



## Tissue pathway for non-neoplastic thoracic pathology

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).  
For full details on our accreditation visit: [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

## Foreword

The tissue pathways published by The Royal College of Pathologists (RCPATH) are guidelines which enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances.

It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be carefully considered by the reporting pathologist; just as adherence to the guidelines may not constitute defense against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

This tissue pathway has been developed in consultation with the following stakeholders:

- British Thoracic Society
- Society for Cardiothoracic Surgeons of Great Britain and Ireland.

The information used to develop this tissue pathway was collected from electronic searches of the medical literature, previous recommendations of the RCPATH, and local guidelines in the United Kingdom. Published evidence was evaluated using modified SIGN guidance. The level of evidence was either grade C or D, or met the GPP/good practice point criteria. Consensus of evidence in the tissue pathways was achieved by expert review. Gaps in the evidence were identified by College Fellows via feedback received from consultation.

Implementation of the tissue pathway to its full extent may have some cost implications or require some local organisational changes, as the delivery of thoracic pathology services varies widely between hospitals.

A formal revision cycle for all tissue pathways takes place on a four-yearly basis. However, each year the College will ask the author of the tissue pathways, in conjunction with the relevant subspecialty advisor to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for two weeks for Fellows' attention. If Fellows do not object to the changes, the short notice of change will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College.

The pathway has been reviewed by the Working Group on Cancer Services (WGCS) and was placed on the College website for consultation with the membership from 13 March to 13 April 2013. All comments received from the WGCS and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Acting Director of Communications.

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Unit and are available on request. The author of this document has declared that there are no conflicts of interest.

## 1 Introduction

This document deals with the handling of specimens in relation to non-neoplastic thoracic pathology. Handling of histology specimens for lung cancer, mesothelioma and thymic epithelial tumours, including biopsies, is dealt with in the respective cancer datasets. The tissue pathways are important as they provide a consistent approach to managing histological samples in thoracic pathology, highlighting ancillary techniques when appropriate. Samples from the lung are especially important in relation to potential occupational lung diseases such as asbestosis, and the lungs are also a common site for often unsuspected infections. In addition, the lung is an organ where reactive conditions may mimic neoplasms, for example Wegener's granulomatosis. Pulmonary involvement by systemic disorders is also not infrequently seen.

This document replaces previous versions that included the handling of lung samples and also reflects evidence-based recommendations that have recently been published for the management of diffuse lung diseases (referenced in relevant sections below).

### Target users of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists. It is recommended that each department should have a lead for thoracic pathology.

## 2 Staffing, workload and facilities

### Staffing and workload

The laboratory should have sufficient pathologists, biomedical scientists and clerical staff to cover all of its functions. In general, staffing levels should follow the workload guidelines of The Royal College of Pathologists (RCPATH). Pathologists should:

- participate in audit
- participate in The Royal College of Pathologists' Continuing Professional Development (CPD) scheme.

The lead pathologist responsible for reporting thoracic specimens should have appropriate expertise in thoracic pathology. Whilst it is ideal that all pathologists involved in lung multidisciplinary teams (MDTs) should participate in the national pulmonary EQA scheme, it is recognised that the volume of cases in certain hospitals may be low, and that thoracic cases may be limited to biopsy material. Participation in an EQA scheme is therefore expected for those in regional hospitals that deal with the breadth of pulmonary pathology, but only recommended for those with limited throughput on the proviso that their lung cancer service delivery has a recognised regional or national point of referral. Cover should be available at an appropriate level during periods of leave.

### Laboratory facilities and generic laboratory requirements

The reporting of thoracic pathology should be undertaken in an appropriate laboratory environment. Provision should be made for macroscopic and microscopic photography, especially for resection specimens that may be discussed at local multi-disciplinary meetings.

The laboratory should:

- be equipped to allow the recommended technical procedures to be performed safely
- be enrolled with Clinical Pathology Accreditation (UK) Ltd
- participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique

- participate in the UK National External Quality Assurance Scheme for Immunocytochemistry
- have access to light microscopy and common special stains
- have access to immunohistochemistry
- have access to genetics services
- have access to microbiology and virology services.

