Tissue pathway for medical renal biopsies

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Comments: This document supersedes the 2008 publication of the same name. In accordance with the College’s pre-publications policy, this document was on The Royal College of Pathologists’ website for consultation from 18 April to 16 May 2013. Fourteen items of feedback were received. The authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments.

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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 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 defence 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:

- National Renal Pathology EQA Scheme membership
- Renal Association.

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

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. 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.

A formal revision cycle for all tissue pathways takes place on a four-yearly basis. However, each year the College will ask the authors of the tissue pathways, in conjunction with the relevant sub-specialty 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 18 April to 16 May 2013. All comments received from the WGCS and membership were addressed by the authors 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 authors of this document have declared that there are no conflicts of interest.
1 Introduction

The medical renal biopsy forms an important part of the diagnosis and management of patients presenting with acute kidney injury, proteinuria/nephrotic syndrome and chronic kidney disease. It is an invasive procedure associated with a risk of serious and potentially life-threatening complications. The decision of whether to perform a renal biopsy is based on a careful risk-benefit assessment. Once the decision to perform a renal biopsy has been made, it is essential that laboratory and diagnostic procedures are in place to optimise the clinical benefit obtained from the biopsy. The final diagnosis frequently depends on combining clinical, biochemical and serological data with that from light microscopy, immunohistology and electron microscopy. If any of these elements is lacking, it may not be possible to reach a diagnosis. The following recommendations are regarded as the minimum acceptable practice for medical renal biopsies. For a more detailed description of best practice, see ACP Best Practice No. 160.1

Much of the content of the tissue pathways represents custom and practice, and is based on the substantial clinical experience of the authors. Published evidence to support the recommendations has been identified by PubMed search and referenced where appropriate. The strength of supporting evidence for specific elements is indicated using modified SIGN guidance.

Target users of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists. The recommendations will also be of value to histology laboratory managers and the users of a renal pathology service (nephrologists and transplant surgeons).

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).

Optimally, two or more pathologists in a unit should be competent in the reporting of renal biopsies, in order to provide cover for periods of leave. It is recognised that in some smaller units only one pathologist may have specialist expertise, and in such cases cover for periods of leave should be arranged with renal pathologists in other units.

All pathologists reporting renal biopsies should participate in the renal pathology EQA scheme. A renal transplant pathology educational slide scheme is available for those reporting renal transplant biopsies. All pathologists should also participate in audit and in the RCPath’s Continuing Professional Development (CPD) scheme, and have access to specialist referral opinions on a local network or national basis.

The maximum workload for a full-time renal pathologist will depend on the case mix of the biopsies, but should not be greater than 1200 renal biopsies per year.

An evidence-based minimum workload is, as yet, not clearly defined. However, pathologists must bear in mind their diagnostic experience, ongoing CPD activity and EQA outcomes in assessing their ability to maintain an acceptable level of reporting expertise. When the renal workload is low (<100 biopsies/year), no more than two pathologists should report the biopsies, and when it is very low, passing the renal workload to a larger unit should be considered, as maintaining an acceptable level of expertise may be difficult if only small numbers of biopsies are reported.
If an on-call service is offered for out-of-hours urgent renal biopsies, this should be staffed only by pathologists that contribute to the routine renal pathology service or have been specially trained to report urgent renal biopsies. Urgent renal biopsy reports should be provided on the basis of paraffin sections produced on a rapid processing schedule, not frozen sections. Although frozen sections of donor kidneys are routinely requested in some transplant units, there is no clear evidence to support the use of frozen sections in the assessment of the suitability of kidneys for transplantation. The diagnosis of suspected tumours in organ donors is not part of an out-of-hours medical renal biopsy service; these specimens should be reported by a pathologist with the appropriate subspecialty expertise. For a suspected renal tumour, this is a urological pathologist.

If there is a pathological suspicion of post-transplant lymphoproliferative disease or lymphoma in a native renal biopsy, a haematopathologist should be consulted.

**Laboratory facilities**

The laboratory should be equipped to allow the recommended technical procedures to be performed safely, be enrolled with Clinical Pathology Accreditation (UK) Ltd (CPA) and participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique.

In addition to routine light microscopy, there must be access to immunohistology (immunofluorescence and/or immunoperoxidase techniques) and electron microscopy. Electron microscopy is especially important in biopsies from paediatric patients. Electron microscopy facilities may be offsite. Laboratories handling renal biopsies should participate in the National EQA Scheme for renal stains, and the UK National External Quality Assurance Scheme for immunocytochemistry.

The light microscopy, immunohistology and electron microscopy from a single case should all be reported by the same pathologist. Reporting each in isolation may result in serious misdiagnosis.

