

Tissue pathway for dermatopathology

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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.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The tissue pathways published by The Royal College of Pathologists (RCPATH) are guidelines that 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 defence against a claim of negligence, so a decision to deviate from them should not be deemed negligent or a failure of duty of care.

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

The stakeholder consulted for this document was the British Association of Dermatologists (through its representatives on the RCPATH's Specialty Advisory Committee on Dermatopathology).

This document is the second edition of a College guideline. Statements and advice are supported by published evidence where possible. Information has been obtained from various sources, including peer-reviewed publications, 'best practice' documents, expert opinion and standard textbooks. In order to identify relevant peer-reviewed studies, a PubMed search was done using key words. Feedback from the consultation process of the College also contributed to the content.

No major organisational changes or cost implications have been identified that would hinder the implementation of the tissue pathway.

To grade available evidence, a modification of the Scottish Intercollegiate Guidelines Network (SIGN) guidance for the development of clinical practice guidelines was used (see Appendix A). The grade does not necessarily equate to the clinical importance of the advice or recommendation.

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. However, each year, the College will ask the authors of the tissue pathways, in conjunction with the relevant subspecialty adviser 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 members' attention. If members 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 and will be placed on the College website for consultation with the membership from 25 May to 22 June 2016. All comments received from the Working Group and the membership will be addressed by the authors to the satisfaction of the Working Group Tissue Pathway Coordinator and the Director of Publishing and Engagement.

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 Director of Clinical Effectiveness and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

This document provides guidance on the specimen handling and reporting of skin biopsies obtained from inflammatory dermatoses, non-neoplastic and benign neoplastic disorders of the skin. The specimens discussed in this guideline are currently reported by most histopathology departments in the UK. To put this in perspective, such specimens may represent over 80% of all skin biopsies received from the community.¹ Although this figure may be slightly lower in laboratories catering mainly to dermatologists and plastic surgeons, the number of cases is nevertheless significant considering the large overall number of dermatopathological specimens. The purpose of these guidelines is to assist histopathologists in promoting good practice of the handling and reporting of such specimens so as to ensure a high standard of patient care.

1.1 Target users of this guideline

The primary users of this tissue pathway document are trainee and consultant cellular pathologists. These recommendations will also be of value to biomedical scientists involved in macroscopic description and dissection of skin biopsies.

2 Staffing, workload and laboratory facilities: general considerations

2.1 Staffing and workload

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

- participate in audit
- participate in the RCPATH Continuing Professional Development (CPD) scheme.

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

2.2 Laboratory facilities

The laboratory should:

- be equipped to allow the recommended technical procedure to be performed safely
- be enrolled with the Clinical Pathology Accreditation/UK Accreditation Service (CPA/UKAS) UK Ltd
- participate in the UK National External Quality Assessment (EQA) Scheme for various cellular pathology techniques
- participate in the UK National EQA Scheme for immunohistochemistry and immunofluorescence (if applicable).

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-CT) or antecedent versions of 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.

3 Inflammatory skin disorders

3.1 Staffing

The accurate diagnosis of inflammatory conditions of the skin requires the integration of the histopathological features with the clinical picture. This can be difficult when such skin biopsies are seen infrequently or if the pathologist is unfamiliar with the clinical aspects of these disorders. It is therefore useful to have a lead subspecialist with a special interest in inflammatory skin disorders for centres which handle significant numbers of such cases. Such lead subspecialists in England and Wales must participate in the National Specialist Dermatopathology EQA Scheme, which has the specific purpose of accrediting specialist dermatopathologists on specialist skin cancer multidisciplinary teams in these regions. For subspecialist leads for inflammatory conditions elsewhere, and especially those in non-teaching hospitals, it is desirable for pathologists to join this scheme to ensure high standards of overall diagnostic performance. Histopathologists and dermatologists with appropriate training and experience in dermatopathology can obtain specialist qualifications offered by The Royal College of Pathologists (Diploma in Dermatopathology) and/or the European Union of Medical Specialists (International Board Certification in Dermatopathology). They are also encouraged to join relevant national bodies like the British Society for Dermatopathology.

