Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**BTS Guidelines for the Investigation and Management of Pulmonary Nodules**	**Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**
Year	**2013**	**2015**	**2013**
K-Agree II score	**52**	**85**	**83**
Recommendation	Not applicable	Not applicable	Not applicable
Supporting text	Not applicable	Not applicable	Not applicable
Grades of recommendation	Not applicable	Not applicable	Not applicable
Acceptability			
Similarity of population (prevalence, incidence, etc.)	Not applicable	Not applicable	Not applicable
Similarity of value and preference	Not applicable	Not applicable	Not applicable
Similarity of benefit by recommendation	Not applicable	Not applicable	Not applicable
Generally, acceptable	Not applicable	Not applicable	Not applicable
Applicability			

Applicability of intervention/instrument	Not applicable	Not applicable	Not applicable
Applicability of essential technique	Not applicable	Not applicable	Not applicable
No legal and institutional barriers	Not applicable	Not applicable	Not applicable
Generally, applicable	Not applicable	Not applicable	Not applicable

4) What is the appropriate management of acute PTNB-related complications?

4-1) What is the appropriate management of pneumothorax?

Source of recommendation	**Guidelines for radiologically guided lung biopsy**	**Executive Summary: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	**BTS for the investigation and management of pulmonary nodules**
Year	**2003**	**2013**	**2013**	**2015**
K-Agree II score	**63**	**52**	**80**	**85**
Recommendation	‣Operators should try to achieve the lowest quoted complication rates. These should be similar to, or better than, those from the national survey: pneumothorax (20.5% of biopsies), pneumothorax requiring a chest drain (3.1%). ‣ An erect chest radiograph should be performed 1 hour after the biopsy and is sufficient to detect the majority of post biopsy pneumothoraces. [B] ‣ Patients should be informed of the risks of delayed pneumothoraces. [B] ‣ No specific observations are necessary after the biopsy procedure, but patients should remain in a place where staff can be alerted if new symptoms develop in the first	Not applicable	Not applicable	‣Pneumothorax is the most common complication of CT-guided biopsies; by far the largest study showed an incidence of 15%, with 6.6% of patients requiring an intercostal drain insertion. Consistent factors that increase the risk are lower FEV1 and presence of emphysema along the needle tract. ‣ Consider the risk of pneumothorax when deciding on a transthoracic needle biopsy.

	hour. [C] ‣ The chest radiograph should be reviewed by a suitably qualified member of staff. [B] ‣ If a pneumothorax has developed, the clinical condition of the patient and their home circumstances should be considered before deciding on further management. [B] ‣ The operator should be able to identify and appropriately manage the complications of lung biopsy procedures. Resuscitation facilities and chest drain equipment should be immediately available. [B] ‣ When a complication has occurred, the pulse, blood pressure and oxygen saturations should be monitored and recorded in a severely unwell patient. [C]			
Supporting text		Not applicable	Not applicable	
Grades of recommendation	Strong recommencdation; medium-quality evidence [B to C]	Not applicable	Not applicable	Recommendation Grade C; Evidence level 3
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Not applicable	Not applicable	Yes
Similarity of value and preference	Yes	Not applicable	Not applicable	Yes
Similarity of benefit by recommendation	Yes	Not applicable	Not applicable	Yes
Generally, acceptable	Yes	Not applicable	Not applicable	Yes
Applicability				
Applicability of intervention/instrument	Yes	Not applicable	Not applicable	Yes
Applicability of essential technique	Yes	Not applicable	Not applicable	Yes
No legal and institutional barriers	Yes	Not applicable	Not applicable	Yes
Generally, applicable	Yes	Not applicable	Not applicable	Yes

4-2) What is the appropriate management of hemoptysis?

