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

Tissue pathways for urological pathology

September 2024

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Unique document number	G099
Document name	Tissue pathways for urological pathology
Version number	3
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Date active	September 2024 **(to be implemented within 3 months)**
Date for review	September 2029
Comments	This document replaces the 2nd edition of *Tissue Pathways for urological pathology* published in 2017. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for an abridged consultation from 14 May to 11 June. Responses and authors' comments are available to view at https://www.rcpath.org/profession/publications/documents-in-development.html. **Dr Brian Rous,** **Clinical Lead for Guideline Review**

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Registered charity in England and Wales, no. 261035

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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 and, in these circumstances, a clear rationale for any variation should be provided.

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

The following stakeholders were contacted for this document:

- The British Association of Urological Pathologists (BAUP)
- The British Association of Urological Surgeons (BAUS).

The information used to develop this tissue pathway was obtained by undertaking a systematic search of PubMed database, previous recommendations of the RCPath and local guidelines in the UK. Key terms searched included urological pathology, biopsy, resection, grossing, morphology and immunohistochemistry (IHC). The dates searched were between 1 January 2010 and March 2024. Published evidence was evaluated using modified SIGN guidance (see Appendix A). Consensus of evidence in the guideline was achieved by expert review. The level of evidence was either grade B**,** C or D, or met the good practice point (GPP) criteria. Gaps in the evidence were identified by College members via feedback received during consultation. The guidelines themselves constitute the tools for implementation and dissemination of good practice.

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

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 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 2 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.

This pathway has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and was placed on the College website for consultation with the membership from 14 May to 11 June. All comments received from the Working Group and membership were addressed by the author 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 previous version of this guideline, *Tissue pathway for urological pathology*, was published in July 2017.[1] It has now been updated to reduce overlap and possible conflicts with cancer datasets and other tissue pathways, and to ensure that the document complies with the revised format of the tissue pathway series. This document provides guidance on the handling of specimens and reporting of tissue specimens from the kidney, urinary collecting system, prostate, penis, scrotum and testis and relates primarily to those tissues taken for the investigation or treatment of benign or pre-neoplastic conditions at these anatomical sites. The specimens described in this guideline are currently reported by most histopathology departments in the UK. The purpose of this guideline is to promote a uniform good practice of specimen handling and reporting in histopathology departments and to assist cellular pathologists in providing a high standard of care for patients in the reporting of benign and pre-neoplastic urological specimens.

The tissue pathways are important as they provide a consistent approach to managing this range of pathological specimens and highlight the use of ancillary techniques when appropriate. Literature on the handling of samples resected for benign and non-neoplastic conditions is limited, but a good overview and clear guidance can be found in several

standard urological pathology reference books.[2,3] For urological tumours in particular, the diagnosis of malignancy may not have been made at the time of tissue resection, and this must be considered when the tissue is examined and sampled for histology. When any urological malignancy is diagnosed, it is essential that pathologists are familiar with the relevant RCPath datasets on urological cancers, which should be followed accordingly.[4–8] When referring to all urological cancers in the sections to follow in this tissue pathways document, they should be managed and reported as per the relevant datasets on urological cancers.

1.1 Target users of this guideline

The target primary users of the tissue pathway are trainee and consultant cellular pathologists. These recommendations will also be of value to qualified biomedical scientists involved in macroscopic description and dissection of urological specimens.

1.2 Generic issues relating to staffing, workload and facilities

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

- The diagnostic laboratory should have sufficient pathologists, biomedical scientists and clerical staff to cover all of its functions. In general, staffing levels will follow RCPath workload guidelines.[9]
- Histopathology laboratories should have a lead pathologist for each of the main subspecialties with responsibility for liaising with relevant local and clinical multidisciplinary teams (MDTs) and ensuring that the relevant specimens are examined, sampled and reported appropriately and in a consistent and timely fashion.
- Pathologists should:
  - participate in audits
  - participate in the RCPath continuing professional development scheme
  - participate in relevant external quality assessment (EQA) schemes of a general or specialist nature. Lead pathologists or those whose work consists predominantly of urological pathology should participate in the uropathology EQA scheme, which is now based exclusively on scanned slides via their pathology department, and have standard urological pathology texts available for reference.
  - have access to specialist referral opinions on a local, regional or national basis. This need will be influenced by the local level of expertise.

- The laboratory should:
  - be equipped to allow the recommended technical procedures to be performed safely
  - be accredited by or awaiting accreditation by the UK Accreditation Service (UKAS) or equivalent
  - participate in the UK National External Quality Assurance Scheme (UK NEQAS) for cellular pathology technique
  - participate in the UK NEQAS for IHC, immunofluorescence and fluorescent in-situ hybridisation (if these techniques are used in the diagnostic pathway).
- Reports should be held on a secure 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 or SNOMED-CT. It is acknowledged that existing laboratory information systems (LIMS) may not meet this standard; however, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.
- Compliance with the RCPath key assurance indicators for pathology.[10]
- Services to ensure that cellular pathology turnaround times are monitored and audited against locally agreed turnaround times to support patient pathways.[10]
- Workload data should be recorded in a format that facilitates the determination of the resources involved.[10]

1.3 Specimen submission and dissection

Most specimens are received in the laboratory in 10% neutral buffered formalin as routine diagnostic or therapeutic specimens according to standard procedures. The specimen must be accompanied by a form that includes full patient details, name of the clinical consultant, date of procedure, type of specimen, indication for the surgical procedure, relevant patient history including details of previous histology, and relevant clinical/radiological/endoscopic findings.

Each specimen container should be labelled with the patient's details, the site of the biopsy and date of the procedure. Formalin should cover the specimen entirely to ensure proper fixation. No interference with the specimen should be allowed unless agreed, prior

to receipt in the histopathology laboratory. The following guidelines should be observed in selecting and submitting tissue for microscopic study.

1.4 Weighing and measuring of specimens

Macroscopic specimen description is an integral part of the pathology report providing information about the histologically unsampled specimen. It is common practice to routinely record the size of specimens in 3 dimensions and weigh all specimens. However, many of these measurements are generally of little clinical utility and should be documented only if relevant for patient management. Weight may be a simpler and more reproducible indicator of the amount of tissue removed from the patient for some specimen types,[11] but does not need to be routinely reported.

1.5 Embedding, sectioning and staining

Small biopsies that will fit in 1 cassette are generally submitted in total. Intact biopsies should be orientated carefully and embedded on edge, with the epithelial surface perpendicular to the face of the block to be cut by the microtome. Diagnostic biopsies of larger size may need to be entirely submitted, but there are exceptions. See organ-specific instructions for sampling.

It is important to examine the contents of the container and the under-surface of the lid carefully to ensure that any stray fragments of tissue are recovered. In small biopsies, the numbers of fragments, maximum dimension of largest fragment, colour and texture of all fragments (e.g. friable) should be recorded. If fragments are very small, adequate precautions, such as placing between layers of foam (or wrapping in paper), should be taken to prevent tissue loss during processing. All the material submitted must be processed for histological examination.

Excisional biopsies containing a tumour should be blocked to show margins. India ink (or equivalent) can be used to mark margins with care taken to ensure than the ink does not spread elsewhere. All pieces are usually embedded as a group in 1 block. However, there is often a differential diagnosis of malignancy; blocking the abnormal area into more than 1 cassette to preserve tissue for immunohistochemical or molecular analysis should be considered in relevant cases.

Tissues must be thin (2–3 mm or less than the thickness of the cassette) and must not be crowded into the cassette. Thick or crowded tissue cannot be processed properly and poor sections will result, especially if the tissue contains fat. A single H&E-stained section

representing a full face of each block is adequate for the initial microscopic examination of larger specimens, but small fragmented biopsies and punch biopsies should be sectioned as recommended for the individual site. Depending on the histological findings, additional levels may be requested.

Ensure adequate fixation of large specimens such as bladder resections, nephrectomies and prostatectomies before cut-up to facilitate the production of thinner, better anatomically orientated sections.

[Level of evidence – GPP.]

1.6 Block selection and record

Specimen dimensions are measured in millimetres. When sampling a specimen, document the site from which each block is taken if relevant. Each cassette must have a unique identifying number/letter ideally applied with a microwriter, and the number of pieces of tissue in each cassette recorded if up to 10 or less (describe as ‘multiple’ if greater). For most specimens, no special facilities are required for specimen dissection.

Digital photography is now routine. It is good practice to photograph certain specimens, such as larger resection specimens and specimens that may have clinicopathological and medicolegal implications. This allows a permanent record of the macroscopic appearance and location of blocks to be recorded and filed in the patient records. Access to these images through a networked drive is preferable to facilitate rapid access and time effectiveness. Photography of all large specimens is an invaluable resource for MDT meetings, teaching and research and some LIMS facilitate embedded gross images for a complete encompassing pathology record for each patient. Microsoft teams (NHS SharePoint) is an alternative and Microsoft teams channels may be easier for some laboratories to manage than some network drives.