Given the vital role of clinicopathological correlation, it is important that biopsies from inflammatory dermatoses are reported in a setting where there is scope to undertake this exercise. For the most part, it requires the referring clinician to provide as much information about the rash as possible, for example symptoms, duration, morphology of individual lesions, distribution, treatment history and relevant systemic illnesses, if any. Also useful is to include a list of clinical differential diagnoses which the pathologist could address if it is not possible to arrive at a specific diagnosis.

Since most of the histopathological features of biopsies of inflammatory skin lesions have a corresponding clinical correlate, having access to clinical images greatly enhances the accuracy of the final histopathological diagnosis.²

[Level of evidence – D]

These clinical images may be in either a digital form (as part of a clinical image database) or print form. In select cases, assessment of inflammatory skin biopsies may involve examining the patient in a clinic or at a clinicopathological correlation meeting in conjunction with a clinical colleague. Such activities should be acknowledged as part of direct clinical care in job plans.

3.2 Specimen submission

Most skin biopsies for inflammatory dermatosis are received in buffered formalin fixative.

Nail clippings taken for suspected fungal infection are usually submitted dry. These, along with nail plate biopsies to evaluate causes of nail pigmentation, are rigid and often need softening with agents like phenol, sodium hydroxide or similar proprietary reagents before processing.

Hair samples from hair pluck (trichogram) and hair pull tests are sometimes submitted in order to estimate the telogen:anagen ratio and extent of hair loss respectively. Study of hair samples under the microscope is also valuable for the diagnosis of hair shaft disorders.

Fresh unfixed tissue may be received as frozen section biopsies and also for direct immunofluorescence, although a suitable transport medium like Michel's medium is equally effective for the latter. Samples transported in Michel's medium retain the immunoreactivity for several days and give results comparable to biopsies which are immediately frozen and sectioned on a cryostat.³ The clinician should ensure that any unfixed specimen is free from Hazard Group 3 risk of infection before sending it to the laboratory. Appropriate systems (like

incident reporting, decontamination of the cryostat, risk assessment of the exposed staff) should be in place as part of the departmental standard operating procedure (SOP) to deal with inadvertent exposure to a significant biological hazard during preparation and production of frozen sections.

[Level of evidence – GPP]

Specimens for electron microscopy should be sent in an appropriate fixative, such as glutaraldehyde. Scanning electron microscopy for hair shaft disorders is a technique that is available only in a few specialised centres. Advice from such referral centres should be sought ideally prior to obtaining and transporting such specimens.

3.3 Specimen dissection

From time to time, clinicians may need to be reminded about the impact of specimen adequacy on the histopathological interpretation of inflammatory skin disorders. Although punch biopsies of adequate thickness are generally adequate for most inflammatory dermatoses, deeper incisional biopsies that include the fat are recommended when a panniculitis, calciphylaxis or medium vessel vasculitis is suspected clinically. Superficial shave biopsies and curettages are generally inadequate for assessment of most inflammatory skin disorders.⁴

It is envisaged that most biopsies from inflammatory dermatoses will be dissected by biomedical scientists as part of their extended role in specimen description, dissection and block taking. This is discussed further in Section 4, 'Non-neoplastic and benign neoplastic skin disorders'.

Although smaller punch biopsies may be submitted intact, those with diameter of 4 mm or greater may be bisected. Larger incisional biopsies should be bisected along their long axis.

Adopting the right dissection technique is critical for skin biopsies done for assessment of alopecia. The standard diagnostic material for alopecia is usually a 4 mm punch biopsy, which may be sectioned either vertically or transversely, with both techniques having unique advantages and disadvantages. Vertical sections offer the benefit of visualisation of the dermo-epidermal junction and the entire thickness of the dermis, with precise localisation of the dermal inflammatory infiltrate with relative ease. Transverse sections are far superior for detection of focal follicular pathology, quantitative assessment of hair follicles and providing information on follicular cycling and the relationship between terminal and vellus hair follicles. It is generally agreed that a combination of vertical and transverse sectioning should be the standard practice in histopathological assessment of alopecia where two specimens are available.^{5,6}

[Level of evidence – C]

The biopsy for vertical section is sometimes received pre-bisected by the clinician, with one half sent for direct immunofluorescence studies. If only one specimen is provided for evaluation, the ultimate choice of sectioning (vertical versus transverse) depends on the clinical context.⁷ Novel techniques (e.g. Hovort technique) have evolved that can incorporate both vertical and transverse sectioning on a single specimen.⁸ Although vertical sections are adequate for most scarring alopecias, transverse sections are essential for non-scarring alopecias where quantitative morphometric data are required.