Reports should be held on an electronic database that has facilities to search and retrieve specific data items, and that is indexed according to Systematised Nomenclature of Medicine Clinical Terms (SNOMED) T, M and P codes. It is acknowledged that existing laboratory information systems may not meet this standard; however, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.

Workload data should be recorded in a format that facilitates the determination of the resources involved and which, if applicable, is suitable for mapping to Healthcare Resource Groups (HRGs).

### **3 Biopsy samples (lung, pleura and mediastinum including thymus)**

#### **3.1 Specimen submission**

Specimens are immediately placed in formalin, unless there are prior arrangements for fresh samples to be submitted. If infection is suspected, separate samples should be sent to microbiology, taking precautions appropriate for the level of the potential biohazard. This may require decontamination of cryostats, as a common occurrence is unsuspected mycobacterial infection mimicking malignancy being identified at frozen section. Laboratories should have a policy in place to manage this situation.

#### **3.2 Specimen dissection and block selection**

All of the material should be submitted, with a brief description of the number and size of pieces.

#### **3.3 Embedding and sectioning**

All pieces are usually embedded as a group in one block. However, there is not infrequently a differential diagnosis of malignancy, and blocking into more than one block to preserve tissue for molecular analysis should be considered in relevant cases. At the discretion of the individual laboratory, dependent on the need for tissue preservation and the size of the sample, up to three step-sections (20–30 µm between each stained section) should be prepared, keeping a spare unstained section at each level for any special stains that might be required. One should aim to be around 40% of the way through the sample by the third level. If no abnormalities are identified at any of these levels and tissue remains in the block, further step sections should be taken, as features such as granulomas may be scanty within the tissue.

#### **3.4 Staining and evaluation of sections**

Haematoxylin and eosin (H&E) is usually sufficient to identify common pathological changes. If infection (e.g. tuberculosis or Pneumocystis) is suspected, appropriate stains (e.g. Ziehl-Neelsen, Grocott, PAS) will be necessary. Elastic van Gieson (EVG) stains are of value if considering a vasculitic process or looking for evidence of interstitial fibrosis. A PAS stain is also of value in assessing cases of suspected alveolar lipoproteinosis. A Perls' stain should be undertaken if there is pigment present, in order to assess the extent of haemosiderin

deposition. Congo red staining should be considered if amyloidosis is suspected. Immunohistochemistry (S-100, CD1a) is sometimes required to diagnose disorders such as Langerhans cell histiocytosis (LCH) and to assess lymphoproliferative disorders (such as lymphoid interstitial pneumonia and hyper IgG4 disease).

### **3.5 Report content**

The report should comment on the adequacy of the specimen (e.g. is there sufficient parenchyma for examination if an interstitial lung disease is being investigated? Does a pleural biopsy contain pleura and not chest wall?) and the nature of any morphological changes.

The conclusion should provide a differential diagnosis of the causes of identified histological patterns. Of note, transbronchial biopsies are frequently uninformative in many diffuse parenchymal lung disorders; in particular the interstitial pneumonias are not diagnosable on such tissues, other than the presence of organising pneumonia. Even then, clinical correlation is required to diagnose cryptogenic organising pneumonia (COP). Pathologists should not be pressured into the making the diagnosis of such histological patterns when it is not appropriate.<sup>1</sup>

For pulmonary needle biopsies, a comment that non-specific inflammatory changes may represent changes due to obstruction by hitherto unsampled pathology may also be of value, in that there may often be florid obstructive changes in relation to a neoplasm that inadvertently are sampled rather than the tumour itself.

For pleural biopsies, the presence of areas showing lamellar fibrosis characteristic of a pleural plaque should be documented, as should the type and extent of any inflammatory changes.