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 Specimen submission and dissection**

**Native renal biopsies**

Optimally these are divided whilst fresh. In circumstances when this is not possible (for example renal unit and laboratory in different hospitals), the specimen can be transported in suitable fixatives for light and electron microscopy, and buffer/transport medium if frozen tissue for immunofluorescence is required. Wherever practicable, a sample of cortex large enough to contain at least one glomerulus should be fixed for electron microscopy.
Renal transplant biopsies

These may be submitted entirely in formalin unless:

- the laboratory requires fresh tissue for C4d immunostaining, in which case a 2 mm fragment must be submitted fresh and rapidly frozen
- there is a suspicion of recurrent or de novo glomerular disease, in which case the procedure for native renal biopsies should be followed.

4 Sectioning and staining

Minimum light microscopy (LM) stains – native renal biopsies

Haematoxylin and eosin (H&E) with at least two levels, stains for basement membranes (periodic acid-Schiff and silver), stain for connective tissue and vessels (such as elastic van Gieson [EVG] or other trichrome), a stain for amyloid.

Renal transplant biopsies for graft dysfunction

At least three H&E levels and two PAS levels, silver and connective tissue stains [Level of evidence C].

Retention of unstained sections between levels is recommended for immunohistochemistry as indicated.

5 Further investigations

5.1 Electron microscopy (EM)

The need for EM should be assessed on the light microscopic appearances, but the majority of biopsies with suspected glomerular disease are investigated in this way [Level of evidence D]. If EM is required, this should be available within two weeks.

5.2 Immunohistology

Native renal biopsies

Immunohistology is used in all cases unless there is no suspicion of glomerular disease or the diagnosis is already evident beyond any doubt.

Minimum routine panel:

- IgG
- IgA
- IgM
- C3 or C9
- *kappa and lambda light chains for adult renal biopsies.

Other antibodies, including C1q, IgG4, amyloid A and myoglobin, should be available for use if indicated.

Two methods are in common use: immunofluorescence (IF) in frozen sections and immunoperoxidase (IP) in paraffin sections. For the detection of immune deposits, IF has the advantages of providing quantitative data (the strength of fluorescence correlates with
amount of antigen present), high sensitivity and less background artefact. IP has the
advantages of providing a permanent record without the requirement for photomicrographs,
and providing better detail of tissue architecture, enabling more precise localisation of
immune deposits.

* Note that the demonstration of light chain restriction in glomerular deposits is usually
possible by IF staining of frozen sections but is frequently unsuccessful using IP stains in
paraffin sections. A method of IF using pronase-digested paraffin sections may increase
the sensitivity of detection of light chains.5

Renal transplant biopsies

This depends on the clinical context of the biopsy. Immunohistology for C4d (antibody
mediated rejection)6 and SV40 T Ag (polyoma virus infection)7 should be available for all
biopsies if required [Level of evidence B].

Detection of peritubular C4d is less sensitive using IP methods on paraffin sections than IF
on frozen sections.2 The native renal biopsy immunohistology panel and electron microscopy
are used for transplant biopsies when there is a possibility of recurrent or de novo
glomerulonephritis.

Antibodies which should be available but which may be sourced by referral to specialist
laboratories:

- fibronectin
- type III collagen
- specific collagen type IV alpha chains
- specific amyloid proteins
- viruses known to infect the kidney.

5.3 Molecular investigations

These are not regarded as routine at present, but there needs to be a route for referral of
relevant cases to a specialist genetic service where there is evidence of an inherited renal
disease.

6 Report content

The pathology report should provide a summary of the clinical history, gross description of
the specimen and details of tissue sampling for IF, LM and EM. The microscopy report
should refer specifically to:

- glomeruli
- tubules
- interstitium
- vessels
- immunohistology
- electron microscopy

and should include a summary/comment at the end of the report.8

For inflammatory renal disease, in addition to the diagnosis, the report must include
indications of disease activity (grade) and chronicity (stage). For certain types of
glomerulonephritis, the use of internationally accepted classifications is recommended [Levels of evidence B–D].\textsuperscript{9–12}

If the adequacy of the biopsy is thought to cast significant doubt about the reliability of the interpretation, this should be stated explicitly.

For renal transplant biopsies, it is recommended that rejection is typed according to Banff 2007 criteria [Level of evidence C].\textsuperscript{2, 6, 13} Other aspects of the Banff classification, such as grades of chronic damage, should be used if local clinical staff find this helpful. However, the use of the Banff classification should not inhibit the pathologist from discussing how the biopsy result might be translated into clinical treatment, especially in the 'suspicious for acute rejection' category.