[Level of evidence – GPP]

Dealing with transverse section biopsies requires some training of the laboratory personnel and it is important for laboratories to adopt suitable SOPs to this effect following discussion with clinical colleagues involved in the care of alopecia patients. The standard practice is to

bisect the punch biopsy transversely 1 mm below the epidermis, ink the cut surface and place the two pieces in a different cassette, separate from the vertically sectioned biopsy.⁹

[Level of evidence – D]

3.4 Embedding options, sectioning and staining

Most biopsies from inflammatory dermatoses are embedded with the cut surface parallel to the long axis of the specimen. Nail clippings should be embedded on edge.

Biopsies from inflammatory skin disorders usually require examination of more than one section and many laboratories cut three or more sections routinely at the time of initial processing. While ‘pre-ordered’ additional sections may improve turn-around time and diagnostic accuracy, they increase expenditure, in terms of both processing and slide storage.¹⁰

[Level of evidence – D]

In any event, the pathologist should not hesitate to order additional sections if the histopathological features in the original sections fail to demonstrate sufficient histopathological features from which a diagnosis can be made. This is particularly relevant where the clinical differential diagnosis includes disorders with the possibility of focal pathological changes such as subtle acantholytic disorders, porokeratosis and folliculitis. It is equally important not to exhaust the material within the block, especially in cases which may require additional stains or referral for a second opinion.

[Level of evidence – GPP]

Transverse sections from alopecia biopsies should be embedded with their inked cut surface down and the microtome blade adjusted to obtain full-face, good quality sections. These biopsies routinely require a considerable number of sections in order to visualise the hair follicles in their entirety. Practice in this matter is variable and ranges from exhausting the entire block and studying every section produced to obtaining at least six initial levels while accepting that sampling error may be an issue.¹¹ In a small number of cases, a diagnosis can be made on the original sections without resorting to additional levels.

[Level of evidence – D]

Individual centres may adopt a protocol which could vary from serial sections, level sections to step sections on microtome settings. It is useful to bear in mind is that, irrespective of the method used, the isthmus is the most important level of the hair follicle where follicular counts and ratios are most accurately assessed.

Sections are routinely stained with haematoxylin and eosin (H&E) and special stains and/or immunohistochemistry ordered where appropriate.

3.5 Additional investigations

3.5.1 Special stains

A detailed discussion on the application of special histochemical stains in inflammatory dermatopathology is beyond the scope of this document but may be found in any standard textbook of pathology or dermatopathology and publications on this subject.^{12,13} In short, a laboratory should have access to a range of special stains, such as those which help in demonstrating mucin and other connective tissue substances, a range of microorganisms, various pigments and cutaneous deposits, to name a few. A few select scenarios are mentioned in this section where there is likely to be some practice variation or recent advances in the field.

Periodic acid Schiff with diastase digestion (DPAS) is perhaps the most commonly used special stain in the context of inflammatory dermatoses. It is useful in the detection of fungal elements, basement membrane zone thickening (e.g. connective tissue disorders like lupus erythematosus and dermatomyositis and early stages of lichen sclerosus) and for highlighting intraepidermal and perivascular hyaline deposits (porphyria and pseudoporphyria). Many centres perform DPAS staining as a routine in all inflammatory skin biopsies. Although this practice ensures a faster turn-around, it is unnecessary in cases where a definitive diagnosis of non-infective disorder can be readily rendered on examining an H&E-stained section (e.g. granuloma annulare). If a selective approach is adopted, the pathologist should be familiar with the common clinical clues (expanding annular lesion not responding to topical steroids) and histopathological clues (parakeratin and neutrophils) of a superficial fungal infection and have a low threshold of requesting fungal stains in such situations. In cases where the suspicion for a superficial fungal infection is particularly strong, it may be advisable to perform a DPAS stain on ribbon sections to avoid the risk of a sampling error.