1.7 Case consultations

Departmental consultation to allow sharing of experience is good practice and provides a learning opportunity for trainees and advanced practitioners. It is recommended that a record of the consultation is maintained in either the LIMS (SNOMED CT code), digital system (chat function available in many) or other secure IT system. Discrepancies and the need for additional work (levels, special stains, IHC) may be a part of this record in post-reporting reviews.[12] This process can be audited as a part of quality assurance procedures. Double reporting is recommended only when mandated by RCPath cancer

datasets or other relevant guidelines. It is recommended that policy for double reporting is documented in departmental standard operating procedures (SOPs).

1.8 Ancillary tests

IHC has been included in specific areas of this guidance. Molecular tests have not been included as their use is predominantly for malignancies.

[Level of evidence – GPP.]

2 The kidney and renal pelvis

2.1 Nephrectomy non-malignant

2.1.1 Indications for surgery

- Removal of non-functioning kidney (simple nephrectomy) in patients with an irreversibly damaged kidney because of symptomatic chronic infection, obstruction, calculous disease, ischaemia (atheromatous/non-atheromatous) or severe traumatic injury.
- To treat severe unilateral parenchymal damage from nephrosclerosis, pyelonephritis, reflux or congenital dysplasia of the kidney.[13]
- Failed renal transplant.[14]
- Assessment of primary disease, e.g. pelvi-ureteric junction (PUJ) obstruction[15,16] chronic obstructive or reflux uropathy, adult polycystic kidney disease (APCKD) or xanthogranulomatous pyelonephritis (XGP).[17]
- Clinical presentation, radiological features and gross appearance of XGP may closely mimic a renal neoplasm making a correct pre-operative diagnosis difficult.
- Staghorn calculus.
- Radiation nephropathy, which may be either acute or chronic and related to dose.
- To exclude malignancy (e.g. multilocular cystic lesions, incidental carcinoma in a polycystic kidney, long-term dialysis associated cystic lesions).[18,19]

[Level of evidence – C.]

2.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Difficult cystic lesions may be referred for a specialist opinion.

2.1.3 Specimen dissection

- Measure the kidney in 3 dimensions.
- The adrenal gland and hilar lymph nodes are rarely present in simple nephrectomies but if present should be noted and sampled.
- If a mass is seen in the specimen, then examination and sampling should be in accordance with the recommendations in the appropriate cancer dataset.[6,8]
- Check the renal artery for stenosis and take a block to confirm cause, if present (e.g. atheroma, arterial fibromuscular dysplasia).
- The initial incision should pass through the midline of the kidney in the coronal plane.
- In the absence of any focal lesion, a single cassette including a section of kidney including the renal pelvis and a section of the ureter would be sufficient.
- XGP is due to renal outflow obstruction in the setting of infection and dilated calyces with yellow/brown calculi seen (often staghorn calculi). XGP may grossly mimic a renal neoplasm (on radiological imaging and macroscopy).[17]
- Cystic lesions should be carefully examined and solid areas sampled to exclude renal cell carcinoma. It has been recommended that at least 1 block/cm maximum dimension of the lesion should be submitted from multicystic lesions to exclude incidental background carcinoma, and for assessment of cysts in congenital disease. The utility of such recommendations has been questioned because the maximum dimension reflects the amount of fluid rather than cellularity of the lesion.[20] For paediatric multicystic conditions, whole mounts may be considered if available.
- Transplant nephrectomies should be handled and reported in accordance with the recommendations of the tissue pathways for renal transplant biopsies.[14]

[Level of evidence – GPP.]

2.1.4 Laboratory sectioning and staining

- Routine processing for light microscopy (LM).
- Usually require only 1 H&E section per block.

- There is rarely the need to extract formalin-fixed, paraffin-embedded material for subsequent electron microscopy (EM) examination.
- May require histochemical, immunofluorescent and immunohistochemical analysis of background kidney to diagnose/categorise co-existing glomerulonephritis (covered in the tissue pathway for medical renal biopsies).[21]
- Renal special set on kidney if indicated by H&E features – this includes basement membrane stain (PAS, Jones Silver), fibrous tissue stains (EVG, Masson trichrome) and Congo red (amyloid).[22] The silver stain is also useful for assessing vascular abnormalities.
- If a co-existing glomerulonephritis is suspected, then the case should be referred to a renal pathology specialist and reported in accordance with recommendations of the tissue pathway for medical renal biopsies.[20] There is an occasional need to extract formalin-fixed, paraffin-embedded material for subsequent EM examination.

[Level of evidence – C.]

2.1.5 Report content

- Note the presence or absence of malignancy, background urothelial changes (dysplasia, carcinoma in situ [CIS]) and type and aetiology of chronic damage.
- Ensure pattern and size of cysts are described and features of renal dysplasia looked for (e.g. presence of cartilage, fibromuscular collars around ducts and primitive glomeruli). Solid areas and nephron-like elements are absent from cyst walls. In acquired cysts, the inner surface is usually smooth and there is no communication with the renal pelvis.
- Cystic nephroma (classified now under mixed epithelial and stromal tumour, WHO 2022) should be excluded.[23] It is unilateral, solitary and multiloculated with non-communicating cysts sharply demarcated from adjacent kidney by a thick fibrous capsule with a nodular surface. Cysts have flat to hobnail epithelial lining and there is no renal parenchyma within the cysts (so not polycystic disease). The stroma may contain smooth muscle, skeletal muscle, cartilage or resemble ovarian stroma.
- Examine cysts in APCKD for features of malignancy. Micropapillary adenomas are common in the cyst lining.

- Identify the cause of renal artery narrowing, if present, (e.g. atheromatous plaque, fibromuscular dysplasia, vasculitis) and the degree of ischaemic parenchymal renal damage.
- Confirm radiation nephropathy if clinically indicated (e.g. glomerulosclerosis, glomerular fibrinoid necrosis, thickened glomerular capillary walls, mesangiolysis, fibrinoid necrosis of arterioles and small arteries with variable thrombosis).
- Severity of chronic renal parenchymal damage is prognostically important for postoperative risk of progressive renal insufficiency.[19]
- If an incidental carcinoma is identified, it should be reported according to the latest RCPath datasets for histopathological reporting of adult renal parenchyma and neoplasms tumours of the urinary collecting system.[6,8]

2.2 PUJ biopsy

- Primary causes of PUJ obstruction (PUJO) are usually congenital and may be the result of muscle bundle disarray or absence, increased collagen deposition, or abnormal anatomical location of the renal pelvis.[15]
- Secondary causes are conditions such as crossing lower pole aberrant renal vessel (usually anterior), congenital abnormalities of the kidney (horseshoe kidneys or duplex anomalies), scarring secondary to surgery.[15]

2.2.1 Indications for surgery

- PUJO with less than 40% in the split function of the affected kidney.
- Renal parenchymal atrophy due to severe bilateral PUJO.
- Recurrent infections despite using prophylactic antibiotics.
- Symptomatic obstructive PUJO, or associated with an abdominal mass.

2.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Refer problematic cases to the lead urological pathologist.

2.2.3 Specimen dissection

- The specimen may be funnel shaped if unopened. The presence and size of any strictures should be described.

- The specimen is opened along the long axis. If the specimen has been opened prior to receipt in the laboratory, it may look like a triangular fragment of mucosa.
- The mucosal surface is examined for lesions and irregularities in texture.
- The outer surface is examined for mass lesions and fibrosis.
- A couple of sections taken along the long axis are submitted in 1 cassette.

2.2.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Histochemical and immunohistochemical stains are generally not required but occasional use of IHC may be required to exclude or confirm urothelial dysplasia, CIS or malignancy (see below).[15]
- Rarely any requirement for EM or molecular investigations (e.g. patients who may have a genetic abnormality, possible neurogenic or myogenic factors).

2.2.5 Report content

- Confirmation of PUJO or correlation with the clinical findings.
- Histological findings in this condition are not distinctive and usually have no bearing on the treatment or patient outcome.
- External compression must be excluded.
- Presence or absence of malignancy, background urothelial changes (dysplasia, CIS), type and aetiology of chronic damage.

This may require an immunohistochemical panel (CK5, CK20, p53, CD44s) for confirmation.[24]

[Level of evidence – GPP.]

3 The ureter

3.1 Ureteric biopsy

Recent advances in the field of retrograde ureteroscopy include the development of small calibre fibre-optic endoscopes, improved optics and small calibre instruments enabling biopsy confirmation of previously inaccessible ureteric lesions. Miniaturisation of

ureteroscopic instrumentation with smaller fibre-optics and enhanced digital imagers, improved biopsy accessories, and new energy sources will continue to improve and generate enhanced diagnostic material.

