



Tissue pathways for renal transplant biopsies

January 2021

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Unique document number	G186
Document name	Tissue pathways for renal transplant biopsies
Version number	1
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Date active	January 2021
Date for full review	January 2026
Comments	In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for a two-week consultation from 10 November to 24 November 2020. Responses and authors' comments are available to view on publication of the final document. Dr Brian Rous Clinical Lead for Guideline Review

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Registered charity in England and Wales, no. 261035
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NICE has accredited the process used by the Royal College of Pathologists to produce its Tissue Pathways guidance. Accreditation is valid for five years from 25 July 2017. 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. 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 were contacted to consult on this document:

- UK National Renal Pathology EQA membership
- UK National Renal Transplant EQA membership
- British Transplantation Society
- The Renal Association.

The information used to develop this tissue pathway was collected from electronic searches of the medical literature (PubMed database between 1 January 1997 and 31 December 2019), previous recommendations of the RCPATH and local guidelines in the UK. Key terms used for electronic searches included 'renal transplant biopsy' and any publications referring to clinical practice guidelines were included. Published evidence was evaluated using modified SIGN guidance (see Appendix C). 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. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in Appendix D.

No major organisational changes have been identified that would hinder the implementation of the tissue pathway. One area of resource implication would be the provision of an on-call weekend service (see section 4).

A formal revision cycle for all tissue pathways takes place on a five-year 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 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 changes will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the College website. All changes will be documented in the data control section of the relevant pathway.

This tissue pathway has been reviewed by the Clinical Effectiveness team, Working Group on Cancer Services and Lay Governance Group. It was placed on the College website for consultation with the membership from 10 November to 24 November 2020. All comments received from the Working Group and membership were 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 Clinical Effectiveness team and are available on request. Dr Roufousse holds consultancy agreements with Achillion pharmaceuticals and Rigol pharmaceuticals who are running clinical trials

into therapeutics for patients with kidney transplants. Dr Roufousse is also a member of the Banff Foundation for Allograft Pathology Scientific Programme Committee. Dr Roufousse gives her assurances that these conflicts of interest have not influenced the content of this dataset. All other authors have no conflicts of interest.

1 Introduction

Transplant renal biopsies provide essential diagnostic and prognostic information on the renal allograft, guiding management of patients with a renal transplant. There are three main types of renal transplant biopsies depending on the clinical circumstances: implantation biopsies, indication biopsies and surveillance biopsies.

Implantation biopsies ('time zero' biopsies, pre- or post-implantation) are performed at the time of transplantation surgery. These set a 'baseline' of chronic damage in the donor kidney that assists in the interpretation of changes in post-transplantation biopsies. In some instances, donor kidney biopsies are used to inform the suitability of the kidney for transplantation.

Indication biopsies are performed to investigate acute or chronic graft dysfunction. The Renal Association and Kidney Disease Improving Global Outcomes (KDIGO) guidelines state that a renal transplant biopsy is indicated:

- if there is a persistent unexplained elevation of creatinine or failure to return to baseline after an episode of biopsy proven acute rejection (BPAR)
- every seven to ten days during delayed graft function
- if expected renal function is not achieved within four to eight weeks
- if sustained new onset proteinuria develops (protein:creatinine ratio >50 mg/mmol or albumin:creatinine ratio >35 mg/mmol)^{1,2}
- if there is unexplained proteinuria ≥ 3.0 g/g creatinine or ≥ 3.0 g per 24 hours.²

[Levels of evidence – C and D.]

Surveillance (protocol) biopsies are performed at pre-determined time points post-transplantation in patients with no indications for biopsy to determine response to treatment or to detect potential subclinical pathology. There is little evidence (using current immunosuppression regimens) that treatment of subclinical acute rejection improves outcomes.³ Owing to the lack of consensus opinion on the benefits of implantation and surveillance biopsies, these are not uniformly performed across centres in the UK.

A renal transplant biopsy is an invasive procedure associated with a risk of serious and potentially life-threatening complications. The decision of whether to perform a renal transplant biopsy is based on a careful risk–benefit assessment. Once the decision to perform a transplant 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 (in particular anti-HLA serology) with data from light microscopy, immunohistology (e.g. C4d and BK) and, in some cases, electron microscopy (EM). It may not be possible to reach a diagnosis if any one of these elements is lacking.

The following recommendations are regarded as the minimum acceptable practice for transplant renal biopsies and this tissue pathway is a reflection of custom and general practice in consultation with experienced renal transplant histopathologists. Reference will also be made to the Banff Classification for Allograft Pathology, which has been endorsed internationally by the transplant pathology community since its publication in 1991.