Source of recommendation	Guidelines for radiologically guided lung biopsy	Executive Summary: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	BTS for the investigation and management of pulmonary nodules
Year	**2003**	**2013**	**2013**	**2015**
K-Agree II score	**63**	**52**	**80**	**85**
Recommendation	▸Operators should try to achieve the lowest quoted complication rates. These should be similar to, or better than, those from the national survey: pneumothorax (20.5% of biopsies), pneumothorax requiring a chest drain (3.1%). ▸ An erect chest radiograph should be performed 1 hour after the biopsy and is sufficient to detect the majority of post biopsy pneumothoraces. [B] ▸ Patients should be informed of the risks of delayed pneumothoraces. [B] ▸ No specific observations are necessary after the biopsy procedure, but patients should remain in a place where staff can be alerted if new symptoms develop in the first hour. [C] ▸ The chest radiograph should be reviewed by a suitably qualified member of staff. [B] ▸ If a pneumothorax has developed, the clinical condition of the patient and their home circumstances should be considered before deciding on further management. [B] ▸ The operator should be able to identify and appropriately manage the complications of lung biopsy procedures. Resuscitation facilities and chest drain equipment should be immediately available. [B] ▸ When a complication has occurred, the pulse, blood pressure and oxygen saturations should be	Not applicable	Not applicable	▸Pneumothorax is the most common complication of CT-guided biopsies; by far the largest study showed an incidence of 15%, with 6.6% of patients requiring an intercostal drain insertion. Consistent factors that increase the risk are lower FEV1 and presence of emphysema along the needle tract. ▸ Consider the risk of pneumothorax when deciding on a transthoracic needle biopsy.

	monitored and recorded in a severely unwell patient. [C]			
Supporting text		Not applicable	Not applicable	
Grades of recommendation	Strong recommencdation; medium-quality evidence [B to C]	Not applicable	Not applicable	Recommendation Grade C; Evidence level 3
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Not applicable	Not applicable	Yes
Similarity of value and preference	Yes	Not applicable	Not applicable	Yes
Similarity of benefit by recommendation	Yes	Not applicable	Not applicable	Yes
Generally, acceptable	Yes	Not applicable	Not applicable	Yes
Applicability				
Applicability of intervention/instrument	Yes	Not applicable	Not applicable	Yes
Applicability of essential technique	Yes	Not applicable	Not applicable	Yes
No legal and institutional barriers	Yes	Not applicable	Not applicable	Yes
Generally, applicable	Yes	Not applicable	Not applicable	Yes

4-3) What is the appropriate management of air embolism and hemothorax?

Source of recommendation	Guidelines for radiologically guided lung biopsy	Executive Summary: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	BTS for the investigation and management of pulmonary nodules
Year	**2003**	**2013**	**2013**	**2015**
K-Agree II score	**63**	**52**	**80**	**85**
Recommendation	▸ The operator should be able to identify and appropriately manage the complications of lung biopsy procedures. Resuscitation facilities and chest drain equipment should be immediately available. [B] ▸ When a complication has occurred, the pulse, blood pressure and oxygen saturations should be monitored and recorded in a severely unwell patient. [C]	Not applicable	Not applicable	Not applicable
Supporting text	Air embolism -Treatment is to administer 100% oxygen and anticonvulsants where necessary. The patient should be placed in the Trendelenburg position or in a left lateral decubitus position in case of a residual gas collection within the left heart. Steroids and aspirin are also recommended. Hyperbaric oxygen therapy has been used with a successful outcome in one case report. Hemothorax -When a large haemothorax develops, the patient should be given supportive care and the clinical team contacted. Signs of this are usually evident within the first hour. Assistance from general or thoracic	Not applicable	Not applicable	Not applicable

	surgeons and interventional vascular radiologists may be needed.			
Grades of recommendation	Strong recommencdation; medium-quality evidence [B to C]	Not applicable	Not applicable	Not applicable
Acceptability				
Similarity of population (prevalence, incidence, etc.)	Yes	Not applicable	Not applicable	Not applicable
Similarity of value and preference	Yes	Not applicable	Not applicable	Not applicable
Similarity of benefit by recommendation	Yes	Not applicable	Not applicable	Not applicable
Generally, acceptable	Yes	Not applicable	Not applicable	Not applicable
Applicability				
Applicability of intervention/instrument	Yes	Not applicable	Not applicable	Not applicable
Applicability of essential technique	Yes	Not applicable	Not applicable	Not applicable
No legal and institutional barriers	Yes	Not applicable	Not applicable	Not applicable
Generally, applicable	Yes	Not applicable	Not applicable	Not applicable