3.1.1 Indications for procedure

- Abnormal imaging findings; filling defect. A number of benign lesions can present with filling defects, including radiolucent stones, blood clots, sloughed renal papillae, hamartomatous lesions, ureteritis cystica, nephrogenic metaplasia, fibroepithelial polyps, florid von Brunn's nests, tuberculosis, schistosomiasis, amyloid, malakoplakia, Teflon (Macroplastique) reaction and endometriosis.
- Evaluation of ureteric injury.
- Therapeutic indications include incision and biopsy of ureteric strictures.
- To exclude dysplasia, CIS and malignancy.
- To correlate with aspirated urine/fluid result if taken simultaneously.

3.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

3.1.3 Specimen dissection

- Tiny pieces of tissue (several millimetres) retrieved using either 'cold' cup forceps or a small diathermy loop are counted, measured, processed intact and examined histologically through 3 levels.
- Larger specimens (much less common) should be weighed collectively, the number of fragments counted and all tissue embedded.
- Determine the number and size of biopsies (in millimetres). The term 'multiple' should be restricted to cases with greater than 10 pieces.
- To avoid loss of smaller endoscopic biopsies during processing, ink with eosin and wrap in filter paper or similar commercial products.
- Embed all fragments in their entirety. Embedding fragments in a line facilitates histological assessment.

3.1.4 Laboratory sectioning and staining

- Routine processing for LM.
- 1 H&E section per cassette, with 3 levels examined.

- May require unstained sections between levels, if there is suspicion of CIS.
- May be appropriate to cut additional sections at initial processing if there is a likelihood that these will be required.
- Rarely need histochemical stains.
- Can occasionally require immunohistochemical analysis.

3.1.5 Report content

- Confirm benign changes if stricture is present.
- Radiation injury subsequent to treatment for cervical or prostate cancer shows peri-ureteric and submucosal fibrosis with atypical fibroblasts.
- Immunoglobulin G4-related disease (IgG4-RD; sclerosing retroperitoneal fibrosis) is difficult to confirm and shows non-specific inflammatory changes and occasional granulomatous inflammation. Patterns include storiform type fibrosis, lymphoplasmacytoid inflammation and obliterative inflammatory changes in vessels (IgG4 antibody is occasionally useful if >40% ratio of IgG4-bearing plasma cells to IgG-bearing plasma cells).[25]
- Exclude benign tumours, the commonest being exophytic and inverted urothelial papillomas, villous adenomas and leiomyomas.
- Ureteritis cystica may be diffuse along the ureter. These lesions are typically incidentally discovered during evaluation of the urinary tract for other causes and appear as numerous small uniform filling defects. Florid von Brunn’s nests in the upper urinary tract can closely mimic nested urothelial carcinoma and diagnosis in these sites can be difficult, especially on small biopsies.[26]
- Mullerianosis (endocervicosis, endosalpingiosis and endometriosis) results in either an intrinsic or extrinsic mass but is histologically similar to typical mullerianosis elsewhere.
- Injected polydimethylsiloxane particles, gel or Teflon for vesico-ureteral reflux causes a marked foreign body reaction and may grossly mimic cancer.[27]
- Exclude the presence or absence of malignancy, background urothelial changes (dysplasia, CIS).
- This may require an immunohistochemical panel (CK5, CK20, p53, CD44s) for confirmation.[24]

- Uretero-ileal anastomotic sites for ileal conduits show various chronic microscopic changes, e.g. cystically dilated intestinal glands, urothelial lined cysts, mucus pools and intestinal epithelial-lined cysts.

[Level of evidence – C.]

3.2 Ureteric resection

3.2.1 Indications for surgery

- Confirm nature of pathology (stricture).
- Confirm other pathology: congenital anomalies (duplex or triplicate ureter), ureteritis cystica, nephrogenic metaplasia, endometriosis, sclerosing retroperitoneal fibrosis (IgG4-RD).
- Exclude dysplasia, CIS and malignancy.

3.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

3.2.3 Specimen dissection

- Measure length – usually funnel-shaped in PUJ specimens (see above).
- Place probe to identify ureter.
- Longitudinal sections from pelvic portion and transverse sections from ureter to include distal margin.
- Submit in total if small sample.

3.2.4 Laboratory sectioning and staining

- Routine processing for LM.
- 1 H&E section per cassette, no need for routine unstained levels.
- Histochemical and immunohistochemical stains generally not required.
- Rarely any requirement for EM or molecular investigations.

3.2.5 Report content

- Document presence of ureteric narrowing.
- Note presence of nephrogenic metaplasia, endometriosis, amyloid, ureteritis cystica and sclerosing retroperitoneal fibrosis.

- Comment on dysplasia or CIS. Occasionally, use of IHC (CK20, p53, CD44s) to exclude or confirm urothelial dysplasia, CIS or malignancy and for confirmation of lesions such as nephrogenic metaplasia (CK7/20, AMACR, PAX2, PAX8).[24]
- All carcinomas should be reported according to the latest RCPath cancer dataset for tumours of the urinary collecting system.[8]

[Level of evidence – B.]

4 The bladder

4.1 Bladder biopsies

4.1.1 Indications for procedure

- Exclude primary urothelial dysplasia, CIS or malignancy.
- Follow up cystoscopy after previous urothelial carcinoma or intravesical treatment such as Bacillus Calmette-Guerin (BCG), mitomycin C therapy, thiotepa (triethylenethiophosphoramide), valrubicin and cyclophosphamide. Confirm benign pathology such as infectious and non-infectious cystitis, nephrogenic metaplasia, trigonal squamous and keratinising squamous metaplasia, interstitial cystitis, ketamine cystitis, amyloid, Teflon (macroplastique) reaction, malakoplakia or specific infections, e.g. schistosomiasis.
- Radiation cystitis (pseudocarcinomatous urothelial hyperplasia).
- Cystitis cystica et glandularis with and without intestinal metaplasia may mimic bladder cancer. The presence of intestinal metaplasia has been shown to bear no increased risk of cancer even if diffuse.[3]
- Assessment of other forms of cystitis (papillary, eosinophilic) and aetiological factors.
- Florid proliferation of von Brunn nests.
- Abnormal urine cytology with normal cystoscopy (random bladder biopsies generally taken).

4.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

4.1.3 Specimen dissection

- Determine the number and size of biopsies (in millimetres). The term ‘multiple’ should be restricted to cases with more than 10 pieces.
- To avoid loss of smaller cystoscopic (and cold cup) biopsies during processing, ink (eosin/India) and wrap in filter paper or similar commercial products.
- Larger specimens (much less common) should be weighed collectively, the number of fragments counted and all tissue embedded.
- In the case of multiple biopsies, avoid embedding a large number of fragments in the same cassette, as it may be difficult to keep them properly orientated and at the same level if they are numerous. Embed no more than 3 in each cassette.
- Embed all fragments in their entirety. Embedding fragments in a line facilitates histological assessment.

4.1.4 Laboratory sectioning and staining

- Routine processing for LM. 1 H&E section per cassette, and 3 levels sections examined.
- May require unstained sections between levels, if there is suspicion of CIS.
- May be appropriate to cut additional sections at initial processing if there is a likelihood that these will be required.
- Optional processing for EM when necessary. This requires fixation in 3% glutaraldehyde. If samples are fixed initially in formalin, they are transferred to glutaraldehyde at the earliest opportunity.
- Availability of histochemical stains occasionally used including Congo Red ± $KMnO_4$, PAS ± diastase, von Kossa, Ziehl-Neelsen (ZN), Toluidine blue or other mast cell stain.
- Availability of IHC for CK20 and/or other markers (including p53 or CD44s, AMACR) for diagnosis of CIS or incidental papillary lesions; also used for further typing of amyloid with AA protein, kappa/lambda light chains and transthyretin.[24]
- Rarely any requirement for molecular investigations.

