The Royal College of Pathologists
Pathology: the science behind the cure

Tissue pathways for native medical renal biopsies

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Comments	This document will replace the 3rd edition of the *Tissue pathway for native medical renal biopsies*, published in 2019. In accordance with the College's pre-publications policy, this document will be on the Royal College of Pathologists' website for consultation from 10 June to 8 July. Responses and authors' comments will be available to view on request. **Dr Brian Rous, Clinical Lead for Guideline Review**

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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. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may, therefore, be required to report a specimen in a way that maximises benefit to the patient.

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

The following stakeholders will be contacted to consult on this document:

- UK Renal Pathology External Quality Assessment (EQA) membership
- UK Renal Pathology Network circulation list
- UK Kidney Association.

The information used to develop this tissue pathway was obtained by undertaking a systematic search of the PubMed database and from previous RCPath recommendations and local guidelines in the UK and internationally. Key terms searched included ‘kidney biopsy’, ‘guideline’ and ‘reporting’. Dates searched were between January 2000 and March 2025. Published evidence was evaluated using modified SIGN guidance (see Appendix B). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence will be identified by College members via feedback received during consultation.

A formal revision cycle for all tissue pathways takes place on a 5-yearly basis. However, each year, the College will ask the author/s of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether 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 2 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 College website.

This pathway has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and it will be placed on the College website for consultation with the membership from 10 June to 8 July. All comments received from the Working Group and membership will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

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 Professional Guidelines team and are available on request. The authors have declared 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, nephritic 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 (LM), immunohistology (immunofluorescence [IF] or immunohistochemistry [IHC]) and electron microscopy (EM). If any of these elements are lacking, it may not be possible to reach a diagnosis.

The following recommendations are regarded as the minimum acceptable practice for medical renal biopsies. 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 a PubMed search and referenced where appropriate. The strength of supporting evidence for specific elements is indicated using modified SIGN guidance.

1.1 Target users and health benefits of this tissue pathway

The target primary users of the tissue pathway are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are those clinicians who request and carry out renal medical biopsies (nephrologists and transplant surgeons), and those who commission renal services.

1.2 Generic issues relating to staffing, workload and facilities

The following recommendations should be met for a general level of acceptable practice.

- 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 RCPath.
- Optimally, 2 or more pathologists in a unit should be competent in the reporting of renal biopsies to provide cover for periods of leave. It is recognised that in some smaller units only 1 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 audits
  - participate in the RCPath's continuing professional development (CPD) scheme
  - participate in the national UK Renal Pathology EQA scheme
  - have access to specialist referral opinions on a regional 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 1,200 renal biopsies per year. An evidence-based minimum workload is 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 (<200 biopsies/year), no more than 2 pathologists should be involved in providing the service. When it is very low (<100 biopsies/year), 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.
- The laboratories handling renal biopsies should:
  - be equipped to allow the recommended technical procedures to be performed safely and in a timely fashion

  - be accredited by the United Kingdom Accreditation Service (UKAS) or equivalent.

- Workload data and turnaround times should be recorded and monitored in a format that facilitates determination of the resources involved and any issues with the lab services that might hinder a high-quality service being provided.
- Reports should be held on an electronic database that has facilities to search and retrieve specific data items and that is indexed according to SNOMED T, M, D and P codes or SNOMED CT.

2 Laboratory protocols

2.1 Laboratory facilities

- In addition to routine LM, there must be access to IF and/or immunoperoxidase (IP) techniques, see below, and EM. Some immunohistology services and EM facilities may be off-site.
- Laboratories handling renal biopsies should participate in the UK National EQA scheme for renal stains and the UK National EQA scheme for immunohistology.
- Digital scanning and reporting is appropriate if the pathologist is trained in digital reporting of renal biopsies and the platform used has been validated for this purpose.[1] It should be recognised that digital pathology has weaknesses in the reporting of medical renal biopsies, namely the lack of z-plane can make recognition of fibrinoid necrosis and membrane spikes difficult; lack of light polarisation in the scanner can be another drawback that may require glass slides to be viewed alongside digital images.