The timeliness of the verbal and written reports should be appropriate to the clinical urgency.

In addition to a written report, discussion of the case with a nephrologist or transplant surgeon is frequently of clinical value.

A SNOMED code is required for all biopsies.

7 Criteria for audit of the tissue pathway

Staffing and workload: annual review of numbers and types of specimens reported by each pathologist; EQA and RCPath CPD compliance.

Report content: audit of the completeness of recording each of the core data items in the histopathology report; use of internationally accepted classification systems for glomerular diseases and renal transplant biopsies.

Timeliness of report: audit of turnaround times for verbal and written LM and EM reports.

The key performance indicators (KPIs) as recommended by the RCPath (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.
8 References


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.

<table>
<thead>
<tr>
<th>AGREE standard</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope and purpose</strong></td>
<td></td>
</tr>
<tr>
<td>1. The overall objective(s) of the guideline is (are) specifically described</td>
<td>Foreword, 1</td>
</tr>
<tr>
<td>2. The clinical question(s) covered by the guidelines is (are) specifically described</td>
<td>1</td>
</tr>
<tr>
<td>3. The patients to whom the guideline is meant to apply are specifically described</td>
<td>1</td>
</tr>
<tr>
<td><strong>Stakeholder involvement</strong></td>
<td></td>
</tr>
<tr>
<td>4. The guideline development group includes individuals from all the relevant professional groups</td>
<td>Foreword</td>
</tr>
<tr>
<td>5. The patients’ views and preferences have been sought</td>
<td>Not applicable*</td>
</tr>
<tr>
<td>6. The target users of the guideline are clearly defined</td>
<td>1</td>
</tr>
<tr>
<td>7. The guideline has been piloted among target users</td>
<td>1</td>
</tr>
<tr>
<td><strong>Rigour of development</strong></td>
<td></td>
</tr>
<tr>
<td>8. Systematic methods were used to search for evidence</td>
<td>Foreword</td>
</tr>
<tr>
<td>9. The criteria for selecting the evidence are clearly described</td>
<td>Foreword</td>
</tr>
<tr>
<td>10. The methods used for formulating the recommendations are clearly described</td>
<td>Foreword</td>
</tr>
<tr>
<td>11. The health benefits, side effects and risks have been considered in formulating the recommendations</td>
<td>Foreword</td>
</tr>
<tr>
<td>12. There is an explicit link between the recommendations and the supporting evidence</td>
<td>Foreword, 3–6</td>
</tr>
<tr>
<td>13. The guideline has been externally reviewed by experts prior to its publication</td>
<td>Foreword</td>
</tr>
<tr>
<td>14. A procedure for updating the guideline is provided</td>
<td>Foreword</td>
</tr>
<tr>
<td><strong>Clarity of presentation</strong></td>
<td></td>
</tr>
<tr>
<td>15. The recommendations are specific and unambiguous</td>
<td>2–6</td>
</tr>
<tr>
<td>16. The different options for management of the condition are clearly presented</td>
<td>2–6</td>
</tr>
<tr>
<td>17. Key recommendations are easily identifiable</td>
<td>2–6</td>
</tr>
<tr>
<td>18. The guideline is supported with tools for application</td>
<td>2–6</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td></td>
</tr>
<tr>
<td>19. The potential organisational barriers in applying the recommendations have been discussed</td>
<td>Foreword</td>
</tr>
<tr>
<td>20. The potential cost implications of applying the recommendations have been considered</td>
<td>Foreword</td>
</tr>
<tr>
<td>21. The guideline presents key review criteria for monitoring and/audit purposes</td>
<td>7</td>
</tr>
<tr>
<td><strong>Editorial independence</strong></td>
<td></td>
</tr>
<tr>
<td>22. The guideline is editorially independent from the funding body</td>
<td>Foreword</td>
</tr>
<tr>
<td>23. Conflicts of interest of guideline development members have been recorded</td>
<td>Foreword</td>
</tr>
</tbody>
</table>

* 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)

<table>
<thead>
<tr>
<th>Grade (level) of evidence</th>
<th>Nature of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade A</strong></td>
<td>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 or 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.</td>
</tr>
<tr>
<td><strong>Grade B</strong></td>
<td>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 or Extrapolation evidence from studies described in A.</td>
</tr>
<tr>
<td><strong>Grade C</strong></td>
<td>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 or Extrapolation evidence from studies described in B.</td>
</tr>
<tr>
<td><strong>Grade D</strong></td>
<td>Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.</td>
</tr>
<tr>
<td><strong>Good practice point (GPP)</strong></td>
<td>Recommended best practice based on the clinical experience of the authors of the writing group</td>
</tr>
</tbody>
</table>