4.1.5 Report content

- A separate description for each separately submitted set of biopsies is required unless they all show the same or similar features.
- If adequate clinical/cystoscopic details are not provided, this should be stated. Some features (i.e. interstitial cystitis/bladder pain syndrome) can only be interpreted with appropriate clinical and cystoscopic findings with biopsy performed to exclude CIS or malignancy. Non-Hunner-type and Hunner-type interstitial cystitis/bladder pain syndrome are recognised. Non-Hunner-type interstitial cystitis is characterised by severe fibrosis and increased mast cell infiltration, whereas Hunner-type interstitial cystitis is characterised by severe inflammation and urothelial denudation in the entire bladder. Fibrosis in the bladder is linked to both an increase in urine frequency and a reduction in bladder capacity in interstitial cystitis/bladder pain syndrome patients.[28] MDT meetings may be helpful with regard to final interpretation.
- Detail presence or absence of urothelial dysplasia/CIS or malignancy.
- Ketamine cystitis can show urothelial ulceration and atypia that can mimic CIS (associated with increased p53 and MIB1, but negative CK20). Microscopically, the urothelium is denuded with inflammatory granulation tissue and infiltrated by mast cells and eosinophils. The longer term cancer risk remains unknown.[29]
- Detail surface urothelial changes or metaplasia (e.g. squamous, glandular, nephrogenic). Squamous metaplasia can arise in the bladder secondary to chronic cystitis, schistosomiasis, diverticulum or non-functioning bladder. Squamous epithelium in biopsies from the trigone area of females should not be interpreted as squamous metaplasia. If keratinisation is present, this is a risk factor for subsequent development of carcinoma (mostly squamous cell carcinoma) and other complications such as bladder contracture and obstruction.[30]
- Verrucous squamous hyperplasia is a recently described entity that has been associated with the development of squamous cell carcinoma of the bladder.[31]
- Glandular metaplasia of intestinal type is not associated with an increased risk for the development of adenocarcinoma but when associated with dysplasia there is an increased risk for subsequent adenocarcinoma. Therefore, examine carefully for evidence of dysplasia.

- Comment on loss/ulceration or denudation of urothelium where this increases the chances of missing CIS.
- Confirm benign conditions such as amyloid, malakoplakia, collagen polyp, endometriosis and related endocervicosis.
- Note the presence or absence of inflammation; acute or chronic, follicular, eosinophilic, radiation cystitis or granulomatous post-BCG treatment can produce urothelial changes that can mimic cancer histologically. Intravesical therapeutic procedures including mitomycin C, cyclophosphamide, BCG and systemic therapeutic agents such as platinum-based chemotherapy agents and radiotherapy produce a host of changes and alterations in the urothelium and bladder wall, and some of them may mimic carcinoma. The pathologist must, therefore, be aware of these morphologies, particularly as the diagnosis of these lesions relies on H&E-based histopathological evaluation.[32]
- Confirm features of radiation cystitis following treatment for prostate/cervical cancer in particular. Changes can be misinterpreted as neoplastic. Pseudoepitheliomatous (pseudocarcinomatous) hyperplasia can be found in association with radiation cystitis, as well as other forms of bladder injury and can mimic squamous cell carcinoma.[33]
- There is a need for follow up in the case of specific infections such as viable schistosomal ova and to exclude infectious conditions such as tuberculosis.

[Level of evidence – C.]

4.2 Partial cystectomy

Partial cystectomy, also known as segmental resection of the bladder, is a surgical method of removing a selected full-thickness portion of the bladder wall. It is being performed less frequently in benign conditions but is used in selected cancer cases (e.g. tumours in dome, preservation of bladder function and palliation).

4.2.1 Indications for surgery

- Resection of bladder diverticula, cavernous haemangioma, paraganglioma, leiomyoma, refractory interstitial cystitis, colovesical fistula, vesicovaginal fistula and localised endometriosis of the bladder.
- In the case of diverticulum, stagnation of urine, calculus formation and superimposed infection occur when they reach a large size and require surgery.

- Patient choice, palliation of severe local symptoms, preservation of native bladder function and continence.
- Suspected malignancy (some non-urothelial cancers [urachal/adenocarcinoma] – report as per cancer dataset).
- Palliation for pain, bleeding or trauma.

4.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

4.2.3 Specimen dissection

- The specimen should be fixed in a volume of formalin that is at least sufficient to cover it. Time of fixation should usually be 48 hours after resection, but adequacy of fixation can be estimated fairly reliably by visual inspection. Photographs may be useful. They are required in cases of trauma.
- Ink any relevant margins if there is a possibility of neoplasia.
- Describe the external appearance. Perforations/defects in the wall: record number, site, size and distance from nearest margin. Look for fistulas and apply probe to confirm. Consider the possibility that the defects are artefactual or iatrogenic.
- Record measurements including dimensions of specimen (in millimetres).
- Record appearance of the mucosa. Take blocks to confirm gross findings. The most common locations of diverticula are the lateral walls. Measure the size in millimetres and exclude tumours.
- Record the presence of focal lesions, e.g. ulcer, abscess, stricture, polyp and tumour.
- Record the presence of any papillary tumour, any ulcerated or inflammatory areas.
- Tumours should be described and sampled according to the latest RCPath cancer dataset for tumours of the urinary collecting system.[8]

4.2.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Deeper levels may be useful if the slide does not show the full face of the block.

- May need histochemical stains (ZN, PAS, Congo Red) and occasional use of IHC to exclude or confirm background neoplasia.

4.2.5 Report content

- Describe inflammatory changes and confirm benign pathological changes (fistula, haemangiomas and endometriosis).
- The most common histological findings in a bladder diverticulum are inflammation, granulation tissue, erosion, florid cystitis cystica and glandularis, and non-keratinising squamous metaplasia. The boundary between the lamina propria and the peri-vesical fat in most bladder diverticula is usually readily defined by a band of dense fibrous tissue of variable thickness.
- Report any identified malignancy in accordance with the recommendations of the RCPath dataset for tumours of the urinary collecting system.[8]

[Level of evidence – GPP.]

4.3 Cystectomy

Most cystectomies are performed as part of the management of bladder cancer. The following discussion relates to rare cystectomies performed for clinically benign conditions.

4.3.1 Indications for surgery

- Intractable lower urinary tract symptoms (LUTS) – severe pain, frequency and urgency.
- Interstitial cystitis, neurogenic bladder and radiation cystitis.
- Urinary diversion, urogenital fistula, detrusor failure, severe urethral stricture secondary to tuberculosis or schistosomiasis and sequelae/complications.
- Palliation for pain, bleeding or urinary frequency.
- Trauma.
- Severe or refractory incontinence.[34]

4.3.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

4.3.3 Specimen dissection

- Specimen should be fixed in a volume of formalin that is at least sufficient to cover it. Some prefer to fix such specimens intact by overdistention with formalin (made easier if the catheter is still in situ) whereas others open and pin the specimen and cover it with formalin.[35]
- Fixation should usually be for 48 hours after resection, but adequacy of fixation can be estimated fairly reliably by visual inspection. Photographs may be useful. They are required in cases of trauma.
- Ink any relevant margins if there is a possibility of neoplasia.
- Describe the external appearance. Perforations/defects in the wall: record number, site, size and distance from nearest margin. Consider the possibility that the defects are artefactual or iatrogenic.
- Record appearance of the mucosa. Wash out bladder contents gently with tepid or cold water. Excess washing or hot water may damage the mucosa.
- Take blocks to confirm gross findings.
- Note any focal lesions, e.g. ulcer, fistula, abscess, stricture, polyp and tumour. Record the presence of any papillary tumour, ulcerated or inflammatory areas.
- Cystectomies for bladder cancer should be examined and reported as per latest RCPath dataset for tumours of the urinary collecting system.[8]
- Any identified lymph nodes must be described and their site(s) of origin specified.

4.3.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Deeper levels may be useful if the slide does not show the full face of the block.
- May need histochemical stains (ZN, PAS, Congo Red) and occasional use of IHC to exclude or confirm neoplasia (see below).

4.3.5 Report content

- Describe inflammatory changes and confirm benign pathological changes.[36]

- Report the presence or absence of malignancy, background urothelial changes (dysplasia, CIS), type and aetiology of chronic damage. Do IHC if required to confirm changes (CK5/6, CD44, p53, CK20). Classify, grade and stage any tumour identified.[37]
- Note the presence of submucosal inflammation and oedema, denuded epithelium, ulceration, epithelial and basement membrane thickness, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis.

[Level of evidence – GPP.]

5 The urethra

5.1 Urethral biopsy

5.1.1 Indications for procedure

- Urethral caruncle, polypoid cystitis, benign stricture, nephrogenic metaplasia, prostatic urethral polyp and malakoplakia.
- Urethroscopy may be undertaken in isolation or, more commonly, in tandem with cystoscopy
  - small urethral lesions are snared using ‘cold’ cup forceps or resected with a small diathermy loop.

5.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

5.1.3 Specimen dissection

- Tiny pieces of tissue (several millimetres) retrieved using either ‘cold’ cup forceps or a small diathermy loop are counted, measured, processed intact and examined histologically through 3 levels.