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 clinicians who request and carry out renal transplant 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.
- all pathologists reporting renal transplant biopsies should:
 - participate in audits
 - participate in the RCPATH's continuing professional development (CPD) scheme
 - participate in national UK renal pathology external quality assessment (EQA) scheme(s)
 - have access to specialist referral opinions on a regional network or national basis
- the laboratories handling renal transplant biopsies should:
 - be equipped to allow the recommended technical procedures to be performed safely
 - be accredited by UK Accreditation Service (UKAS) or equivalent
- workload data should be recorded and monitored in a format that facilitates determination of the resources involved
- reports should be held on an electronic database that has facilities to search and retrieve specific data items, and is indexed according to SNOMED T, M, D and P codes or SNOMED-CT.

Optimally, two or more pathologists in a unit should be competent in the reporting of renal transplant biopsies to provide cover for periods of leave. Often the pathologists reporting native medical renal biopsies will also report transplant renal biopsies. 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.

In previous guidelines for combined native and transplant renal biopsies, the maximum workload for a full-time renal pathologist was dependent on the case mix of the biopsies, but should not be greater than 1,200 biopsies per year. An evidence-based minimum workload is not clearly defined. 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. No more than two pathologists should report transplant biopsies when the workload is low (<100 biopsies/year). When the workload is very low (<50 biopsies), it may be necessary to pass the renal transplant biopsy workload to a larger unit since maintaining an acceptable level of expertise may be difficult.

2 Laboratory protocols

2.1 Laboratory facilities

In addition to routine light microscopy (LM), there must be access to immunohistology (immunofluorescence [IF] and/or immunoperoxidase [IP] techniques) and EM. EM facilities may be off-site.

Laboratories handling renal transplant biopsies should participate in the UK national EQA scheme for renal stains and the UK national EQA scheme for immunocytochemistry.

2.2 Specimen submission and dissection

Ideally, two cores of renal tissue should be obtained at transplant biopsy since this will increase the sensitivity of the investigation.⁴

[Level of evidence – C.]

In some circumstances (see sections 2.4 and 2.5), tissue may need to be divided for EM and IF. If available, a dissecting microscope is helpful for division of the biopsy while fresh. If the renal unit and laboratory are in different hospitals, the divided specimens should be transported in suitable fixatives for LM and EM and in buffer/transport medium for IF. For EM, a sample of cortex large enough to contain at least one glomerulus and at least ten peritubular capillaries should be fixed wherever practical.

2.2.1 Implantation biopsies

A biopsy may be taken to assess organ quality at implantation, in particular the degree of chronic damage at baseline. If taken before implantation, this may be used to inform the decision to implant.

Implantation biopsies may be wedge, punch or core biopsies. For wedge and punch biopsies, some centres perform frozen sections. Samples can also be divided to ensure rapid fixation and processing as per urgent core biopsy. Banff guidelines for the processing of implantation biopsies found frozen and formalin-fixed, paraffin-embedded wedge biopsies to be comparable.⁵ In situations where a biopsy (frozen or otherwise) is taken for a suspected renal lesion/tumour within the donor, appropriate urological tissue pathways should be consulted to guide practice. The specimen handling, dissection and sectioning techniques outlined in this document are not appropriate for this purpose.

2.2.2 Explanted transplants

Transplants may be explanted when there is a clinical indication (e.g. recurrent infection, pain or to avoid immunogenicity of the graft after its failure). In such cases, the indication for nephrectomy should be documented to aid accurate sampling. Immediately after removal, the kidney should be placed in formalin. The kidney should be bisected along the hilum after receipt in the laboratory and allowed to fix in formalin for 24 hours before sampling to ensure adequate fixation. The kidney should be measured from pole to pole, weighed and a short macroscopic description documented. The minimum sampling of a nephrectomy specimen should include:

- one block of hilar vessels and ureter if present
- one block of lobar and arcuate vessels
- one block of urothelial mucosa
- two blocks of renal parenchyma to include the cortex and medulla.

Any other areas of abnormality/regions of interest should also be sampled. The kidney should be specifically checked for focal lesions and if any are identified, reference should be made to the appropriate urological tumour pathways and datasets.

2.3 Staining

Minimum LM stains for transplant renal biopsies are:

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

Note that retention of unstained sections between levels is recommended for immunohistochemistry as indicated.