*[The majority of data in relation to preparation of different type of biopsies is based on expert opinion – Level of evidence D.]*

## **4 Video-assisted thoracoscopic (VATS) and open pulmonary (surgical lung) biopsies**

### **4.1 Specimen submission**

In the context of non-neoplastic pulmonary disease, surgical lung biopsies are almost always taken to investigate suspected diffuse parenchymal lung disease (DPLD), most frequently to differentiate between the patterns of interstitial pneumonias. However, they may also be taken for suspected vascular disorders, most commonly vasculitis. High-resolution computed tomography (HRCT) has removed the need for surgical biopsy in a large proportion of patients who present with DPLDs, but this type of biopsy still plays a significant role in the diagnosis in a minority of patients and will remain so, as some DPLDs do not have specific HRCT features, in particular in paediatric lung disease where HRCT is less specific. Furthermore, both atypical presentations and unexpected longitudinal behaviour are still encountered, which may prompt the clinician to request a biopsy.

Ideally, biopsy sites are targeted pre-operatively through HRCT correlation, at least two sites are sampled, and biopsies of at least 30 mm along the visceral pleural plane are taken to maximise diagnostic yield.

Should infection be suspected, a second, separate specimen is sent fresh and directly for microbiological study. If tissue is in short supply and a staple line is present, then the tissue

attached to the staple line, which would otherwise be redundant, can be used for microbiology.

Ideally, and particularly in paediatric cases, small, separate pieces of tissue are snap frozen and fixed in glutaraldehyde to facilitate additional genetic or ultrastructural investigations if required.

Under ideal circumstances, the remaining tissue should be gently inflated with formalin via a small bore needle, taking care not to over-expand the tissue as this can cause artefact that mimics lymphangiectasia, especially in children. Over-inflation also may wash out alveolar contents, for example macrophages that are key to the diagnosis of respiratory bronchiolitis. The specimen is then fixed overnight.

#### **4.2 Specimen dissection and block selection**

The specimen will normally be a wedge of subpleural lung, stapled along the surgical margin. The description should include its dimensions and any parenchymal or pleural abnormalities. The row of staples is cut off (unless already used). The axis of slicing will depend on the volume of tissue, but ideally sections with the largest possible area should be taken.

#### **4.3 Embedding and sectioning**

A single section of each slice of tissue embedded provides an adequate picture of the extent, distribution and nature of any pathology present.

#### **4.4 Staining and evaluation of sections**

H&E is usually sufficient for the investigation of diffuse pulmonary disease, although a stain to highlight collagen and the pulmonary vasculature is recommended (e.g. EVG, haematoxylin and van Gieson, Movat's stain).

If asbestos is suspected as a cause of interstitial fibrosis, thick (25–30 µm) unstained sections or normal thickness sections stained by the Perls' Prussian blue method should be examined for asbestos bodies. A Perls' stain is also of value in identifying haemosiderosis, both primary and secondary, and distinguishing this pigment from that of smokers' macrophages, the latter showing more varied pigment composition and less dense staining for haemosiderin.

If pulmonary infection (e.g. tuberculosis, Pneumocystis) is suspected, appropriate stains (e.g. Ziehl-Neelsen, Grocott, PAS) will be necessary.

Immunohistochemistry is used at the discretion of the pathologist for identification of tumours and some DPLDs, particularly Langerhans cell histiocytosis in which the characteristic infiltrate will be highlighted by its immunoreactivity for S-100 protein and the CD1a antigen.

Ultrastructure is infrequently used nowadays in a diagnostic setting, but is of value when assessing inborn errors of metabolism and some surfactant protein gene mutations. It is therefore worth ensuring assessable tissue is available, especially in children, even if the decision after reviewing the sections is that analysis is not required.

#### **4.5 Report content**

Comments on the adequacy of the specimen should be included in the report. In end-stage 'honeycombing' fibrosis, it may be impossible to determine the causative histological pattern/disease, although it may still be of value in excluding/identifying diseases such as sarcoidosis and neoplasms. This situation can be avoided in the majority of cases by pre-operative targeting of multiple biopsy sites (see above).