5.1.4 Laboratory sectioning and staining

- Usually require only 1 H&E section per block.
- Routine processing for LM.
- Rarely need histochemical stains.
- Can occasionally require immunohistochemical analysis (CK7/20, CD44s, p53).[27]

5.1.5 Report content

- Confirmation of benign pathology, most commonly caruncle or polypoid urethritis, both of which may be confused with a papillary neoplasm.
- Be aware of minor changes in the male/female urethra in relation to subepithelial supporting structures.
- If stricture, confirm benign changes.
- Record the presence or absence of malignancy, background urothelial changes (dysplasia, CIS) with confirmatory IHC if required (CK5, CK7/20, CD44s, p53).[27]

5.2 Urethrectomy

5.2.1 Indications for surgery

- Most urethrectomy resection specimens are for neoplasia as part of a cystectectomy/cystoprostatectomy in those deemed high risk for recurrence. Details of previous histology should be available, particularly if there is a history of dysplasia or carcinoma.
- Occasionally isolated urethrectomy is performed. Urethrectomy is performed for a stricture, bladder cancer in continuity with cystoprostatectomy, recurrence of bladder cancer in the urethral stump (secondary urethrectomy) and for primary urethral carcinoma.

5.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

5.2.3 Specimen dissection

- The specimen may be in several tubular fragments labelled separately or with attached sutures to aid orientation. In the absence of such markers, definitive orientation may not be possible.
- Record the number of fragments and maximum dimension of each.
- The remaining urethra is serially sectioned transversely throughout its length at 3 mm intervals and the sections laid out sequentially for examination and photography, if desired.

- Sample any focal lesions, e.g. ulcer (at least 1 block each). If tumour is seen, it should be described and sampled in accordance with the RCPath dataset for tumours of the urinary collecting system.[8]

5.2.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Can require both histochemical and immunohistochemical analysis.

5.2.5 Report content

- Confirm benign changes such as caruncle, prolapse, diverticulum, leiomyoma or viral papilloma.
- Record inflammatory changes present and correlate with history (e.g. stricture).
- Record the presence or absence of malignancy, background urothelial changes (dysplasia, CIS) with confirmatory IHC if required (CK5, CK7/20, CD44s, p53).[27]
- Exclude rare malignancies such as Littre's gland, Skene's gland and Cowper gland carcinomas.[38]

[Level of evidence – C.]

6 The prostate

Prostate needle core biopsy has been discussed thoroughly within the dataset for histopathology reports for prostatic carcinoma[4] and does not require further discussion in this document.

6.1 Transurethral resection of the prostate

6.1.1 Indications for surgery

- Exclude prostatic or other malignancy (remember urothelial carcinoma, stromal malignancies, phyllodes tumour).
- Confirm nature of pathology – usually benign prostatic glandular or stromal hyperplasia (benign prostatic hyperplasia [BPH]).[39]
- For the relief of bladder outlet obstruction symptoms in patients with known prostate cancer (channel transurethral resection of the prostate [TURP]).

- Necrosis and infarction with associated inflammation may be seen in redo-TURP specimens after green light laser vaporisation therapy for BPH.
- Transurethral resection is undertaken for obstructive or irritative LUTS, not as an alternative diagnostic investigation to detect prostate cancer. Note, in patients with prior negative prostatic biopsies, there is a low but definite chance of detecting prostatic cancer on TURP, which increases with abnormal clinical findings on rectal examination (digital rectal examination) or raised prostatic specific antigen (PSA) level; however, the majority of clinically significant cancers are detected on MRI.[39] This is due to a subset of cancers arising within the central or anterior (transition) zones, which are less likely to be detected with standard biopsy protocols not specifically targeting these areas. The clinical significance of some smaller volume cancers is not established.
- The prevalence of prostate cancer in TURPS varies from 8% to 17% (newer versus older series, respectively).[40,41] Clinically relevant cancer in procedures done for BPH (TURPs and enucleations, respectively) is seen in approximately 1.5% of specimens.[42]

6.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Occasional problematic cases may need intradepartmental opinion, clinicopathological correlation by discussion with the urologist and, rarely, referral of the case for a second specialist opinion.

6.1.3 Specimen dissection

- Weigh the chippings in grams. In general, gross examination of chippings does not provide distinctive evidence of tumour.
- In cases where clinical history specifies a clinical suspicion of carcinoma, or if the patient is post treatment following radiotherapy, cryotherapy or high-intensity frequency ultrasound, embed the whole specimen to detect residual carcinoma.
- Prostatic chippings do not require sectioning prior to fixation. The generally recommended sampling protocol is to embed all of first 12 g in 5–6 cassettes and a further 2 g (1 cassette) for every additional 5 g.[43,44] However, this protocol was designed in the pre-MRI era and its clinical utility has been questioned.[43,45] Although these additional blocks may detect a higher proportion of tumours, they do not lead to upstaging or upgrading of T1a tumours if the tumour was present in the first 6 blocks.

In general, random chippings are submitted, but if any particular chips are firmer or appear yellow/orange, they should be submitted first.

- Determining optimum sampling depends on a number of factors, as in any statistical sampling protocol. The site and extent of any tumour determines the percentage of chippings it will be seen in. Submission of all chippings in larger cases may not be cost- or time-effective.[46]

[Level of evidence – C.]

6.1.4 Laboratory sectioning and staining

- Routine processing for LM.
- 1 H&E section per cassette, no need for routine unstained levels.
- Immunohistochemical staining of serial sections from blocks with foci suspicious of carcinoma (ideally including antibodies against basal cell markers: first-line high-molecular-weight cytokeratins – LP34, CK5/6 or 34βe12 [all react with CK5]; p63 or cocktails of both ± positive marker for prostatic carcinoma racemase/P504S/AMACR).[47]
- The role of AMACR in routine practice is very useful, although some use it in cocktails with basal cell markers. Prostatic intraepithelial neoplasia (PIN) usually expresses AMACR. Note that similar expression may also be seen in benign mimics of cancer such as adenosis and nephrogenic metaplasia.[47]
- Rarely any requirement for EM or molecular investigations.

6.1.5 Report content

- Detail the presence of stromal or glandular hyperplasia/hypertrophy, infarction, urothelial or squamous metaplasia.
- Benign mimics present may cause diagnostic dilemmas, such as normal gland structures, benign proliferations, atrophic lesions, hyperplastic or metaplastic changes, and inflammatory processes. Some of these are preferentially found in certain anatomic areas of the prostate such as the transition zone and therefore more often seen in TURP specimens. Use of IHC (e.g. PIN Cocktail antibodies) can prevent overdiagnosis.[43]
- Note the absence of invasive prostatic adenocarcinoma, atypical foci suspicious of carcinoma or PIN.[38,42] In cases where PIN or suspicious foci are seen, they should be

reported as per the recommendations of the RCPath dataset for histopathology reports for prostatic carcinoma.[4]

- Note the presence of the surrounding urothelium and comment on any urothelial abnormality present, looking for co-existing urothelial carcinoma or in situ change.

[Level of evidence – C.]

6.2 Open prostatectomy (enucleation)

6.2.1 Indications for procedure

- As for TURP specimens.
- Exclude prostatic or other malignancy.
- As distinct from TURP, this procedure allows surgical exposure of the prostate with direct visualisation. There is also optimised preservation of urinary continence and better haemorrhage control with minimal bladder trauma.
- Open prostatectomy specimens are rarely encountered in contemporary practice due to other preferential treatment options for obstructive LUTS.

6.2.2 Staffing and workload

- This can be reported by a general pathologist with experience of urological pathology. Occasional problematic cases may need intradepartmental opinion and clinicopathological correlation by discussion with the urologist in cases of suspicious foci. Referral of the case for a second specialist opinion is rarely needed.

6.2.3 Specimen dissection

- There are few data on optimum block selection in enucleation specimens and the best method is treating these similarly to TURP resections.
- Enucleations or prostatectomies are generally restricted to large prostates in patients with lower urinary obstructive symptoms. Such specimens can benefit from incision to allow formalin penetration. Inking of margins is not necessary as these are not radical resections and, given the multifocality of prostatic cancer, demonstration of negative margins does not necessarily equate with absence of residual disease.
- Weigh gland in grams (often in several nodular pieces).
- Representative samples submitted by taking up to 1 block for each 5 g. Areas that look different from the rest, yellow or white, should be sampled.[44,45]

6.2.4 Laboratory sectioning and staining

- 1 H&E section per cassette, no need for routine unstained levels as per prostate biopsies.
- Immunohistochemical staining of serial sections from blocks with ASAP.[47]
- Rarely any requirement for EM or molecular investigations.

6.2.5 Report content

- Note that some benign entities such as atrophy, adenosis, nephrogenic hyperplasia, basal cell hyperplasia, Cowper's gland prominence/hyperplasia (bulbourethral glands around the prostatic apex) and proliferations and mesonephric remnants/hyperplasia potentially mimic prostatic cancer and may be responsible for misdiagnosis in routine specimens.[48] IHC can be used for confirmation.
- Note the absence of PIN, invasive prostatic carcinoma or atypical foci suspicious of carcinoma.
- If cancer is found, it should be reported as per the recommendations of the RCPath dataset for histopathology reports for prostatic carcinoma.[4]

[Level of evidence – C.]