The Banff recommendation for slide preparation is seven slides containing multiple sequential sections with three stained for H&E, three for PAS or silver and one with a connective tissue and vessel stain. These guidelines were first introduced in the Banff Classification for Allograft Pathology published in 1997. They were further supported by a UK study that showed there is likely to be significant under diagnosis and under-grading of acute rejection if this protocol is not followed.^{6,7}

[Level of evidence – C.]

In cases where the results of special stains could impact patient management, they should be available and communicated to a nephrologist the next working day after the biopsy was received by the laboratory at the latest.

2.4 Immunohistology

The Renal Association guidelines recommend that routine C4d and polyomavirus (SV40 antigen) staining should be performed on all transplant biopsies.¹ A positive C4d stain displays strong linear circumferential positivity in peritubular capillaries, either by IF or IP.^{8,9} In cases where the immunohistochemistry results could affect patient management, they should be available and communicated to a nephrologist the next working day after the biopsy was received by the laboratory at the latest.

[Level of evidence – C.]

If there is suspicion of glomerular disease, either on the basis of clinical features (e.g. proteinuria or a history of glomerular disease leading to end-stage renal failure) or light microscopic features, the following panel should be performed: IgG, IgA, IgM, C3 and C1q, and kappa and lambda light chains for adult renal biopsies. This panel is used for native kidney diseases and readers are referred to the *Tissue pathway for native medical renal biopsies* for more details on the immunohistological method.¹⁰

2.5 Electron microscopy

According to the Banff 2019 update, tissue samples should be taken in all cases if possible, and fixed and embedded as a resin block. As a minimum, samples should be taken if there is any suspicion of glomerular disease.¹¹

The need to perform ultrastructural examination should be assessed on the basis of clinical and light microscopic features. As for native biopsies, EM should be performed to assist in the diagnosis of glomerular disease, including early recurrent glomerular disease. The current Banff guidelines also highlight the diagnostic value of EM in establishing evidence of antibody-

mediated rejection (ABMR). They recommend that EM should be performed in cases in which patients are at risk for ABMR, all sensitised individuals, in patients with documented donor-specific antibodies (DSA) any time post-transplantation and/or who have had a prior biopsy showing features of ABMR (C4d staining, glomerulitis and/or peritubular capillaritis).¹¹ EM can also be useful in for-cause biopsies ≥ 3 months post-transplantation and in all biopsies performed ≥ 6 months post-transplantation, to determine if early changes of transplant glomerulopathy are present and to prompt testing for DSA. Given the limited treatment options for chronic ABMR, there may be reduced clinical impetus to perform EM in these circumstances. Restricted access to EM facilities may limit compliance with these Banff recommendations.

If the results of EM are crucial for patient management, the report should be available within two weeks. Semi-thin sections should be examined from the EM block. Diagnostically important LM lesions that are absent in paraffin sections might be present in the EM block. If the EM service is provided remotely, semi-thin and EM images (usually digital) should be provided to the pathologist responsible for reporting the renal biopsy.

3 The renal transplant biopsy report

Prior to the development of the Banff Classification for Allograft Pathology, there was no consensus for reporting of renal transplant biopsies. It is recognised that not all recommendations and scoring systems in the Banff classification are grounded in firm evidence. According to a UK-wide survey undertaken with members of the renal transplant EQA and presented at the annual meeting of the British Division of the International Academy of Pathology (Nottingham 2016), 66% of UK renal pathologists use the Banff Classification for Allograft Pathology (either in the form of Banff scores or Banff categories) during the routine reporting of transplant biopsies. At this same meeting, 78% of UK renal pathologists supported the development of the RCPATH guideline for transplant pathology.¹² Recording the severity of BPAR using Banff criteria is one of the Audit Measures for the Post-operative Care of the Kidney Transplant Recipient.¹ Therefore, this guidance will refer to the Banff Classification for Allograft Pathology without mandating its use.

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 serious misdiagnosis.

The specimen should fulfil adequacy criteria to ensure an accurate diagnosis. Minimal sampling is seven glomeruli and one artery, whereas adequacy is defined by at least ten glomeruli and a minimum of two arteries.⁶ The Renal Association guidelines state that ideally two cores containing medullary tissue should be examined.¹ While a cortex sample is needed to diagnose rejection, a sample of medulla is important for early BK virus nephropathy. While it is important that the biopsy report contains specific information on the adequacy of a sample, and a comment on how this might affect the final diagnosis (e.g. lack of sufficient cortex or arteries may lead to under-diagnosis of rejection), in some scenarios a technically inadequate biopsy may nevertheless contain diagnostic information. If this is the case, this information should be communicated in the report.