For the idiopathic interstitial pneumonias (IIPs), the 2002 American Thoracic Society/ European Respiratory Society classification is used.<sup>2</sup> By far the most common IIP is usual interstitial pneumonia (UIP, idiopathic pulmonary fibrosis). A comment on the degree of confidence for the diagnosis (UIP, probable UIP, possible UIP, definitely not UIP) has been recommended in an international consensus document on management of idiopathic pulmonary fibrosis, and in this context of suspected IPF, a case that only shows end-stage (honeycomb) fibrosis may be viewed as 'probable UIP'.<sup>3</sup> For other IIPs, a comment on the extent and pattern of any fibrosis should also be provided. There is also a proposed classification for paediatric diffuse parenchymal lung disease.<sup>4,5</sup>

Once the pathologist has diagnosed a histological pattern, multidisciplinary review should occur, ideally through formal and regular team meetings but, as a minimum, review of imaging and clinical data for individual cases, after which a final clinicopathological diagnosis can be given.<sup>6,7</sup>

For other DPLDs, the nature, pattern and severity of any pathological changes must be described, taking care to assess all anatomic compartments as, for example, collagen vascular disease can present with coexistent interstitial pneumonias and vascular disease. Again, multidisciplinary review should be part of the diagnostic algorithm. If a specific diagnosis cannot be made, a differential diagnosis for the causes of any reported changes should be given.

In cases where a diagnosis of asbestosis is suspected, controversy remains over how many asbestos bodies are required for diagnosis. Identification of a single asbestos body in the setting of diffuse interstitial fibrosis raises the possibility of asbestosis, but in order to make a firm diagnosis, two or more asbestos bodies per 1 cm<sup>2</sup> should be identified in a normal thickness (3–5 µm) section, in the presence of established fibrosis.<sup>8</sup> Multidisciplinary review of such cases is again recommended.

In the investigation of pulmonary vascular disease, the distribution of changes such as vascular medial muscularisation and the presence of fibrinoid change and/or plexiform or angiomatoid lesions must be sought and described. Pathologists should distinguish veno-occlusive disease from those of pulmonary arterial hypertension.<sup>9</sup>

*[There is consistent evidence that multidisciplinary review is the best management process for accuracy of diagnosis in interstitial lung disease – Level of evidence B. Expert opinion is that a similar process is recommended for other non-neoplastic diseases – Level of evidence D). Evidence is reviewed in the cited classification proposals.]*

## **5 Thoracoscopic/open pleural biopsies and non-neoplastic pleural resections**

### **5.1 Specimen submission**

Should infection be suspected, submission of a second, separate specimen for microbiological study is encouraged. This must be submitted fresh, the specimen for histopathology being placed immediately in an adequate volume of formalin.

### **5.2 Specimen dissection and block selection**

For biopsies, the whole specimen is submitted with a brief description of its size and appearance; pleura infiltrated by a neoplasm is often conspicuously nodular. For resections, a decortication (for non-neoplastic disease) is usually performed to relieve respiratory impairment due to compression of the lung by thickened, chronically inflamed or fibrotic pleura, subsequent to inflammation, most often empyema. The specimen will consist of pieces of pleura of varying size that should be fully described, noting the consistency of the



changes, the presence of any focal pathology, and the presence and nature of any exudate. Blocks should be selected as appropriate at the discretion of the pathologist.

### **5.3 Embedding and sectioning**

It is recommended that, when possible, pieces of tissue are blocked perpendicular to the specimen surface so that there is good orientation from the surface to the deep aspect, as this allows assessment of maturation, a useful feature in the distinction of desmoplastic mesothelioma from reactive pleural fibrosis. A single section from each block is usually adequate to reveal the nature of any pathology present.

### **5.4 Staining and evaluation of sections**

H&E is usually sufficient to identify basic pathological changes, with other stains as required by the pathologist.

If pulmonary infection (e.g. tuberculosis, Pneumocystis) is suspected, appropriate stains (e.g. Ziehl-Neelsen, Grocott, PAS) should be undertaken. EVG stains are of value if considering a vasculitic process.