2.2 Specimen submission and dissection

- Native renal biopsies should be examined under a dissecting microscope or equivalent and divided while fresh, taking care not to stretch or crush the sample or to let it dry out. Wherever practicable, a sample of cortex large enough to contain at least 1 glomerulus (and preferably a few) should be taken for each of IF and EM.
- Once divided, samples must be rapidly placed in appropriate fixatives for LM and EM and appropriate transport medium for IF, unless the sample is frozen at point of biopsy. A variety of fixatives can be used for the LM sample, with neutral buffered formalin (NBF) being the most common. For the EM sample, glutaraldehyde- or paraformaldehyde-based fixatives afford best preservation for ultrastructural

examination. NBF is sometimes used as a transport medium for EM; it is advised to transfer the sample as quickly as possible after the biopsy is taken from NBF to glutaraldehyde- or paraformaldehyde-based fixatives, as ultrastructural morphology is altered by the methanol present in NBF formulations.

2.3 Sectioning and staining

- Sections from the paraffin block for LM should be cut at 1–3 µm thickness.
- Sections from the frozen block for IF should be cut at 3–4 µm thickness. At least 7 sections are cut for the standard IF panel (see below); it is usual practice to cut some spare sections at the same time to retain for any repeat or additional stains needed.
- Minimum paraffin block LM stains for native renal biopsies are haematoxylin and eosin (H&E), stains for basement membranes (periodic acid-Schiff and methenamine silver), stain for connective tissue and vessels (such as elastic van Gieson or trichrome) and a stain for amyloid (such as Congo red).
- A minimum number of 6 levels is recommended from the paraffin block for LM, to include at least 2 H&E. The optimum number of levels and stains that should be examined depends in part on the diagnoses being considered; it is higher for conditions characterised by focal lesions (such as the distinction of minimal change nephropathy from focal segmental glomerulosclerosis). When designing the local sectioning protocol, consideration should be given to sectioning and retaining spare sections between the stained sections, as going back to the block to cut additional sections later may result in loss of tissue.

[Level of evidence – C. A specified set of special stains and a minimum number of levels is needed to adequately capture all relevant diagnostic features.]

2.4 Immunohistology

The use of immunohistology is required in all cases. The minimum routine panel for the investigation of glomerular disease is IgG, IgA, IgM, C3 and C1q, with the addition of kappa and lambda light chains for adult renal biopsies. Antibody testing can be performed in house or outsourced to another accredited laboratory. However, to meet acceptable turnaround times, in-house access to the minimal panel of testing is recommended.

Other additional antibodies are not infrequently required in diagnostic renal pathology, and the list evolves in response to new scientific evidence. These additional antibodies are

listed in Appendix A. If reaching the correct diagnosis impacts clinical management and is not possible without an antibody, it is listed as ‘essential’, even though in some cases the diagnosis is very rare. Access to some of these antibodies is currently limited in the UK; this evidence-based best practice guidance should enable their implementation. Some antibodies afford a more precise diagnosis and additional useful information, but their impact on patient management is not yet firmly established. These are listed in Appendix A as ‘desirable’.

[Level of evidence – C. Access to a minimal IHC panel is needed for diagnosis of native renal disease.]

Immunohistological methods for immunoglobulin (Ig) and complement staining include the following.

- IF on frozen tissue (IF-F) is the gold standard for Igs and complement staining, as it has the highest specificity and sensitivity and enables quantification of positivity. This can be performed manually or on an auto-stainer.
- IP on paraffin (IP-P) and IF on paraffin (IF-P) were first developed as salvage techniques for cases where there was no frozen tissue or no glomeruli in the frozen tissue. The use of IP-P has become widespread as the primary method for renal immunohistology in the UK, despite lower sensitivity and specificity than IF-F.[2–6] Like IP-P, IF-P is less sensitive than IF-F in several situations, e.g. for C3 staining. IF-P suffers less than IP-P from background staining, although occasionally interpretation may be limited by serum staining.[7,8] In a few indications, IF-P is actually more sensitive than IF-F or may even be required to reach a diagnosis, i.e. diagnoses that require unmasking of light chains, such as light chain proximal tubulopathy, and diseases with ‘masked’ Igs.[8,9]
- If IP-P alone is employed, it will result in occasional diagnostic errors. IP-P is ineffective for the demonstration of anti-GBM disease and light chain restriction; it also is frequently difficult to report as a result of high background staining of plasma and matrix proteins. As certain new diagnostic entities have been discovered and characterised, further limitations of IP-P have become apparent, for example C3 glomerulopathies (that rely on differential quantitative expression between Ig and C3 for diagnosis); ‘masked’ Ig-related diseases (where diagnosis depends on demonstration of different staining patterns comparing IF-F to IF/IP-P); and heavy chain-only paraprotein-related diseases that require IgG subtype staining.[10]

Following these developments, best practice for pathology laboratories receiving medical renal biopsies is defined as follows.