3.1 The pathology report

The pathology report should provide a summary of the clinical history, gross description of the specimen, details of tissue sampling for IF, LM and EM, and a summary/comment at the end. If the clinical information provided is clearly deficient, the requesting clinician should be contacted, or the diagnostic limitations resulting from lack of clinical information made clear in the pathology report. The report should specify the type of transplant biopsy (usually indication, with some centres also practicing implantation or surveillance/protocol biopsies) and state how many samples of cortex and medulla are included. The microscopy report should refer specifically to:

- glomeruli
- tubules
- interstitium
- vessels, including separate descriptions of peritubular capillaries, arterioles and arteries
- immunohistology
- EM.

A diagnosis of rejection (T-cell-mediated, antibody-mediated or both) and its qualification as active or chronic active requires assessment of the degree and extent of inflammation and scarring in a range of microanatomical compartments. As a minimum, the report should record the presence of inflammation within glomeruli, tubules, interstitium (scarred and non-scarred), peritubular capillaries and arteries; and the presence of features of chronicity such as: double contours along glomerular capillary walls, tubular atrophy, interstitial fibrosis and arterial intimal thickening.¹³ The use of an internationally accepted and up-to-date classification such as the Banff Classification for Allograft Pathology is recommended. The Banff classification relies on a self-organising group creating consensus opinion. However, it should be noted that not all of the opinions reached by consensus are based on strong evidence.¹⁴ There is variable intra- and inter-observer reproducibility within Banff lesion scores, with some being good but many being moderate or poor. Banff diagnostic categories and Banff lesion scores are summarised in a reference guide to the Banff classification.¹⁵

[Levels of evidence – B–D.]

Appendix A details a transplant renal biopsy dataset, which indicates the minimum level of information that should be available in the clinical report. Appendix B details a comprehensive list of rejection and non-rejection diagnoses. A selection of at least one item from each list will cover the vast majority of renal transplant biopsy findings. The list was designed for use in a national renal transplant biopsy EQA, but could form the basis of a coding system for future central registry practices. The use of the dataset and list of diagnoses is not mandated at this stage.

3.2 Implantation biopsies

Several scoring systems (e.g. Remuzzi/Karpinski) exist for implantation biopsies, but there is a standard report endorsed by Banff.⁵ There is no evidence-based consensus on whether implantation biopsies should be used in decisions on organ use. Reliance on donor kidney biopsies may be associated with an inappropriately high discard rate of potentially transplantable kidneys.¹⁶ Implantation biopsies can be useful as a record of changes that are donor related (e.g. arteriolar hyalinosis related to donor hypertension/diabetes and not chronic calcineurin inhibitor toxicity).

3.3 Verbal reports

In addition to a written report, discussion of the case with a nephrologist is frequently of clinical value. Discussion often provides a more specific diagnosis and may direct supplementary studies that may be required on the biopsy sample. If a verbal report on the biopsy findings is issued to the clinician, this should be recorded and authorised as a preliminary report. The timeliness of the verbal and written reports should be appropriate to the clinical urgency.

4 On-call renal transplant biopsy services

It is standard practice in renal transplant services to provide same day rapid processing for urgent transplant biopsies with a written report, provided the sample has arrived in the

laboratory in time for this to be achieved within normal working hours. It is also recommended practice to provide an out-of-hours on-call service for transplant biopsies over the weekend and bank holidays. NICE guidelines state that adults who have a suspected acute rejection episode should have a transplant kidney biopsy carried out and reported on within 24 hours to inform treatment decisions, which should be started as soon as possible.¹⁷ HLA incompatible transplants should have access to emergency renal histopathology six days a week. (We recognise that the ideal is seven days a week.¹⁸) It is acknowledged that this service is not currently available in all UK centres. Moreover, such UK-wide implementation would have significant resource and financial implications. The purpose of this tissue pathway is to provide the user with the current best evidence and promote best practice where possible. For renal transplant indication biopsies, urgent biopsy reports should be based on paraffin sections produced on a rapid processing schedule rather than frozen sections.

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.

4.1 Staffing

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.

4.2 Remote reporting

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 (see www.rcpath.org/discover-pathology/public-affairs/digital-pathology.html).

5 Criteria for audit

As recommended by the RCPATH as key performance indicators (see Key Performance Indicators – Proposals for implementation, July 2013, www.rcpath.org/profession/guidelines/kpis-for-laboratory-services.html):

- histopathology cases should be reported, confirmed and authorised within seven and ten calendar days of the procedure.
 - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.
 - standard: 80% of EM specimens should be reported within two weeks of request.