7 The penis and scrotum

7.1 Penile biopsy

7.1.1 Indications for procedure

- The clinical appearance of many benign conditions overlaps with neoplastic and pre-neoplastic lesions, particularly penile intraepithelial neoplasia (PeIN). Therefore, biopsy may be necessary to exclude dysplasia and malignancy.
- Confirm benign pathological conditions.
- Occasionally Wegener's can present with penile ulceration and may mimic malignancy, requiring biopsy for confirmation.
- Exclusion of infectious diseases such as syphilis, herpes simplex, lymphogranuloma venereum and chancroid.

7.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. There is an occasional need for a penile pathologist (supranetwork level) or specialist dermatopathology opinion.

7.1.3 Specimen dissection

- Fragments are counted and measured in aggregate. It is important to search the container and the under-surface of its lid to ensure that all fragments of tissue are recovered.
- Larger pieces are measured individually. Embed as received, bisect or cut further. For a punch, bisect if larger than 3 mm and epithelium is clearly visible for orientation.
- For an ellipse, if narrower than 3 mm, embed as received. If an incisional biopsy, bisect in longitudinal section. Wider/larger excisional biopsies are cut in transverse section to include the nearest resection margins. Ink the margins as orientated by the marking sutures.
- Identifiable surface lesions are described and measured, and the macroscopic distance from the closest margin noted if excisional biopsy.

7.1.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require 3 H&E levels per block.
- May require both histochemical and immunohistochemical analysis to exclude or confirm neoplasia.

7.1.5 Report content

- Report median raphe cysts (midline in ventral shaft) and mucoid cysts.
- Report benign lesions such as lentiginous melanosis (glans and foreskin), cutaneous verruciform xanthoma (rare – shaft of penis), epithelioid haemangioma and leiomyoma.
- Inflammatory conditions include lichen sclerosus (LS), previously known as balanitis xerotica obliterans (BXO; may occasionally be seen on the shaft), Zoon’s balanoposthitis (balanitis circumscripta plasmacellularis) and Fournier’s gangrene (necrotising fasciitis).

- Zoon's balanitis is usually a disease of the glans but may extend onto the foreskin. Zoon's balanoposthitis shows attenuated or eroded epithelium overlying a dense infiltrate. The infiltrate contains numerous plasma cells, which often form sheets. Vascular ectasia, haemosiderin pigment laden macrophages and extravasated erythrocytes are common.
- Condyloma acuminatum and large viral warty lesions can be difficult to distinguish from warty squamous carcinomas. Biopsy often only provides superficial fragments. Clinical terms, giant condyloma and Buschke-Lowenstein tumour are no longer recommended.
- Infective lesions such as syphilis are rare but characterised by the presence of obliterative endarteritis with a surrounding plasma cell infiltrate that is characteristic of all stages. Spirochetes can be identified and the Treponema pallidum immunostain is more sensitive than the Warthin-Starry stain.[49]
- Granulomatous polyangitis (previously known as Wegener's) can cause penile ulceration often with destructive urethritis (c-ANCA/PR3 positivity).
- Exclude PeIN (HPV-independent differentiated PeIN and HPV-associated PeIN; the use of the term undifferentiated PeIN is now discouraged).[50] There is no need to distinguish between Bowen's disease and erythroplasia of Queyrat, which are clinically rather than pathologically defined lesions. It is more appropriate to describe as PeIN with (undifferentiated) or without (differentiated) warty features. Bowenoid papulosis also has similar histology to PeIN (undifferentiated) but clinically has multiple warty lesions along the shaft. Squamous hyperplasia and pseudoepitheliomatous hyperplasia consists of proliferative, pseudoinfiltrative urothelial nests and may be misinterpreted as low-grade squamous cell carcinoma. Similarly, verrucous carcinoma is frequently underdiagnosed.
- Rarely, the glans penis can show extramammary Paget's, usually in association with urothelial carcinomas (or urothelial CIS) of the urethra or bladder. IHC may be required for definitive diagnosis (see 7.3.5).[51]

[Level of evidence – GPP.]

7.2 Prepuce specimens

7.2.1 Indications for surgery

- Most common indication is for elective circumcision.
- The clinical appearance of many benign conditions overlaps with neoplastic and preneoplastic lesions particularly PeIN. Therefore, biopsy is mandatory to exclude dysplasia and malignancy.
- Confirm benign pathology[52] – condyloma, penile cysts and papules, IS/BXO, Zoon's balanitis, paraffinoma and verruciform xanthoma.
- Exclude PeIN and malignancy.

7.2.2 Staffing and workload (See Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

7.2.3 Specimen dissection

- Measure, inspect and orientate.
- Ideally, pin the 4 corners of the specimen with the mucosa orientated on 1 side and the skin on the other.
- If there is a history of dysplasia/PeIN, identify the coronal sulcus and ink the margins (the surgical cut area – coronal and penile shaft margins).
- Fix the specimen overnight in formalin.
- Specimen photography may rarely be necessary (prior to cutting if specimen is orientated).
- Cut serial transverse sections clockwise.
- Include any obvious areas of surface scarring or raised lesions.
- Embed at least 2 thin sections per block (to aid orientation).

7.2.4 Laboratory sectioning and staining

- Usually require only 1 H&E section per block.
- Occasionally need histochemical stains like PAS for fungal infection, Elastic van Gieson (EVG) to help confirm LS (the zone of homogenised dermal collagen does not usually contain elastic fibres in contrast to the lower dermis where there is an increase in elastic fibres) or Congo red stain for amyloid.

- PeIN if present should be documented as HPV-associated or HPV-independent (WHO blue book recommendation[53]). P16 IHC is available in most UK laboratories or if available, HPV in-situ hybridisation.[50]

7.2.5 Report content

- Comment on any evidence of LS/BXO, Zoon's balanitis (inner foreskin/glans). Histopathological findings of Zoon's include superficial erosions, haemosiderin deposition and basal vacuolar degeneration. Epidermal lozenge-shaped keratinocytes with dense dermal inflammatory infiltrate composed predominantly of dermal plasma cells, with scattered neutrophils and lymphocytes and upper dermal fibrosis, are often seen. Less common benign lesions include epidermal inclusion cyst, pilonidal type sinus and penile traumatic neuroma.[52,54] Rarely, dermatoses (e.g. lichen planus) can affect the prepuce or glans but these are usually associated with disease elsewhere.
- Note recent case reports of granulomatous inflammation with vasculitis in association with the anti-anginal drug nicorandil.[55]
- Report non-specific inflammatory changes in balanoposthitis. Mucinous metaplasia is occasionally seen in older patients. Exclude sexually transmitted infections (e.g. syphilis and herpes simplex).
- Paraffin granuloma of the foreskin (paraffinoma) is a type of inflammatory lipogranuloma that develops after the injection of artificial oils, such as paraffin or silicon, into the foreskin or the subcutaneous tissue of the penis for the purpose of penis enlargement or cosmesis.[56]
- Exclude PeIN or malignancy particularly with LS/BXO. Any cancer should be reported as per the recommendations of the RCPath dataset for penile and distal urethral cancer.[5]

[Level of evidence – C.]

7.3 Scrotal biopsy

7.3.1 Indications for procedure

- Biopsy is necessary to confirm benign pathology.
- Removal of suspected cystic lesion or calcified nodule (idiopathic scrotal calcinosis).
- Exclude dysplasia and malignancy.

7.3.2 Staffing and workload

This can be reported by a general pathologist with experience of urological pathology (see Introduction above).

7.3.3 Specimen dissection

- Fragments are counted and measured in aggregate. It is important to search the container and the under-surface of its lid to ensure that all fragments of tissue are recovered.
- Larger pieces are measured individually. Embed these as received, bisect or cut further if necessary.
- For a punch, bisect if larger than 3 mm and epithelium is clearly visible for orientation.
- For an ellipse, if narrower than 3 mm, embed as received. If wider, bisect in longitudinal section. Wider/larger lesions are cut in transverse section to include the nearest resection margins. Ink the margins as orientated by the marking sutures.
- Cystic lesions or nodules may require decalcification.
- Identifiable surface lesions are described and measured, and the macroscopic distance from the closest margin noted.

7.3.4 Laboratory sectioning and staining

- Routine processing for LM.
- May require 3 H&E levels per block.
- Can require both histochemical and immunohistochemical analysis, e.g. Extramammary Paget's disease (EMPD) of scrotal skin is positive with CK7, CAM 5.2, CEA, EMA, PAS, MUC1, MUC5AC and negative for 34βe12 (high-molecular-weight keratin), CK20 (to exclude pagetoid spread from urothelial tumours, which are CK20, p63 and GATA3 positive), SOX10, HMB45, Melan-A, PRAME and S100.[57,58]

7.3.5 Report content

- Non-neoplastic lesions of scrotum include fat necrosis, idiopathic scrotal calcinosis (multiple nodules in skin, which may arise from keratinous cysts that have lost their lining), hidradenitis suppurativa, massive localised lymphoedema in morbidly obese patients, sclerosing lipogranuloma and post-traumatic spindle cell nodules.