- IF-F is the gold standard. It should not be routinely replaced by either IP-P or IF-P.
- Laboratories should provide or have access to an IF service for fresh tissue (if needed using transport medium).
- Laboratories should provide or have access to an IF service for paraffin samples (IF-P).
- Indications for performing IF-P are defined in the literature and include:
  - frozen tissue not available or lacks glomeruli
  - suspected light chain proximal tubulopathy/podocytopathy and/or crystalglobulin-induced nephropathy
  - membranoproliferative glomerulonephritis with negative staining for Ig and complement by IF-F (e.g. cryoglobulinemic GN to unmask light and/or heavy chains)
  - C3 glomerulonephritis, in particular if associated with monoclonal gammopathy or autoimmune disease (to exclude masked monoclonal Igs)
  - membranous nephropathy with negative or weak staining for IgG
  - fibrillary GN with apparent monotypic IgG deposits by IF-F.[11]

[Level of evidence – C. IF-F is the most accurate technique for Ig and complement staining of native renal biopsies; IF-P is needed for diagnosis of rare diseases with masked light and/or heavy Ig chains.]

- Where IP-P is used as a substitute to IF-F, the lab should validate its IP-P technique against IF-F on frozen. This can be done, for example, by staining with IP-P for a full Ig and complement panel on spare paraffin sections from a range of glomerular pathologies with defined IF-F patterns. The pathologist should advise referring clinicians on sensitivity, specificity and limitations of their local IP-P protocol, so that the clinical team can make informed decisions on sample taking, test ordering and report interpretation, according to patient presentation.

2.5 Electron microscopy

- The need for EM should be assessed on the basis of LM appearances. However, the majority of native renal biopsies with suspected glomerular disease are investigated in this way unless a definitive diagnosis is made on LM. If EM is required, this should be available within 2 weeks.

[Level of evidence – D. Access to EM is essential for some native kidney diagnoses.]

- If EM technical services are being provided remotely by a specialist unit, then the semithin sections from the EM block and the digital EM images should be provided to the pathologist responsible for reporting the renal biopsy. Diagnostically important lesions might be visible by LM in the semithin sections from the EM block but absent from the sections of the paraffin-embedded tissue block for LM.

3 The renal biopsy report

- The LM, immunohistology and EM from a single case should ideally all be reported by the same pathologist. Reporting each in isolation may result in a serious misdiagnosis.
- The pathology report should provide a summary of the clinical history, gross description of the specimen and details of tissue sampling for LM, IF and EM, and it should include a summary/comment at the end.[11] If the clinical information provided is clearly deficient, then the requesting clinician should be contacted or the diagnostic limitations resulting from the lack of clinical information made clear in the pathology report. The microscopy report should refer specifically to:
  - glomeruli
  - tubules
  - interstitium
  - vessels.
  - immunohistology
  - EM.
- The immunohistology report should state the technique used, the number of glomeruli examined (for IF-F) and the location, abundance, intensity and appearance (granular versus linear or smudgy) of any positivity.

- The EM report should state the number of glomeruli examined and comment as a minimum on the presence of electron dense deposits (appearance, location and extent), features of the glomerular basement membranes and podocyte foot process effacement. Where indicated, examination of other kidney structures (tubules, peritubular capillaries, interstitium and blood vessels) is carried out and reported.
- Terminology and definitions used in the report should follow internationally agreed standards.[12]
- For inflammatory renal disease, in addition to the diagnosis, the report must include indications of disease activity (grade) and chronicity (stage).[13] For many types of kidney disease, international consensus classifications have been developed and published.[14,15] The use of widely accepted classifications is recommended. These include the recent revisions of the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification of lupus nephritis[16] and of the Oxford classification of IgA nephropathy.[17]

[Levels of evidence – B and D. Classification systems are recommended when reporting various native kidney diseases, with variable levels of evidence depending on the classification and the disease.]