With the agreement of service users, variance from the standard key performance indicators for renal transplant biopsies is appropriate. In certain circumstances, issuing a provisional report before all results are available is clinically ineffective and may lead to inappropriate therapy.

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Appendix A Minimal dataset for reporting of renal transplant biopsies

Surname: Forenames: Date of birth: Sex:
Hospital: Hospital No: NHS No:
Date of surgery: Date of report authorisation: Report No:
Date of receipt: Pathologist: Clinician:

SPECIMEN DETAILS

Biopsy type:

- Time zero biopsy (pre-implantation) Time zero (post-implantation)
 Indication biopsy (graft dysfunction) Surveillance or protocol biopsy
 Alternative indication, e.g. for DSA or post-treatment Biopsy type unknown

Tissue received: Fixative for LM Sample for IF (fresh/transport medium) Fixative for EM Other:

Light microscopy sample type:

- Core(s), number.....(length, mm)...../...../...../.....
 Punch, number.....(length, mm)/.....
 Wedge, number(length, mm)/.....

LIGHT MICROSCOPY

- Cortex: Present Absent
Medulla: Present Absent

Glomeruli:

Number of glomeruli.....Number of sclerosed glomeruli.....

- Glomerulitis (Banff g): Present Absent N/A
Capillary wall double contours (Banff cg): Present Absent N/A

Glomerular pathology, other (please describe)

Tubules and interstitium:

Tubular atrophy/interstitial fibrosis (nearest 10%) (Banff ct/ci):

- Peritubular capillaritis (Banff ptc): Present Absent N/A
Tubulitis in tubules that are not severely atrophic (Banff t): Present Absent N/A
Interstitial inflammation (non-scarred cortex, Banff i): Present Absent N/A
Interstitial inflammation (scarred cortex, Banff i-IFTA): Present Absent N/A

Tubulointerstitial pathology – other (please describe)

Vessels:

Number of arteries

- Arterial intimal thickening (Banff cv): Present Absent N/A
Vasculitis (Banff v): Present Absent N/A
Chronic allograft arteriopathy (*new onset intimal fibrosis, excluding other causes*): Present Absent N/A
Arteriolar hyalinosis (Banff ah): Present Absent N/A

Vascular pathology – other (please describe)

IMMUNOHISTOCHEMISTRY

- C4d: Positive Negative Equivocal/unknown Not performed
SV40: Positive Negative Equivocal/unknown Not performed

Immunostains – other (please describe)

ELECTRON MICROSCOPY Performed Not performed

- Glomerular capillary wall double contours (Banff cg1a): Present Absent
Peritubular capillary basement membrane multilayering (PTCML): Present Absent

FINAL DIAGNOSI(E)S/COMMENT: *Provide comment/narrative on diagnostic finding(s):.....*

Specify at least 1 diagnosis from rejection list and at least 1 diagnosis from non-rejection list (Appendix B)

Rejection diagnosi(e)s..... Non-rejection diagnosi(e)s.....

Signature: Date: ... / ... / ... SNOMED codes:

Appendix B Minimal dataset for reporting of renal transplant biopsies in list format

Element name	Values	Implementation notes
Biopsy type	Single selection value list: <ul style="list-style-type: none"> • Time zero biopsy (pre-implantation) • Time zero (post-implantation) • Indication biopsy (graft dysfunction) • Surveillance or protocol biopsy • Alternative indication (e.g. for DSA or post-treatment) • Biopsy type unknown 	
Tissue received	Single selection value list: <ul style="list-style-type: none"> • Fixative for LM • Sample for IF (fresh/transport medium) • Fixative for EM • Other 	If other, please state.
Light microscopy sample type	Multiple selection value list: <ul style="list-style-type: none"> • Core(s) • Punch • Wedge 	For each selection, please state the number and the length in mm.
Cortex	Single selection value list: <ul style="list-style-type: none"> • Present • Absent 	
Medulla	Single selection value list: <ul style="list-style-type: none"> • Present • Absent 	
Number of glomeruli	Integer	
Number of sclerosed glomeruli	Integer	
Glomerulitis (Banff g)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Capillary wall double contours (Banff cg)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	