- Lymphoedema of the scrotum is most commonly idiopathic and may have genetic links to syndromes such as Milroy's disease. True lymphoedema following groin and perineal radiotherapy and in association with Crohn's disease is recognised. Chronic lymphoedema may produce verruciform squamous hyperplasia and there is a rare association with scrotal squamous cell carcinoma.
- Note the presence or absence of dysplasia, CIS and malignancy. The classification of scrotal tumours is provided for the first time in the 5th edition of the WHO Blue book,[53] and it follows the schema of penile cancer classification for both precursor lesions and the common squamous carcinoma of the scrotum. Exclude other neoplastic lesions of scrotum such as aggressive angiomyxoma, angiomyofibroblastoma (similar to vulvovaginal angiomyofibroblastoma and spindle cell lipoma), desmoplastic round cell tumour and malignant mesothelioma involving scrotum from the tunica vaginalis/albuginea.
- EMPD in the scrotum affects mostly elderly males and is rare. It can arise either as a primary cutaneous lesion or as secondary to visceral malignancies.[57,58] EMPD when associated with malignancy is usually apocrine adenocarcinoma in type; 25% of the cases have an underlying cutaneous adnexal carcinoma, mostly of apocrine type. An IHC panel to include GATA3, NKX3.1, AR, cytokeratin, CK7, GCDFP15, CEA, PSA, SOX10 and Her2 is useful diagnostically.
- Sarcomas, although rare, should be excluded with leiomyosarcoma and liposarcoma being the commoner types seen.

[Level of evidence – GPP.]

8 The testes

8.1 Testicular biopsy

8.1.1 Indications for procedure

- Assessment of male infertility – usually azoospermia.
- Testicular sperm extraction – multiple testicular biopsies are usually needed and part of the specimen should be histologically assessed to predict the chance for future successful sperm harvesting and to diagnose germ cell neoplasia in situ (GCNIS) of the testis.[59,60]

- Variable practice of biopsy at time of contralateral orchidectomy for malignancy, to assess spermatogenesis and the presence of GCNIS. This is done particularly in small volume testes in younger males. Testicular biopsy during orchidopexy is occasionally recommended in adolescents with cryptorchidism for detection of GCNIS of the testis.
- Biopsy of undescended testis to exclude malignancy or GCNIS.
- Biopsy of vestigial remnants such as the appendix epididymis (remnant of mesonephric duct) and the appendix testis (hydatid of Morgagni), which have undergone torsion or infarction.

8.1.2 Staffing and workload (see Introduction above)

Specialised biopsies are generally uncommon in routine clinical practice. These should be reported by a urological pathologist or someone with expertise in assessment of testicular biopsies for infertility. A close relationship is required with urologists and/or fertility clinicians to ensure good clinicopathological correlation.

8.1.3 Specimen submission

- Core lengths (in millimetres) or tissue dimensions (in millimetres).
- Number of cores/pieces and orientation.
- Submit all tissue for microscopic evaluation.
- May be fixed in Bouin's, Stieves's or Zenker's medium as opposed to formalin for better nuclear preservation and because there is less shrinkage artefact and luminal sloughing of cells, which can obscure cellular detail.[61] IHC performed in tissue fixed in Bouin's is less sensitive due to degradation of DNA and RNA.[61]

8.1.4 Specimen dissection

- To prevent surface trauma and disruption, these specimens require careful handling.
- Recommend wrapping in tissue paper or similar commercial products to prevent loss during processing, as often small samples.
- Embed biopsies from separate testes in different cassettes.

8.1.5 Laboratory sectioning and staining

- Routine processing for LM.
- At least 3 H&E sections per biopsy with 4–5 mm sections. PAS stains are useful to assess the basement membrane.

- May be appropriate to cut additional sections at initial processing or keep spares between the levels, if there is a likelihood that these will be required.
- Rarely need histochemical stains for fibrosis or amyloid.
- Occasional use of IHC to assess tubular germ cell numbers (SALL4) and assessment of maturation arrest (DOG1 stains spermatocytes and spermatids and was absent in spermatogonia) and exclude or confirm background GCNIS, such as OCT3/4, PLAP and podoplanin. OCT3/4 is now the gold standard marker for GCNIS. IHC with OCT3/4 for the detection of GCNIS can be falsely negative if Stieve's or Bouin's solution is used.[61,62]

8.1.6 Report content

- The adequacy of the sample should be noted and where artefact or loss impairs interpretation of the biopsy, this should be stated in the report. Adequacy is best determined by the number of seminiferous tubules (25) or lobules (3–5).[59,60]
- If adequate clinical details are not provided, this should be stated. Clinicopathological meetings help refine interpretation.
- Comment on background atrophy, fibrosis, tubular hyalinisation and dilation or changes to sex cord-stromal cells (Leydig cell hyperplasia) and microlithiasis.
- Qualitatively describe spermatogenesis across the whole biopsy – it often varies between tubules. Recognise the individual germ cell types, which proceed through spermatogenesis, with particular assessment of the presence of maturation arrest and if tubules are lined by Sertoli cells only.
- Assess spermatogenesis with a quantitative scoring system (e.g. Johnsen score and other modifications of the Johnsen score).[63] However, the need for Johnsen counts is now limited as even the slightest degree of spermatogenic activity allows modern fertilisation procedures. 1 method of quantifying the spermatogenesis involved establishing the germ cell to Sertoli cell ratio (a ratio of 13:1 is considered normal for a healthy male and approximately 12 Sertoli cells per tubule considered normal).[64]
- Comment on the presence or absence of any GCNIS.
- Confirm presence of the testicular appendix, which is attached to tunica albuginea at the upper testicular pole and may undergo haemorrhagic infarction by twisting on its pedicle.

[Level of evidence – D.]

8.2 Orchidectomy non-malignant

8.2.1 Indications for surgery

- Removal during surgical procedure (non-descent, atrophy, hernia repairs).
- Testicular regression syndrome (TRS) and previously termed vanishing testes syndrome.
- Torsion.
- Infection, chronic pain and trauma.
- Granulomatous orchitis – some cases are associated with urinary tract infections, history of prostatectomy, inguinal hernia repair and trauma.
- Treat all these specimens as potentially malignant and approach macroscopic cut-up in anticipation of finding an underlying tumour.

8.2.2 Staffing and workload (see Introduction above)

- This can be reported by a general pathologist with experience of urological pathology. Torsion and cryptorchid testes cases are more often seen in the paediatric age group and reported by paediatric pathologists.[64]
- Refer problematic cases to the urological pathologist.
- Cases with tumours should be reported to the local and/or regional MDT.[7]

8.2.3 Specimen dissection

- Measure and orientate.
- If any suspicion of a tumour, describe and sample in accordance with the RCPath dataset for the histological reporting of testicular neoplasms.[7]
- Embed at least:
  - any focal lesions
  - 2–3 random sections in 1 block of background testis
  - embed all testicular tissue (nubbin) in TRS.

8.2.4 Laboratory sectioning and staining

- Routine processing for LM.

- 1 H&E section per cassette, usually 1 level is sufficient.
- Availability of histochemical stains.
- Occasional use of IHC to exclude or confirm background GCNIS such as PLAP, podoplanin and nuclear marker OCT3/4 or wider immunohistochemical panel for any tumours (see below).[65]
- Beware hyalinised or atrophic-looking areas with inflammation and coarse calcification within seminiferous tubules (possible ‘burnt-out’ germ cell tumour). Take levels and if necessary go back to the specimen and re-embed whole testis to look for residual viable tumour and do IHC for GCNIS. In paediatric testes, where the amount of tissue is small, embed all the tissue. This is particularly important in TRS where identification of the spermatic cord allows definitive diagnosis. The incidence of germ cells within these nubbins is low.[66] There is a hypothetical potential future malignancy risk, although literature reports are sparse.
- Granulomatous orchitis shows an irregular rim of lighter-coloured tissue around the periphery and the process seems to extend beyond the testis proper. The cut surface is vaguely nodular, yellowish and hard. It mimics tumour clinically and macroscopically.
- Likewise, before making a diagnosis of epidermoid cyst, exclude post-pubertal type teratoma. If teratoma is diagnosed, the case should be referred to the testis MDT.