- If the adequacy of the biopsy is thought to cast significant doubt on the reliability of the interpretation, this should be stated explicitly.
- In addition to a written report, discussion of the case with a nephrologist is frequently of clinical value. This will often allow a more specific diagnosis than might have been apparent on the biopsy alone, and it may direct supplementary studies that may be required on the biopsy. It is recommended that all renal biopsies are discussed within a multidisciplinary meeting.
- The timeliness of the verbal and written reports should be appropriate to the clinical urgency.

4 On-call renal biopsy services

- If an on-call service is offered for out-of-hours urgent renal biopsies, this should be staffed only by pathologists who 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.
- Remote reporting of digital slides is appropriate for urgent specimens if the pathologist is trained in digital reporting of renal biopsies and the platform used has been validated for this purpose.

5 Criteria for audit

The following are recommended by the RCPath as key performance indicators.[18]

- Histopathology cases are reported, confirmed and authorised within 7 and 10 calendar days of the procedure.
  - Standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.
- With agreement of service users, variance from the standard key performance indicators for renal biopsies is appropriate. In many renal cases, issuing a provisional report – before all IHC and EM is available and before a multidisciplinary team discussion – may result in more clinically ineffective reports (that may lead to inappropriate therapy). With service user agreement, it is recommended that 80% of cases should be reported within 2 weeks.
  - Standard: 80% of EM specimens should be reported within 2 weeks of requesting EM sections and images.

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Appendix A Additional antibodies for native kidney biopsies

Antibody	IF-F, IF-P or IP-P	Level of requirement	Guideline and/or scientific justification
IgG, IgA, IgM, C3, C1q	IF, IF-P, IP	Essential	IF-F is gold standard; IF-P and IP are less sensitive and specific and require individual lab validation against IF gold standard and notice of limitation in diagnostic report
Kappa/lambda (IF-F)	IF-F	Essential	IP may be acceptable in some cases, if validated locally against IF gold standard for that indication
Kappa/lambda (IF-P)	IF-P	Essential	Essential to diagnose 'masked' light chain restriction
IgG1, IgG2, IgG3, IgG4	IF	Desirable	17;18
Heavy and light chain	?	Desirable	19
IgG4	IP	Essential	
C5b-9, C9 and other complement-related proteins (C3dg, FHR5, etc.)	IP	Requirement remains to be defined	
C4d, SV40	IP	Essential	
Immune and myeloid cell typing (CD3, CD20, CD68/pgm1, MPO, Ret40F, CD61)	IP	Essential	
Amyloid A	IP	Essential	
Non-amyloid A-specific amyloid proteins, e.g. LECT2, fibronogen A alpha, cystatin, TTR	IP	Refer to the National Amyloidosis Centre for mass spectrometry and/or specialised antibodies	
Myoglobin	IP	Essential	
Haemoglobin	IP	Desirable	20
Cytomegalovirus	IP	Essential	
Epstein–Barr virus	ISH	Essential	
Adenovirus	IP	Essential	
PLA2R	IP/IF	Essential	

Recommended PLA2R-negative membranous antigen panel (Nell-1, THSD7A, exostosin 1/2, PCDH(protocadherin)-7, NCAM/CD56, Semaphorin 3B, HTRA1	IP/IF	Desirable	21
DNAJB9	IP	Essential	22
Nephrin	?	Requirement remains to be defined	
Uromodulin	IP	Desirable	
Collagen III	IP	Desirable	
Fibronectin	IP	Essential	
Collagen type IV alpha chains 3,4,5		Not required	Alternative: Genetic testing

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	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 population 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 population.
Grade B	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 population or Extrapolation evidence from studies described in A.
Grade C	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 population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix C AGREE II guideline monitoring sheet

The tissue pathways of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. 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	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
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	Foreword
6 The target users of the guideline are clearly defined	Introduction
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 and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–4
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	2–4
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 interests of guideline development group members have been recorded and addressed	Foreword