For the distinction between reactive mesothelial hyperplasia and epithelioid mesothelioma, staining for desmin and EMA may be helpful, although the diagnosis remains primarily morphological. Staining for cytokeratins may be helpful as entrapped reactive mesothelial cells are nearly always limited to the pleura, whilst mesothelioma not infrequently extends into subpleural fat or peripheral lung. Staining for cytokeratins may also be helpful in distinguishing reactive pleural fibrosis from sarcomatoid mesothelioma, as staining decreases towards the deep aspect of the specimen in reactive cases, whilst staining in mesothelioma tends to be stronger and more irregular.<sup>10</sup> (Further information can be found in the College's *Dataset for the histological reporting of mesothelioma*.)

### **5.5 Report content**

The report should state the nature of any pathology present, in particular the type and extent of any inflammatory changes, which should be correlated with the clinical history. As an example, if a patient has had a pneumothorax, features such as mesothelial hyperplasia and eosinophilic pleuritis are consistent with this diagnosis. The presence of areas showing lamellar fibrosis characteristic of a pleural plaque should be documented, as should the type and extent of any inflammatory changes. Cases with granulomatous pleuritis should be closely assessed for mycobacterial infection.

*[Data in this section is based on expert opinion – Level of evidence D.]*

## **6 Lung resections for non-neoplastic disease**

### **6.1 Specimen submission**

Should infection be suspected, submission of a second, separate specimen for microbiological study is encouraged. This is submitted fresh, the specimen for histopathology being placed immediately in an adequate volume of formalin. If the specimen is large enough, distension with formalin via an airway is desirable to aid rapid fixation. In some cases with congenital lung disease, airways may be absent so inflation may need to be undertaken via syringe.

## **6.2 Specimen dissection and block selection**

The specimen will be a wedge, lobe or whole lung. A full description should be made, including the nature and extent of any pathological changes evident on macroscopic examination. In paediatric cases, typically with lung cysts, the bronchial anatomy must be examined closely and any abnormality must be noted. Close attention should also be paid to the pulmonary vasculature to ensure that the aberrant vessels seen in a sequestration are not missed. Photography of the specimen should be considered during cut-up, as architecture is often lost during dissection. Blocks are selected as appropriate at the discretion of the pathologist.

## **6.3 Embedding and sectioning**

A single section from each block is sufficient to provide an adequate picture of the extent, distribution and nature of any pathology present.

## **6.4 Staining and evaluation of sections**

H&E is usually sufficient to reveal the nature of the pathology.

If pulmonary infection (e.g. persistent consolidation, cavitating masses) is suspected, further appropriate stains (e.g. Gram, Ziehl-Neelsen, Grocott, PAS) will be necessary. EVG staining should be undertaken if a vasculitis is suspected.

## **6.5 Report content**

The report should describe any pathological changes that are present and their cause, if appropriate. The cause of any infective pathology is pursued as far as possible by appropriate staining, bearing in mind that microbiological examination is generally more sensitive than histopathology as a means of identifying the organism(s) responsible. Cysts are classified according to current terminology.<sup>11</sup>

# **7 Mediastinal resections for non-neoplastic disease**

## **7.1 Specimen submission**

Should infection be suspected, submission of a second, separate specimen for microbiological study is encouraged. This may include cyst contents. This should be submitted fresh, the specimen for histopathology being placed immediately in an adequate volume of formalin. If the specimen is cystic, distension with formalin may need to be undertaken via syringe.

## **7.2 Specimen dissection and block selection**

The specimen will usually be a thymus. A full description should be provided including the nature and extent of any pathological changes evident on macroscopic examination. The thymus should be weighed, in order to assess true hyperplasia. Photography of the specimen should be considered during cut-up. Blocks are selected as appropriate at the discretion of the pathologist, with extensive sampling of thymic cysts to exclude neoplasia. Other cysts should be characterised in terms of cyst contents, wall thickness and any adherent native mediastinal elements.

## **7.3 Embedding and sectioning**

A single section from each block is sufficient to provide an adequate picture of the extent, distribution and nature of any pathology present.

## 7.4 Staining and evaluation of sections

H&E is usually sufficient to reveal the nature of the pathology.