8.2.5 Report content

- Comment on the degree of spermatogenesis, any GCNIS, fibrosis or any incidental changes to sex cord stromal cells (Leydig cell hyperplasia or nodules).
- Confirm with clinicians if there are cryptorchid and intra-abdominal testes in particular, as these may be associated with intersex syndromes. Comment on degree of tubular atrophy, tubular basement membrane thickening, interstitial hyalinisation, Sertoli cell change and nodules.
- In torsion, it is important to correlate histological changes with the clinical timeframe with respect to testis viability as this can have medicolegal significance (viable/nonviable). The Mikutz grade (1–3) can be applied.[67]
- Granulomatous orchitis shows a granulomatous inflammatory process with lymphocytes, plasma cells, macrophages, fibroblasts and scattered multinucleated

giant cells, but no demonstrable organisms. Marked inflammation can occasionally mask tumours.

- TRS consists of a fibrovascular nodule with associated haemosiderin-laden macrophages and dystrophic calcification. Residual testicular tubules are found in less than 10% of cases.[68]
- Splenogonadal fusion is a rare congenital malformation in which there is an abnormal connection between the spleen and testes, sometimes mimicking a testicular neoplasm. Rarely, germ cell tumours arise in this anomaly, using in the setting of cryptorchidism.[69]
- Histological examination confirms the diagnosis and excludes neoplasia. Wider immunohistochemical panel for any tumours, including cytokeratin, CD30, AFP, Glypican-3, β-hCG, HPL, PLAP, OCT3/4, c-kit, SALL4, CK7, inhibin, SF-1, β-catenin, CD56, synaptophysin and chromogranin.[65]
- Any cancer should be reported as per the recommendations of the RCPath dataset for the histological reporting of testicular neoplasms.[7]

[Level of evidence – D.]

8.3 Hydrocele

8.3.1 Indications for surgery

- Inability to distinguish from an inguinal hernia.
- Failure to resolve spontaneously after an appropriate interval of observation.
- Inability to examine testis properly.
- Association of hydrocele with other pathology (e.g. torsion, tumour).
- Pain or discomfort.
- Male infertility.
- Most cases are idiopathic but may be associated with hernia, trauma, infections (mumps orchitis, filariasis, tuberculosis) or tumours.

8.3.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

8.3.3 Specimen dissection

- Measure strips of hydrocele (hydrocelectomy) – usually thickened tunica.
- Note irregular nodules or areas of firmness – submit these for histology.
- 2–3 representative sections in 1 block if normal appearing.

8.3.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Can require both histochemical and immunohistochemical analysis. May need to exclude mesothelioma in cases with marked mesothelial proliferation. Immunohistochemical panel should include CAM 5.2, calretinin, CK5/6, EMA, CK7, HBME1, D2-40 and BerEP4 (+/- GLUT-1, p53, WT1, Ki-67). Although BAP1 IHC are specific for mesothelioma, alterations are less common in tunical mesotheliomas.[70] EM findings may help confirm the diagnosis.
- Histochemistry with Gram, ZN or PAS required if suspicion of infection.

8.3.5 Report content

- Confirm benign mesothelial lining and fibrous thickening. Mesothelial hyperplasia in the tunica represents the reactive sequelae to persistent or repetitive serosal injury, inflammation in hydroceles and inguinal hernia sacs. Florid mesothelial hyperplasia may give rise to surface papillae, tubules, solid nests and cords, which may be confused with malignant mesothelioma of the tunica vaginalis.[71]
- Record the presence or absence of malignancy (mesothelial).[72] Hydroceles are sometimes seen in association with testicular tumours (10%). Tunica (vaginalis/albuginea) cysts can be multilocular and show positivity for mesothelial markers. Cysts of epididymal or intratesticular (benign cysts and mature teratomas) origin need to be excluded.

[Level of evidence – D.]

9 The epididymis and spermatic cord

9.1 Epididymal biopsy/epididymectomy

9.1.1 Indications for surgery

- Incidental findings on testicular self-examination or routine physical examination
  - failure to transilluminate suggests a solid lesion.
- Often detected incidentally on ultrasound.
- Lump may be painful and require removal.
- Removal due to chronic epididymal pain or post-vasectomy pain syndrome.

9.1.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology. Refer problematic cases to the urological pathologist.

9.1.3 Specimen dissection

- Specimen consists of a cystic structure, which may be multiloculated if a spermatocele.
- Sometimes specimen also contains part of the adjacent normal epididymis (partial epididymectomy).
- Fluid is clear in an epididymal cyst and opaque because of the presence of sperm in a spermatocele.
- Outer surface is examined for mass lesions.
- Cyst is bisected and 2 sections taken to include the epididymis if present.
- If a nodule or mass is present take representative blocks (1 per cm) – more often due to the small size of the specimen, all the lesion can be submitted.

9.1.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- Histochemical stains generally not required.
- Occasionally use of IHC to exclude or confirm benign tumours (adenomatoid) or malignancy.

- Rarely any requirement for EM or molecular investigations.

9.1.5 Report content

- Microscopic examination reveals a cyst with a fibromuscular wall that is lined by bland cuboidal epithelium.
- Spermatocele results from dilation of an efferent ductule and is lined by a single layer of flattened epithelial cells. The wall is composed of fibromuscular stroma. It may sometimes be difficult to see spermatozoa as they are ‘washed’ away during specimen processing.
- Note any other lesions – adenomatoid tumour, epididymitis nodosa, hernia sac entrapped epididymis, granulomatous ischaemic lesion, vasculitis and cystadenoma of epididymis.
- Report the presence or absence of malignancy.

[Level of evidence – GPP.]

9.2 Vasectomy

9.2.1 Indications for procedure

- Normally for sterilisation to confirm complete transaction.
- Occasionally, biopsies of lesions (vasiitis nodosum or benign adenomatoid tumour).
- Rarely, as part of fertility surgery, such as epididymovasotomy. Note problems arising from a fairly minor specimen – medicolegal issues of failed vasectomy and subsequent pregnancy.

9.2.2 Staffing and workload (see Introduction above)

This can be reported by a general pathologist with experience of urological pathology.

9.2.3 Specimen dissection

- Orientate and measure the length of the vas segment and submit 1 block of each vas. It may be expedient to take 2 cross sections from each to obtain a full face section. Where possible, do not embed all of the specimen, to permit extra blocking if initial sections suboptimally embedded.
- Dipping the vas segments in alcian blue at dissection may aid correct orientation at embedding.

- Note any splits or defects.
- In cases of failed sterilisation, block the whole vas (levels may be necessary) to identify possible recanalisation.
- If tumour suspected, macroscopically describe and sample according to the appropriate dataset.
- Nodular periorchitis involves the tunica, epididymis or spermatic cord and forms a mass lesion.

9.2.4 Laboratory sectioning and staining

- Routine processing for LM.
- Usually require only 1 H&E section per block.
- May require levels or re-embedding if the lumen is not clearly visualised.
- Availability of histochemical stains occasionally used including PAS ± diastase or ZN.
- Very occasional use of IHC for adenomatoid tumour (epithelial marker), where the histological features are suboptimal due to crush artefact (CD10 and pan cytokeratin are useful markers to highlight the vas deferens epithelium) or incidental connective tissue lesions.[73]

9.2.5 Report content

- Confirm vas deferens and that the full cross section is seen.
- In failed sterilisation, confirm that it is vas and a full cross section is seen.
- Exclude other associated pathology, e.g. sperm granuloma, vasitis nodosa, proliferative funiculitis and recanalisation.[74,75]
- Nodular periorchitis is a reactive myofibroblastic proliferation involving the tunica, epididymis or spermatic cord, usually in response to some form of injury or infection. It is known by a variety of names (inflammatory pseudotumour, chronic proliferative periorchitis, nodular and diffuse fibrous proliferation, paratesticular fibrous pseudotumour).
- Report any cancers according to the relevant cancer dataset.

[Level of evidence – GPP.]

10 Criteria for audit

The following are recommended by the RCPath as key assurance and key performance indicators:[76,77]

- histopathology cases must be reported, confirmed and authorised within 7–10 calendar days of the procedure
  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

Where clinically appropriate, histopathology cases must be reported, confirmed and authorised within an agreed turnaround time between service providers and service users that may deviate from the 7–10 days standard

10.1 Timeliness of report

Confirmation of compliance with RCPath key assurance indicators for pathology services is required by an annual (as a minimum) audit of performance against locally agreed turnaround times and targets (Key Assurance Indicator 18: Turnaround times linked to patient pathways).

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Appendix A Summary table – Explanation of levels 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 1 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.
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 cancer type 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 cancer type 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 B AGREE II guideline monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset 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, Introduction

12 There is an explicit link between the recommendations and the supporting evidence	3–9
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	2–9
16 The different options for management of the condition or health issue are clearly presented	2–9
17 Key recommendations are easily identifiable	2–9
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	All Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	10
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