[Level of evidence – GPP]

Although Congo red and thioflavin T are still the standard histochemical stains for demonstration of amyloid, immunohistochemistry using cytokeratin stains (like CK5/6 and AE1/AE3) is being increasingly employed for the diagnosis of primary localised cutaneous amyloidosis, where the volume of amyloid deposited is generally small.¹⁴ Transmission electron microscopy is one the most sensitive techniques for identifying amyloid if light microscopy fails to do so. Amyloid fibril analysis (ideally by laser microdissection and tandem mass spectrometry on archival tissue) and genetic testing (using venous blood) are also increasingly being done as a diagnostic work-up for rare autoinflammatory syndromes (like inherited familial periodic fever syndromes).¹⁵ These specialised investigations are generally prompted by a referral by the clinician to the National Amyloidosis Centre and the pathologist usually receives a request to send archival material, including paraffin blocks.

A range of histochemical stains are routinely used for identification of pathogens in inflammatory skin disorders. While most of these stains are relatively easy to perform and interpret, some archaic ones, like Warthin–Starry, are well known for their technical difficulty and heavy background staining. For a wide variety of pathogens, such stains can now be replaced by more effective commercially available immunohistochemical stains.¹⁶

3.5.2 Immunofluorescence

Immunofluorescence studies play a very important role in the assessment of autoimmune blistering disorders; indeed, direct immunofluorescence is considered a diagnostic gold standard.¹⁷

[Level of evidence – D]

The rationale for using immunofluorescence as a diagnostic adjunct is to detect either tissue-bound autoimmune reactants like various immunoglobulins (IgG, IgM, IgA) and complement factors (C3) in the biopsy material (direct immunofluorescence) or circulating antibodies against a defined antigen, usually in the patient's serum or blister fluid (indirect immunofluorescence).

A report for a positive direct immunofluorescence result in a case of an autoimmune blistering disorder should include the following: the primary location (basement membrane zone or intercellular space) and the pattern (linear or granular) of the immune deposition, the type of the immune reactants deposited (immunoglobulins and/or complement factors) and sites of immune deposits, in addition to the primary location (both intercellular and basement membrane zone).¹⁸

[Level of evidence – GPP]

In addition to diagnosis, indirect immunofluorescence is also very useful in monitoring clinical disease activity and response to therapy. Indirect immunofluorescence using rat bladder substrate is particularly helpful in the diagnosis of paraneoplastic pemphigus.¹⁹

Immunofluorescence studies on salt-split skin samples are useful in subepidermal blistering disorders, particularly to distinguish bullous pemphigoid from epidermolysis bullosa acquisita. Immunohistochemistry using laminin, collagen IV and cytokeratin 5/6 on paraffin-embedded sections may be used as an alternative to salt-split skin immunofluorescence but this has a lower diagnostic sensitivity.^{20,21}

[Level of evidence – D]

In addition to autoimmune blistering disorders, immunofluorescence studies may also be useful in connective tissue disorders and vasculitic conditions. Although the deposition of immunoglobulins and complement factors at the dermo-epidermal region (lupus band) is well described, its utility as a diagnostic tool for lupus erythematosus has been largely supplanted by advances in serological testing.²² In patients with suspected or confirmed vasculitis, direct immunofluorescence testing can be a useful adjunct in supporting a diagnosis of IgA-associated vasculitis (Henoch–Schönlein purpura). However, the positive predictive value is low in adults and perivascular IgA deposits may be seen in a wide range of non-vasculitic conditions.²³

[Level of evidence – D]

Direct immunofluorescence *per se* has little role in establishing a diagnosis of vasculitis.

Where facilities exist, it is desirable to take a photomicrograph of a positive immunofluorescence result in order to keep a permanent record. This is particularly useful as a governance tool when the immunofluorescence findings are unexpected in the given clinical context.