If pulmonary infection (e.g. persistent consolidation, cavitating masses) is suspected, further appropriate stains (e.g. Gram, Ziehl-Neelsen, Grocott, PAS) will be necessary. EVG staining is undertaken if a vasculitis is suspected.

## 7.5 Report content

The report must describe any pathological changes that are identified and their cause, if appropriate. The cause of any infective pathology is pursued as far as possible by appropriate staining, bearing in mind that microbiological examination is generally more sensitive than histopathology as a means of identifying the organism(s) responsible. Cysts are classified according to current terminology (e.g. pericardial, thymic, bronchogenic, enteric). Those without obvious site or differential can be classified as a congenital foregut cyst.

*[Data in this section is based on expert opinion – Level of evidence D.]*

## 8 Electron microscopy

Electron microscopy is rarely used now in diagnostic thoracic pathology, having been superseded by immunohistochemistry. However, it still may be of value in the diagnosis of certain disorders, such as pulmonary involvement by inborn errors of metabolism and surfactant protein gene disorders. It is therefore worth considering placing two to three 1 mm<sup>2</sup> pieces of tissue from surgical lung biopsies into glutaraldehyde before fixing the remainder in formalin, especially in paediatric cases. These may not require processing, but can be kept until a decision is made after review of glass slides. Cases with occupational lung disease may require referral to centres with the facility to count and analyse inorganic materials, e.g. asbestos fibres.

## 9 Molecular investigations

At present, molecular investigation of histological samples is not used in a diagnostic setting within non-neoplastic thoracic pathology, although various patterns of non-neoplastic lung disease (such as alveolar proteinosis) may require correlation with results from serological and other molecular tests.

## 10 Criteria for audit of the tissue pathway

The key performance indicators (KPIs) as recommended by the RCPATH ([www.rcpath.org](http://www.rcpath.org)) are as follows.

- The inclusion of SNOMED codes within report:
  - standard: 95% reports should have T and M codes.
- The availability of pathology reports at MDT meetings:
  - standard: 90% of cases discussed at MDT meetings where biopsies or resections have been taken should have pathology reports available for discussion.
- Turnaround times for biopsies and resection specimens:

- standard: 80% diagnostic biopsies will be reported within seven calendar days of the biopsy being taken
- standard: 80% of all histopathology specimens (excluding those requiring decalcification) will be reported within ten calendar days of the specimen being taken.

## 11 References

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## Appendix A AGREE compliance monitoring sheet

The tissue pathways of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines. The sections of this Tissue Pathway that indicate compliance with each of the AGREE standards are indicated in the table.

AGREE standard	Section
<b>Scope and purpose</b>	
1. The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2. The clinical question(s) covered by the guidelines is (are) specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	1
<b>Stakeholder involvement</b>	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The patients' views and preferences have been sought	N/A*
6. The target users of the guideline are clearly defined	1
7. The guideline has been piloted among target users	1
<b>Rigour of development</b>	
8. Systematic methods were used to search for evidence	Foreword
9. The criteria for selecting the evidence are clearly described	Foreword
10. The methods used for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12. There is an explicit link between the recommendations and the supporting evidence	3,4,5,6,7
13. The guideline has been externally reviewed by experts prior to its publication	Foreword
14. A procedure for updating the guideline is provided	Foreword
<b>Clarity of presentation</b>	
15. The recommendations are specific and unambiguous	2-7
16. The different options for management of the condition are clearly presented	2-7
17. Key recommendations are easily identifiable	2-7
18. The guideline is supported with tools for application	2-7
<b>Applicability</b>	
19. The potential organisational barriers in applying the recommendations have been discussed	Foreword
20. The potential cost implications of applying the recommendations have been considered	Foreword
21. The guideline presents key review criteria for monitoring and/audit purposes	10
<b>Editorial independence</b>	
22. The guideline is editorially independent from the funding body	Foreword
23. Conflicts of interest of guideline development members have been recorded	Foreword

\* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this Tissue Pathway because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.

## Appendix B Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008; 337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group</p>