Glomerular pathology, other	Free text	
Tubular atrophy/interstitial fibrosis (nearest 10%) (Banff ct/ci)	Free text	
Peritubular capillaritis (Banff ptc)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Tubulitis in tubules that are not severely atrophic (Banff t)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Interstitial inflammation (non-scarred cortex, Banff i)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Interstitial inflammation (scarred cortex, Banff i-IFTA)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Tubulointerstitial pathology – other	Free text	
Number of arteries	Integer	
Arterial intimal thickening (Banff cv)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Vasculitis (Banff v)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Chronic allograft arteriopathy (new onset intimal fibrosis, excluding other causes)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Arteriolar hyalinosis (Banff ah)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent • N/A 	
Vascular pathology – other	Free text	

C4d	Single selection value list: <ul style="list-style-type: none"> • Positive • Negative • Equivocal/unknown • Not performed 	
SV40	Single selection value list: <ul style="list-style-type: none"> • Positive • Negative • Equivocal/unknown • Not performed 	
Immunostains – other	Free text	
Electron microscopy	Single selection value list: <ul style="list-style-type: none"> • Performed • Not performed 	
Glomerular capillary wall double contours (Banff cg1a)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent 	
Peritubular capillary basement membrane multilayering (PTCML)	Single selection value list: <ul style="list-style-type: none"> • Present • Absent 	
Final diagnosi(e)s/comment	Free text	Specify at least 1 diagnosis from rejection list and at least one diagnosis from non-rejection list.
Rejection diagnosi(e)s	Free text	
Non-rejection diagnosi(e)s	Free text	
SNOMED codes	Free text	

Appendix C List of rejection and non-rejection diagnoses

REJECTION DIAGNOSIS (choose at least 1; multiple choices allowed)

- Inadequate for assessment of rejection
- No evidence of rejection

Antibody-mediated rejection (ABMR) diagnostic category

- Not otherwise specified
- Confirmed active ABMR
- Incomplete (suspicious for) active AMR
- Confirmed chronic active ABMR
- Incomplete (suspicious for) chronic active AMR
- Confirmed chronic ABMR
- Incomplete (suspicious for) chronic ABMR
- C4d-positive without other histological features of rejection

T-cell-mediated rejection (TCMR) diagnostic category

- Not otherwise specified
- Borderline/suspicious for TCMR
- Active TCMR (tubulointerstitial only)
- Active TCMR (with endarteritis)
- Chronic, active TCMR (tubulointerstitial only)
- Chronic, active TCMR (with endarteritis)

NON-REJECTION DIAGNOSIS (choose at least 1; multiple choices allowed)

- Inadequate
- Normal/non-specific minor changes
- Rejection only – no additional pathological abnormalities
- Other pathology not listed
- Glomerular ischemia
- Infarction

Acute tubular injury category

- Not otherwise specified
- Suspicious for calcineurin inhibitor (CNI) toxicity

(Thrombotic) microangiopathy category (glomerular and/or arterial/arteriolar)

- Not otherwise specified
- Acute on light microscopy (LM)
- Subacute/chronic on LM
- EM features only

Interstitial fibrosis and tubular atrophy (IFTA) category

- Mild
- Moderate
- Severe

Significant (moderate to severe) vascular pathology category (excluding thrombotic microangiopathy)

- Significant vascular pathology – not otherwise specified
- Significant arterial intimal thickening – not otherwise specified
- Arterial Intimal fibrosis (non-inflammatory) – likely donor-derived
- Arterial intimal thickening without fibroelastosis (at least partially)
- Significant arteriolar hyalinosis – not otherwise specified
- Significant arteriolar hyalinosis – likely donor-derived

- Significant arteriolar hyalinosis – suspicious for CNI toxicity

Infection diagnostic category

- Infection – not otherwise specified
- Neutrophilic pyelonephritis/suspicious for pyelonephritis
- BK nephropathy
- Granulomatous

Glomerular disease category, recurrent or de novo (excluding rejection-related glomerulopathies and thrombotic microangiopathy)

- Not otherwise specified
- Immune complex – not otherwise specified
- Immune complex – IgA
- Immune complex – membranous
- Immune complex – lupus nephritis
- C3 glomerulopathy
- FSGS – not otherwise specified
- FSGS – likely recurrent
- Diabetic change
- Paraprotein-related

Tubulointerstitial disease (non-rejection) category

- Not otherwise specified
- Granulomatous tubulointerstitial nephritis

Neoplasia diagnostic category

- Neoplasia – not otherwise specified
- Preneoplasia/suspicious for neoplasia
- Post-transplant lymphoproliferative disease

Appendix D 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 E 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 interest of guideline development group members have been recorded and addressed	Foreword