Given the effectiveness of Michel's transport medium, network centralisation of immunofluorescence services can be a cost-effective option, particularly for smaller centres.

3.5.3 Frozen sections

Frozen sections have a limited but useful role in providing a rapid diagnosis and also distinguishing life-threatening blistering dermatoses like staphylococcal scalded skin syndrome and toxic epidermal necrolysis.

3.5.4 Electron microscopy

Transmission electron microscopy has a role in the diagnosis of blistering disorders, cutaneous amyloidosis, ichthyosiform conditions, dermal matrix disorders and some viral infections. Scanning electron microscopy may be used to delineate hair shaft disorders. X-ray microanalysis is useful in the detection of particulate matter in the skin, like tattoo ink and aluminium particles at injection sites, and therefore plays a critical role in establishing the reactive nature in some cases of cutaneous lymphoid hyperplasia (pseudolymphoma).

3.6 Report content

A pattern-based approach is a well-tested method of analysing inflammatory skin disorders and may be adopted for reporting such biopsies. The exact list of reaction patterns and the diagnostic algorithms depend on personal preference but most pathologists tend to adhere to the schemes used by Ackerman or Weedon.^{24,25} Although it is common practice and reasonable to provide an inflammatory tissue reaction pattern in the report, an effort should always be made to favour a specific diagnosis using terms which are used in clinical dermatology. This may not be possible when adequate clinical information is not provided in

the request form, in which case a histopathological differential diagnosis and advice for clinicopathological correlation should be given. Where clinical differential diagnoses have been provided by the clinician, it is useful to address these if the histopathological features do not point towards a specific diagnosis. Recommendation for discussion at a clinicopathological correlation meeting or for additional biopsies may be made where appropriate.

[Level of evidence – GPP]

The report should incorporate the findings of immunofluorescence and other ancillary investigations undertaken.

Some rare inflammatory dermatoses warrant referral to a tertiary specialist centre. This applies to blistering disorders like epidermolysis bullosa, genodermatosis, rare matrix and inherited metabolic disorders which present with cutaneous manifestations.

4 Non-neoplastic and benign neoplastic skin disorders

4.1 Staffing

Most specimens from non-neoplastic and benign neoplastic skin disorders are of relatively low complexity and the delegation of their macroscopic description, dissection and sampling to appropriately trained biomedical scientists through well-defined SOPs should be encouraged. Departments adopting this practice should follow the guidance and safeguards stipulated by The Royal College of Pathologists and the Institute of Biomedical Science in their document *Principles of Good Practice for Biomedical Scientist Involvement in Histopathological Dissection*.²⁶ Such laboratories should have adequate technical staff to perform this extended role, provide appropriate training facilities and audit their performance on a regular basis.

4.2 Specimen submission

Specimens should be submitted fixed in buffered formalin as standard.

Although the RCPATH's guidance document of 2005 *Histopathology and Cytopathology of Limited or No Clinical Value* is now archived, the authors and the College's Specialty Advisory Committee on Dermatopathology are still able to endorse two of its recommendations relevant to skin specimens:

- In secondary care, plastic surgeons in many units triage specimens which they send for histopathology. This applies in particular to small (3 mm or less) multiple skin tags. This can be supported.
- In primary care, there is a widespread good practice clinical consensus that general practitioners undertaking minor surgery and general practitioners with a specialist interest in dermatology should submit all tissue removed for histopathological examination.

The latter recommendation is often part of local protocols to accredit service provision, as endorsed by the National Institute for Health and Care Excellence (NICE), to ensure that any case of skin pre-cancer or cancer is not missed.²⁷

4.3 Specimen dissection and block selection

The size of the specimen should be measured in three dimensions wherever possible. Further description of the specimen and sampling will depend on whether any lesion present is perceived to be a melanocytic neoplasm or not.

Where a definite lesion is identified, it should be described and measured to include the maximum diameter and the elevation. Since it is not always possible to determine at the time of specimen dissection whether a lesion is benign or not, consideration should be given to inking the surgical margins in all excisional specimens as routine. Flexibility in this matter is recommended, however, as lesions which appear as cysts macroscopically need not be inked. For routine and commonly received specimens like cysts, warts and lipomas, a selective approach may be adopted for block taking if the lesion is large, has a uniform appearance and there are no clinical concerns. When such targeted sampling is adopted, sampling should focus on areas which appear 'atypical' macroscopically. Large and heterogeneous lesions may need to be sampled more extensively.

For melanocytic lesions, in addition to the maximum diameter and elevation, it is useful to record features like asymmetry, border irregularity and colour variegation to aid clinical and dermoscopic correlation. Following inking, elliptical specimens should be sectioned transversely and the entire lesion processed if it appears atypical macroscopically. With very large specimens (e.g. serial excisions for congenital naevi), the selective inclusion of any unusual areas of nodularity could be adopted. Punch excision specimens for pigmented lesions may be bisected, although the technical staff may need to be alerted to avoid rough trimming during levelling of the paraffin block so as to preserve diagnostic material. Particular caution should be exercised for lesions which may need sectioning along the edge and examining at multiple levels rather than bisecting through the lesion. In cases which have been previously diagnosed as malignant melanoma or there is strong suspicion of malignancy during dissection, the recommendations of The Royal College of Pathologists' *Dataset for the Histological Reporting of Primary Cutaneous Malignant Melanoma and Regional Lymph Nodes* should be followed.²⁸

4.4 Embedding options and sectioning

Embedding and sectioning are standard. Cystic lesions may need embedding on their edge, particularly when partially sampled.

4.5 Staining

The sections are routinely stained with H&E, with ancillary tests like special stains and immunohistochemistry performed where appropriate.

4.6 Report content

The report should provide a definitive diagnosis or a histopathological differential diagnosis, if appropriate. If additional investigations like special stains, immunohistochemistry or review of a previous biopsy have been undertaken, it is good practice to incorporate this information in the report.

There is an increased expectation among clinicians to comment on the excision status for melanocytic lesions. For benign non-atypical naevi, the level of evidence to support this practice is low and this should be left to the reporting pathologist. It may, however, be useful to document this in the report, as the information may help in making the crucial histopathological distinction between a recurrent naevus showing the 'pseudomelanoma phenomenon' and a genuine malignant melanoma, should a pigmented lesion subsequently appear at the scar site.²⁹ Reporting on the margin status should be done routinely in all cases of atypical/dysplastic naevi, as it influences clinical management. Incompletely excised severely atypical/dysplastic naevi are routinely re-excised with appropriate margins. Margin-positive atypical/dysplastic naevi with mild or moderate grades of atypia with no residual clinical pigmentation tend to be observed rather than re-excised.^{30,31}

[Level of evidence – D]

Including a statement on the adequacy of excision is also crucial for non-melanocytic benign neoplasms which have an unusually high local recurrence rate (e.g. variants of benign fibrous histiocytoma like cellular, atypical and aneurysmal).

Issues which may have delayed processing (e.g. insufficient or incorrect patient details) or compromised interpretation (e.g. poor fixation, crushing or diathermy artefacts) should be documented in the report.

5 Criteria for audit

Implementation of this tissue pathway may be monitored by:

- annual review of cases which need modification of histopathological diagnosis following discussion at a clinicopathological correlation meeting
- audit of completeness of recording of key data items in the histopathology report.

The following is recommended by the RCPATH as a key performance indicator (see *Key Performance Indicators – Proposals for Implementation*, July 2013; <https://www.rcpath.org/resourceLibrary/key-performance-indicators---proposals-for-implementation-.html>):

- Histopathology cases that are reported, confirmed and authorised within 7–10 calendar days of the procedure
Standard: 80% of cases must be reported within seven calendar days and 90% within 10 calendar days.

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Appendix A 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>

Appendix B AGREE II compliance monitoring sheet

The Tissue Pathways of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this Tissue Pathway that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	N/A
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	Throughout
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–4
16 The different options for management of the condition or health issue are clearly presented	2–4
17 Key recommendations are easily identifiable	2–4
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	1–4
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	5
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword