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

Tissue pathways for gastrointestinal and pancreatobiliary pathology

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Foreword

The tissue pathways published by the Royal College of Pathologists (RCPath) are guidelines that enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

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

The following stakeholder was contacted to consult on this document:

- the Pathology Section Committee of the British Society of Gastroenterology (BSG).

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

The information used to develop this tissue pathway was obtained by undertaking a systematic search of PubMed. Key terms searched included ‘gastrointestinal pathology’, ‘biopsy processing and reporting’ and ‘inflammatory and non-neoplastic diseases’. The dates searched were January 2016 to December 2023. Statements and advice are supported by published evidence, where possible. Information is from various sources, including peer reviewed publications, best practice documents, expert opinion and standard textbooks.[1] Recommendations and evidence from established clinical and pathological guidelines are also taken into account. The latter include documents produced by RCPath,[2–6] World Health Organization (WHO),[7] European Crohn’s and Colitis Organisation,[8–12] BSG,[13,14] UK Bowel Cancer Screening Programme,[15] International Collaboration on Cancer Reporting (ICCR)[16,17] and other groups. Published evidence was evaluated using modified SIGN guidance (see Appendix A). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

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

relevant sub-specialty adviser to the College, to consider whether the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the College website.

This tissue 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 15 August to 12 September. 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 tissue 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.

1 Introduction

1.1 Target users and health benefits of this guideline

- Consultant cellular pathologists, biomedical scientists, clinical scientists and trainee pathologists responsible for reporting and/or dissecting gastrointestinal (GI) and/or pancreatobiliary pathology cases.
- Health service managers responsible for service delivery and service improvement.

1.2 Staffing and workload

GI pathology is a major component of most histopathology departments' workload. It may be part of a general rota or may be mostly/exclusively the remit of specialists. The number of pathologists must be sufficient to provide cover and to conform to the College guidance on staffing and workload levels, key assurance indicators and key performance indicators.[18–20] Mucosal biopsies constitute the majority of the GI pathology service.

College key performance indicators recommend that 80% and 90% of all laboratory specimen types are reported within 7 days and 10 days, respectively, of the date of sampling; however, the College key assurance indicators for pathology services recognise the complexity of the delivery of a pathology service and how various external and internal factors might influence turnaround times (TATs). Departments should agree clinically relevant TATs with service users and implement audits to monitor them.[18,20]

1.2.1 External quality assurance and continuing professional development

- Pathologists and biomedical scientist staff responsible for issuing GI pathology reports should participate in the UK national (BSG) GI pathology external quality assurance (EQA) scheme or, if that is not possible, in a local general pathology EQA scheme that includes GI pathology cases.
- If a frozen section or out-of-hours service in GI pathology is offered, this should be provided by those who report GI pathology regularly.

  [Level of evidence – GPP.]
- Pathologists reporting Bowel Cancer Screening Programme (BCSP) cases should participate in the BCSP pathology EQA scheme if available.
- Where necessary, pathologists should have access to a regional or national GI/pancreatobiliary specialist opinion. Guidance with more detail is available from the College.[21]

1.2.2 Laboratory facilities

The laboratory should be equipped adequately, enrolled with the UK Accreditation Service (UKAS), participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique and participate in the UK National External Quality Assurance Scheme for Immunocytochemistry.[20]

For GI pathology, facilities to process large (wholemount) blocks are necessary and coloured inks for identifying resection margins should be available.

Reports should be held on an electronic database that has facilities to search and retrieve specific data items and that is indexed according to Systematised Nomenclature of Medicine (SNOMED) T, M and P codes (or equivalent codes according to SNOMED Clinical Terms [SNOMED CT]).

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

1.3 Specimen submission

1.3.1 Necessary clinical details

- Details of the patient, clinician, date of procedure, indication for the procedure and type of specimen.[1,8,22]
- Relevant surgical or endoscopic findings, as a description or in the form of the endoscopy report where relevant.[23]
- Details of previous histology, particularly if there is a history of dysplasia or carcinoma.
- Details of previous treatment.
- Anatomical sites of origin of all biopsies and resections.
- A statement as to whether polyps or lesions were resected (as 1 fragment or piecemeal) or biopsied/partially resected.
- Clinical information is often available by searching hospital electronic records. However, active provision by the clinical team of the most important and relevant details is preferable to an expectation that pathologists will seek details, especially if there is a possibility of outsourcing and/or reporting by a pathologist in another institution. This reduces the risk of errors. Interpretation of histology without adequate clinical details is often unreliable.

  [Level of evidence – D.]

1.4 Block selection and record

- Include a clear block key.
- Record the site or lesion that each block represents.
- Record the number of pieces of tissue in each cassette.
- Use millimetres (mm) for measurement.
- Ensure that the description is sufficiently clear for another pathologist to be able to understand the purpose and site of origin of each block.
- Where appropriate, use photographs or line drawings to improve clarity.[24]

1.5 Epithelial dysplasia/malignancy

- Oesophageal squamous dysplasia is classified as low grade or high grade.[7]
- Anal intraepithelial neoplasia (squamous) is classified using both a 3-tier system, i.e. anal intraepithelial neoplasia (AIN) 1, AIN 2 and AIN 3, and a 2-tier system, i.e. low-grade squamous intraepithelial lesion (LSIL) (equivalent to AIN 1) and high-grade squamous intraepithelial lesion (HSIL) (equivalent to AIN 2 and AIN 3). There is currently no global consensus on which system is preferable.[25] The use of p16 immunohistochemistry to assist risk stratification is advocated by some authors.[26]
- Columnar (glandular) dysplasia in the oesophagus, stomach, bowel, ampulla of Vater, gallbladder, biliary tree and pancreas is classified as low grade or high grade.[7,15]
- Interobserver reproducibility for grading dysplasia ranges from poor to good. Kappa values are usually lowest for the category of indefinite for dysplasia. Concordance sometimes improves after the adoption of agreed diagnostic criteria.[27–33]

1.5.1 Dysplasia versus regenerative epithelial changes

- Acute inflammation, erosion or ulceration may cause atypical regenerative epithelial changes that resemble dysplasia. Deeper levels may help to distinguish these abnormalities.
- The term ‘indefinite for dysplasia’ indicates that a decision cannot be made about the presence or absence of dysplasia.[34–36] Reasons include atypia in association with acute inflammation/erosion/ulceration, or absence of sufficient tissue to allow confident assessment.
- Immunohistochemistry for p53 is controversial. According to many studies and some guidelines it assists with the distinction between dysplasia and non-dysplastic atypia, especially in the setting of Barrett’s oesophagus, and helps predict progression. However, reliance solely or largely on p53 expression is not recommended.[8,13,14,23,26]

[Level of evidence – GPP.]

1.5.2 Double reporting

- Current guidelines from other societies advise double reporting (preferably including a pathologist whose main area of reporting is GI pathology) for dysplasia or possible dysplasia in inflammatory bowel disease (IBD), particularly if non-polypoid and low grade.[8,9,12,37] They advise the same for dysplasia or possible dysplasia in Barrett’s

oesophagus, particularly for the category of indefinite for dysplasia and for cases where intervention is a consideration.[13] We support this approach, while acknowledging that double reporting of cases with persistent stable low grade dysplasia may not always be necessary or practical.

- Double reporting is obligatory for cancers arising in a polyp from BCSP patients.[15]

Epithelial dysplasia in the GI tract: Recommendations

Columnar dysplasia is classified as low grade or high grade.

Squamous dysplasia of the oesophagus is classified as low grade or high grade.

Dysplasia of anal squamous epithelium is classified as AIN (AIN 1, AIN 2 or AIN 3) and as LSIL or HSIL.

Biopsies that show, or might show, dysplasia (except for adenomas or for dysplasia adjacent to carcinomas) should be reported by at least 2 pathologists who have an established interest in GI pathology.

[Level of evidence – D.]

The term 'indefinite for dysplasia' is often useful if a decision about the presence or absence of dysplasia is not possible.

Cancer reports should follow the guidance in the relevant College dataset.[2–4,6,38] Neoplasms should be typed and graded according to published guidelines or texts.[7] Staging of resected tumours should generally follow the Union of International Cancer Control (UICC) TNM system.[39]

2 Gastrointestinal and pancreatic biopsies

2.1 Biopsies: general considerations

2.1.1 Mucosal biopsy: preparation, dissection and blocks

Fixation

The specimen should be fixed sufficiently before processing. We recommend biopsies should be fixed in formalin for at least 6 hours, although published evidence for an optimal fixation time is sparse.[40,41]

[Level of evidence – D.]

Orientation (mucosal versus submucosal)

Biopsies may be free-floating in formalin in the specimen container on receipt. Alternatively, endoscopists may attempt to orientate biopsies in terms of mucosal and submucosal aspects and/or anatomically by attaching them to filter paper, cellulose acetate paper or similar materials.

If mucosal and submucosal aspects of the biopsies are identifiable in the laboratory, the biopsies should be orientated as accurately as possible during embedding.[42]

Cellulose acetate strips are suitable for cutting with a microtome, but filter paper is unsuitable.

Orientation of biopsies from multiple anatomical sites (e.g. distal versus proximal large bowel)

Biopsies from different parts of the GI tract should be submitted in such a way that their site of origin is unequivocal. Failure to do this, e.g. placement of biopsies from different sites into a single pot, increases the risk of error. An example is placing oesophageal and gastric biopsies together, making distinction of gastric mucosa from Barrett's oesophagus mucosa impossible.

Ideally, biopsies from each part of a particular organ should also be distinguishable, e.g. oesophageal (upper, mid and lower), gastric (body and antrum) and colonoscopic (ileum and various large bowel sites).

Possible approaches to the identification by endoscopists of anatomical site include multiple specimen pots, cellulose acetate strips (or similar) and multi-well cassettes.[8,42,43]

- Biopsies from separate anatomical sites should be in separate pots. Each pot should include a label with the site of origin.
- Endoscopists may arrange biopsies from multiple sites sequentially on a cellulose acetate strip (or similar). The endoscopist should mark the strip to allow identification of the proximal or distal end and should agree in advance the meaning of the mark. This approach may fail because of detachment of biopsy fragments from the strip. It also places limitations on the number of biopsy fragments that the endoscopist can submit from each site.
- Endoscopists may submit biopsies in multi-well cassettes. The well corresponding to each biopsy site requires identification in advance. Several fragments can occupy each well. Careful matching of the well contents, embedded tissue and biopsy

fragments on the haematoxylin and eosin (H&E)-stained slide is necessary. If barcodes are in use, it may be difficult to add them to multi-well cassettes.

- Endoscopists may submit pre-cassetted biopsies. Pre-cassetting of biopsies saves laboratory time at the cut-up stage.
- If biopsies from multiple sites are floating in the same pot, their anatomical site of origin is often impossible to determine unless there are clear distinguishing histological features. Therefore, this approach is not acceptable.

Embedding

- Embed all fragments or cores in their entirety. For free-floating biopsies, carefully examine the side walls of the container as well as the lid, not to miss any fragments.
- Methods to avoid loss of small biopsy fragments include insertion of foam pads into the cassette or wrapping of fragments in a suitable material.
- If there are numerous fragments in a single cassette, laboratory staff may have difficulty orientating them and keeping them at the same level within the paraffin block.
- Embedding fragments in a horizontal or vertical line facilitates histological assessment.[24]
- Arranging fragments in a diagonal line or in a haphazard/random way makes microscopic assessment considerably more difficult and increases risk.
- Larger (e.g. full thickness) biopsies require orientation and may need slicing before embedding.

Reducing the volume of endoscopic biopsy cases

- The number of GI endoscopic biopsy cases continues to increase. Although pathologists do not usually advise clinicians on the management of their work, they may wish to alert clinicians to the existence of guidance documents on unnecessary sampling and on reducing the carbon footprint of endoscopic and laboratory procedures (‘green’ working).[44–46]
- For suspected neoplasia, the sample must be sufficiently generous to allow future molecular testing and other additional investigations. A review suggested a minimum of 8 biopsy fragments for adequate HER-2 assessment of upper GI biopsies.[47]

2.1.2 Mucosal biopsy: macroscopic description

- Record the number of fragments.[42] The terms ‘multiple’ and ‘several’ are imprecise. If there are too many fragments to count, an approximate number is appropriate.
- Record the range of sizes of fragments.
- Record attachment of biopsies to filter paper, cellulose acetate or similar.
- Describe any other material that is present, including foreign material.
- If there is no tissue present, follow local protocols to record this. Some centres attempt a cell block in this circumstance.

Discrepancies

- Discrepancies between the macroscopic count of fragments and the number of fragments identifiable on the slide raise the possibility of uncut tissue in the block, fragmentation of a sample (e.g. a friable polyp), or specimen interchange.
- Discrepancies between the number of biopsy fragments recorded by the endoscopist and the number identifiable in the laboratory may be worth noting but are quite frequent. An increase in number may reflect fragmentation.
- Contamination of samples with additional fragments at endoscopy, during biopsy processing (e.g. carry-over or transfer errors), or at another stage are worth considering if the histological features do not correspond with the clinical details or the sample details. If there is a potential impact on management, confirmation by DNA genotyping may be appropriate (test code R264.1 on the national genomic test directory).

2.1.3 Mucosal biopsy: sections and stains

Minimum stains

H&E. Many laboratories do step sections routinely at 3 levels (e.g. 75 microns apart). This approach is recommended.[24,42] Depending on the specimen type, the laboratory may retain unstained sections from between the levels for subsequent use.

[Level of evidence – D.]

Deeper levels and additional stains

Additional levels may be useful for improving orientation, detecting lesions, distinction of reactive epithelial changes from dysplasia and confirmation of invasive carcinoma. There is consistent evidence that deeper levels may reveal a lesion, e.g. an adenoma, that was

not apparent on the initial sections.[48–51] However, a cautious approach to deeper levels is appropriate if molecular tests on the tissue may be necessary at a later stage.

[Level of evidence – C.]

Periodic acid-Schiff (PAS) with diastase (DPAS) and Ziehl Neelsen (ZN) stains may be useful if granulomas are present, but this depends on the clinical setting. A ZN stain is appropriate if a granuloma shows necrosis.

In the setting of HIV and other forms of immune suppression, stains for fungi, mycobacteria and protozoa may be worth considering if there is inflammation or significant concern about a particular diagnosis,[42] but may yield little or no additional information – especially when applied routinely.[52,53]

A Congo Red stain examined under polarised light helps to confirm or exclude amyloid if a clinician or pathologist suspects the diagnosis. If amyloid is confirmed, further special stains and immunohistochemistry and specialist referral may be appropriate.[54]

Immunohistochemistry

- Immunohistochemical stains for cytomegalovirus (CMV) and/or herpes simplex virus (HSV) are worth considering if there is clinical suspicion, histological ulceration or the presence of equivocal inclusions on examination of H&E slides. Their diagnostic yield is higher than for H&E sections, but some studies cast doubt on the additional clinical value.[52,53]

  [Level of evidence – D.]

- Stains may have more value in immunosuppressed patients (e.g. HIV, severe ulcerative colitis [UC]) and in graft versus host disease (GvHD) than in other settings.[55,56]

  [Level of evidence – GPP.]

- The clinical significance of small numbers of CMV inclusions on immunohistochemistry or of equivocal immunohistochemical staining is uncertain, while the benefits of attempting to quantify inclusions are controversial.[57] Such cases may merit discussion with the clinical team.

- Immunohistochemical staining for CMV within lymphocytes and plasma cells requires cautious interpretation.

2.1.4 Mucosal biopsy: histology report and microscopic description

General

- The adequacy and appropriateness of the sample should be noted and recorded if relevant.
- A separate description should be composed for each separately submitted set of biopsies if they show dissimilar features or if they are from histologically dissimilar sites. However, biopsies from histologically similar sites showing similar abnormalities, e.g. multiple colorectal biopsies all showing the same pattern of inflammation, should be reported together.
- Many histological changes require correlation with clinical and endoscopic findings for accurate interpretation.[8,58,59] If inadequate details prevent full interpretation, the report should record this.

  [Level of evidence – D.]

- Clinicopathological meetings and good communication help refine interpretation.[9,14,60,61]

Mucosal biopsy: recommendations

Adequate clinical details are necessary for accurate interpretation of histology.

[Level of evidence – GPP.]

The anatomical site of origin of GI mucosal biopsies should always be clear to the pathologist.

[Level of evidence – D.]

Step sections routinely at 3 levels (e.g. 75 microns apart) are recommended.

[Level of evidence – GPP.]

Additional levels are often useful if orientation is suboptimal.

Additional levels may be helpful if initial levels do not demonstrate a focal lesion, e.g. a polyp that was apparent clinically.

[Level of evidence – C.]

Clinicopathological meetings are often useful and help improve reporting quality.

[Level of evidence – D.]

2.2 Oesophageal biopsy: additional comments

2.2.1 Clinical

Endoscopists submitting biopsies for initial diagnosis or follow-up of Barrett's oesophagus should submit full details of the endoscopic findings, e.g. Prague classification, the exact site of origin of each set of biopsies and any history of previous Barrett's oesophagus or dysplasia.

2.2.2 Sections and stains

Additional stains

Special stains for mucins may be useful, e.g. PAS +/- Diastase (PAS +/- D) and Alcian Blue (AB), often in the form of an AB-PASD stain.[62] AB positivity helps to confirm intestinal metaplasia by highlighting goblet cell mucin droplets as blue (although not all AB positive cells are goblet cells).[63] PAS staining also helps to identify fungi.

Some guidelines recommend PAS and AB if columnar mucosa is present; others suggest routine special stains and some are sceptical about the value of these stains.[43,62] Opinions and evidence conflict[36,62,64,65] and the approach varies. Many laboratories no longer do the stains routinely and instead rely on pathologists to request them as appropriate, with the aim of reducing the overall volume of work and material.

Deeper levels may be useful, e.g. to detect goblet cells and in particular to assess epithelial atypia thoroughly.[36,49]

[Level of evidence – D.]

2.2.3 Report and microscopic description

Indications for oesophageal biopsy: examples

- Assessment of oesophagitis and its aetiology (e.g. reflux, eosinophilic, infective).
- Diagnosis and assessment of Barrett's oesophagus.

Report

If squamous epithelium and columnar epithelium are present, each requires description. Other appropriate items to include are the presence or absence of metaplastic epithelium, fungi and dysplasia. If there is inflammation, other micro-organisms may be a consideration, e.g. HSV, CMV and mycobacteria.

Elongation of papillae and basal cell hyperplasia may be secondary to reflux but are not specific.

Diagnosis of intestinal metaplasia requires the presence of goblet cells. There is no need to subclassify intestinal metaplasia as complete or incomplete.

Eosinophilic oesophagitis

- The diagnosis of eosinophilic oesophagitis is clinicopathological and is appropriate if numerous eosinophils are seen in the appropriate clinical setting with characteristic histological and endoscopic features.[66,67]
- BSG guidelines advocate a total of at least 6 biopsies from different levels in the oesophagus and require, to make the diagnosis, ≥15 eosinophils per 0.3 mm^2, typical histological features and exclusion of other causes of eosinophilia.[68]
- Suggestive endoscopic features include 'feline' oesophagus, furrows and ridges.
- Microscopic changes that are supportive include superficial eosinophilic layering/aggregates, eosinophilic microabscesses, basal cell hyperplasia, intercellular oedema and elongation of papillae.
- Eosinophil infiltration is often patchy within biopsies, between biopsies and between anatomical sites.
- In follow-up biopsies, a definition of remission is <15 eosinophils per 0.3 mm^2.[68] This may not correlate well with clinical remission.
- The histology of eosinophilic oesophagitis overlaps partly with that of reflux oesophagitis, which is a consideration in the lower oesophagus but rarely involves the mid or more proximal oesophagus.

Barrett's oesophagus

- The diagnosis of Barrett's (columnar lined) oesophagus is mainly endoscopic.
- The pathologist may make a confident diagnosis of Barrett's oesophagus when glandular mucosa is present together with native oesophageal structures (squamous ducts and/or oesophageal submucosal glands), although such native structures are only present in a small proportion of biopsies (e.g. <15%).[13] When oesophageal biopsies contain native structures, the pathologist can conclude: 'Barrett's oesophagus with gastric metaplasia only' or 'Barrett's oesophagus with intestinal metaplasia.'[13] A comment on the presence or absence of intestinal metaplasia is necessary, especially in short segment (<3 cm) disease, where the presence or absence of intestinal metaplasia may determine the need for endoscopic surveillance.[13] Intestinal

metaplasia considerably increases the risk of progression to neoplasia in most studies (e.g. >5-fold).[69]

In biopsies where native oesophageal structures are not present, gastric-type mucosa (with or without intestinal metaplasia) may originate from Barrett's oesophagus, but may also originate from a hiatus hernia or the gastric cardia/proximal stomach.[13] In these circumstances, the diagnosis of Barrett's oesophagus can only be made with confidence by the endoscopist. It is prudent for the pathologist to conclude either 'Oesophageal biopsy – gastric-type mucosa only. Biopsies supportive of the diagnosis of Barrett's oesophagus if taken from the tubular oesophagus' or 'Oesophageal biopsy – glandular mucosa with intestinal metaplasia. Biopsies supportive of the diagnosis of Barrett's oesophagus if taken from the tubular oesophagus'.[13] However, the words 'if taken from the tubular oesophagus' may not be necessary if the clinical details state clearly that the biopsies are indeed from the tubular oesophagus.

Suspected columnar dysplasia should be corroborated by a second pathologist, preferably a pathologist with an established specialist GI interest.[13]

p53 staining for dysplasia in Barrett's oesophagus

The addition of p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of a diagnosis of dysplasia in Barrett's oesophagus and may be considered as an adjunct to routine diagnosis.[13,70] Pathologists may wish to consider p53 staining when they are unsure how to classify columnar epithelial atypia or when they are contemplating a diagnosis of 'indefinite for dysplasia'.

Abnormal patterns of p53 expression include extensive overexpression and loss of expression. However, this remains a controversial topic and there is no standardisation of p53 staining between laboratories globally. Therefore, strong reliance on p53 staining to classify atypia is not advisable.

[Level of evidence – GPP.]

Oesophageal biopsy: recommendations

ABPASD staining may be useful for characterisation of mucins and to detect fungi.

Routine ABPASD staining may be appropriate for some laboratories, but evidence and support for this approach are inconsistent.

[Level of evidence – GPP.]

Diagnosis of intestinal metaplasia in oesophageal biopsies requires the presence of goblet cells.

When reporting biopsies for assessment of Barrett's oesophagus, an approach that considers BSG guidelines is appropriate (please see text).

Histological distinction of eosinophilic oesophagitis from reflux oesophagitis is often difficult if eosinophil numbers are not high. Correlation with clinical and endoscopic findings is advisable.

2.3 Gastric biopsy: additional comments

2.3.1 Sections and stains

Additional stains

- A histochemical (e.g. Giemsa, Cresyl Fast violet) or immunohistochemical stain for *Helicobacter pylori* should be available. Immunohistochemistry is more sensitive and specific, but more expensive.
- The updated Sydney classification system guidelines suggest, as a minimum, staining for *H. pylori* when there is inflammation in the absence of identifiable *Helicobacter*-like organisms.[71] There is conflicting evidence and opinion regarding the diagnostic value, clinical value and cost effectiveness of performing a *H. pylori* stain routinely or in all cases of gastritis.[8,62,64,65,72]
- *H. pylori* are difficult to see in digital images. Therefore, a stain is more often necessary in this setting.
- Following antibiotic or protein pump inhibitor (PPI) treatment, breath tests are unreliable for the detection of *H. pylori*. In this setting, histology (with staining where necessary) may greatly assist clinical management. According to some reports, immunohistochemistry is more sensitive than special stains in this setting.[62,73,74]
- There are several studies that outline a particular approach, sometimes identifying the settings where additional staining for *H. pylori* adds diagnostic value. However, the various studies do not all reach the same conclusions.[72]

- In settings other than post-PPI therapy, pathologists may consider reminding clinicians that non-histological methods to detect *H. pylori* are often preferable and are less expensive.

Recommendation

A *Helicobacter* stain is appropriate if characteristic active chronic inflammation is present, no *H. pylori* are apparent histologically and there is no information about a clinical test for *Helicobacter* (e.g. campylobacter-like organism (CLO) test). It is also appropriate if, after PPI therapy, there is histological inflammation and no *Helicobacter* are apparent on H&E examination.

Other stains

Special stains for mucins help to identify intestinal metaplasia in gastric mucosa. PAS+/-diastase and AB are most often used, ideally ABPASD.[62,71] Some laboratories perform mucin stains routinely, but this approach creates extra work, is a topic of controversy and appears to be less common than in the past.[62,65]

A Perls stain can help to confirm iron deposits in areas of erosion or gastritis ('iron pill gastropathy') and may be necessary to exclude the possibility of other pigments such as melanin in a neoplasm.[75]

2.3.2 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and assessment of gastritis/ulceration.
- Exclusion of intestinal metaplasia or neoplasia.
- Detection of *H. pylori.*
- Characterisation of polyps.

Report: general comments

- Note the number of body-type/fundus-type ('specialised'/oxyntic) and antrum-type/cardia-type ('non-specialised') biopsies. Describe biopsies from different sites separately unless they are the same or very similar.
- Assess the features recommended by the updated Sydney classification: chronic inflammation, activity, intestinal metaplasia, atrophy, dysplasia, *Helicobacter*.[71] The OLGA staging system for gastritis may be in use clinically and depends on the Sydney system.[76]

Report: most common categories of gastritis

- *Helicobacter*-associated chronic gastritis, with or without activity.
- Reactive (chemical) gastropathy/gastritis, including pill gastropathy. Reactive patterns are most often secondary to NSAID use, bile reflux or chemical damage.
- Atrophic gastritis, characterised by chronic inflammation, atrophy and intestinal metaplasia. This pattern can be secondary to *H. pylori* infection (typically antral-predominant or similar in antrum and body) or autoimmune gastritis (typically body-predominant and associated clinically with antibodies to parietal cells and intrinsic factor). By convention, the term may imply the latter.
- If there is atrophy of body/fundus mucosa, there may be neuroendocrine cell (ECL-cell) hyperplasia in the body/fundus. Immunohistochemistry for chromogranin and synaptophysin helps to detect hyperplasia and to assess its severity. Distinction of antral mucosa from oxyntic mucosa can be difficult if there is atrophy and loss of glands. In this setting, a gastrin stain is useful because G-cells (immunopositive for gastrin) are present in the antrum and are usually absent or very sparse in the body/fundus.
- 'Lymphocytic' gastritis: criteria vary, e.g. >25 lymphocytes per 100 epithelial cells. The pattern has several aetiologies and associations, including coeliac disease, *H. pylori*, microscopic colitis, NSAIDs, immune checkpoint inhibitor (ICI) drugs, other drugs and HIV infection.[77,78] Immunohistochemistry is not necessary for the quantification of lymphocytes.
- 'Granulomatous' gastritis can be secondary to Crohn's disease, mycobacterial infection, fungi, other infections, foreign material, crypt/gland rupture, sarcoidosis and a variety of rarer entities.[78] A possible association with *H. pylori* infection is controversial, may vary in strength with geography and is more likely when there is no other cause for the granulomas, but the prevalence of *H. pylori* may actually be the same as in controls.[78–82] In 1 report, most granulomatous gastritis (220/269 cases) occurred in patients with Crohn's disease, sarcoidosis or tuberculosis.[81] In the same study, isolated granulomatous gastritis (i.e. no previous diagnosis and no lower GI granulomas) had a positive predictive value for Crohn's disease of 91% in patients aged <30 years.[81]
- Drugs can cause a variety of patterns. ICIs can cause active chronic gastritis, lymphocytic gastritis, focally enhanced gastritis and other patterns.[83]

Gastric biopsy: recommendations

When reporting gastritis in biopsies, use of the updated 1996 Sydney classification is appropriate. Chronic inflammation, activity, intestinal metaplasia, atrophy and dysplasia require grading. The presence or absence of *H. pylori* requires documentation.

The most common types of gastritis are *Helicobacter*-associated gastritis and reactive gastritis/gastropathy.

As a minimum, a *Helicobacter* stain is appropriate if characteristic inflammation is present, no *Helicobacter* are apparent on H&E assessment and no clinical test for *H. pylori* took place.

[Level of evidence – GPP.]

An ABPASD stain for mucins may be useful for confirming intestinal metaplasia.

Routine use of *Helicobacter* stains and/or mucin stains varies between laboratories. Evidence and support for this approach are inconsistent and may not justify the additional workload.

2.4 Duodenal/jejunal biopsy: additional comments

2.4.1 Sections and stains

- Deeper levels are often useful if villous architecture and intraepithelial lymphocyte numbers are difficult to assess in a poorly orientated or small biopsy.

Immunohistochemistry and polymerase chain reaction

- Immunohistochemistry for T-cell subtypes and polymerase chain reaction (PCR)-based studies for T-cell receptor rearrangement may be appropriate in biopsies with features of coeliac disease if there is evidence of refractory coeliac disease, a suspicion of T-cell neoplasia, or cytological atypia.[84,85] CD3, CD4 and CD8 ratios change in type 2 refractory coeliac disease. Referral to a haematological pathologist may be appropriate.
- Immunohistochemistry for CD3 to determine lymphocyte counts is not recommended.[86,87]
- CD117 immunohistochemistry may help identify *Giardia* trophozoites but is not usually necessary for diagnosis.[88]

- Whipple's disease is an extremely rare cause of enteropathy. A PASD stain helps make the diagnosis, but immunohistochemistry, PCR or electron microscopy are usually necessary for confirmation and are generally only available in specialised centres.

2.4.2 Report and microscopic description

Indications for duodenal/jejunal biopsy: examples

- Exclusion of an enteropathy, particularly coeliac disease.[85]
- Assessment of duodenitis or ulceration.
- Exclusion of dysplasia or of primary/secondary malignancy.
- Most guidelines on coeliac disease affirm the importance of biopsy assessment even when serology is available, although in some children with positive serology a biopsy is not considered necessary.[89,90] A biopsy may not be necessary in adult patients with a tissue transglutaminase (tTG) level more than 10 times the upper limit of normal.[90]

Report

- Samples from normal mucosa from the first part (D1) and second part (D2) of the duodenum are not identical. Ideally, the endoscopist submits them separately. Villi may be more irregular, shorter and more distorted by Brunner glands in D1 than in D2. Submission in the same specimen container could cause diagnostic confusion.
- If duodenal biopsies show evidence of trauma or suboptimal processing to the extent that reliable assessment of villous architecture is not possible, the histology report should record this observation.
- At least 4 biopsy fragments are appropriate for exclusion of coeliac disease, as the yield increases between 1 and 4 fragments. Both D1 and D2 require sampling, because the histological abnormalities are occasionally limited to D1 or D2. The term ultra-short coeliac disease refers to a form that involves D1 only and is typically milder and of younger onset.[45,85,91–94]
- Note features of coeliac disease, e.g. villous atrophy, an increase in intraepithelial lymphocytes (IEL), distribution of IELs, and surface epithelial changes.[84,85]
- An IEL count of >25 per 100 epithelial cells in the villous tips supports the diagnosis and a count of >40 allows more confident diagnosis.[85,95] In the absence of villous

atrophy these counts correlate with Marsh categories 0 and 1/2 but there is no requirement to give a Marsh category in clinical practice.[95,96]

- An IEL count of 21–25 per 100 epithelial cells represents a borderline increase. It is worth recording and interpreting with caution. Deeper levels may be useful.
- There are several possible causes of intraepithelial lymphocytosis, including coeliac disease, *H. pylori* infection, other infections and drugs.
- Seek *Giardia lamblia* and other infective agents, especially in the setting of immunosuppression. *Giardia* trophozoites are easy to miss if sparse.
- Confirmation of the presence of plasma cells in all intestinal biopsies is advisable because absence of plasma cells is easy to miss without active searching and is a useful pointer towards a diagnosis of common variable immune deficiency.[97]

2.5 Ileal biopsy: additional comments

2.5.1 Report and microscopic description

Indications for biopsy: examples

- Assessment of symptoms.
- Confirmation and characterisation of endoscopic ileitis.
- IBD diagnosis, assessment and classification.[14,98–100]

  [Level of evidence – D.]
- Exclusion of possible focal lesion or neoplasia (e.g. abnormal imaging, abnormal endoscopy).
- Confirmation that the endoscopist reached the ileum. Biopsies are taken for this reason, despite the existence of guidelines stating that they are unnecessary.[44,46]

Report

- Normal ileal lymphoid tissue may appear polypoid at endoscopy and can be prominent histologically.
- A diagnosis of ileitis is difficult in the absence of acute inflammation/ulceration or of other unequivocally abnormal features, such as granulomas, pyloric metaplasia or definite villous atrophy.[101,102]

  [Level of evidence – GPP.]

- Endoscopists often take biopsies from abnormal ileal mucosa to confirm or exclude Crohn's disease. Unfortunately, reliable distinction between Crohn's disease and other more common causes of ileitis, such as NSAIDs and infection, is usually difficult unless there are granulomas.[103,104] Granulomas are rarely present but point strongly towards Crohn's disease. Pyloric metaplasia and patchy lamina propria chronic inflammation may also suggest Crohn's disease in some settings.[105]

2.6 Colorectal biopsy: additional comments

2.6.1 Report and microscopic description

Indications for biopsy: examples

- Assessment of symptoms.
- Diagnosis and follow-up of chronic idiopathic IBD and other colitides.
- Confirmation, exclusion or follow-up of polyps, dysplasia or malignancy, including BCSP.[15]

Report: general comments

- For inflammatory conditions, observe (and, if appropriate, record) the distribution of changes within biopsies, between biopsies from the same site and between biopsies from separate sites, as this can be very useful diagnostically in certain settings and particularly in IBD.[98,104]

  [Level of evidence – A.]

- Ileal and colonic biopsies may be present in the same pot and should receive separate descriptions, although their distinction can be difficult if there is inflammation.

Assessment: inflammation

- Decide whether the mucosa is normal or abnormal.
- If there is inflammation, attempt to categorise it as IBD type or another type.
- Terms such as 'non-specific chronic colitis'/'non-specific colitis' are not acceptable.[14,106] When classification is not possible, the report should state this.

  [Level of evidence – GPP.]

Chronic idiopathic inflammatory bowel disease

- BSG IBD biopsy reporting guidelines are recommended.[14] Other guidelines are also available.[8,56,104,107]
- The report should state the probability of IBD, especially in initial biopsies.[14] The features that favour IBD over other colitides most strongly, in the appropriate clinical setting, are basal plasmacytosis and mucosal architectural changes (including crypt distortion and crypt atrophy).[14]

  [Level of evidence – A.]
- If IBD is definite or very likely, the report should record the probability of UC or Crohn's disease. The microscopic features that help distinguish UC and Crohn's disease from each other include non-cryptolytic granulomas, architectural changes and distribution of disease. Granulomas strongly favour Crohn's disease and are more specific than any other feature.[14]

  [Level of evidence – A.]
- IBD is sometimes difficult or impossible to classify further. The term 'IBD unclassified' may be appropriate in this setting, although it is a clinicopathological rather than histological term.[14,107,108] The term 'indeterminate colitis' is not applicable to biopsy reporting.[14,98,109]
- There is no widely agreed grading scheme for histological inflammation or activity in IBD, but a description of the severity of activity is helpful.[14,37]
- Most of the many IBD scoring schemes that are available are designed for clinical trials; the Nancy histological index is the easiest to apply to routine diagnostic pathology practice and is in use in some centres.[11,110]
- Time and treatment may modify the histology of IBD significantly and often lead to discontinuity in UC.[14,111–114] Therefore, classification of IBD in post-treatment biopsies can be difficult. Furthermore, biopsies taken very early in the course of IBD may show few or no histological changes.[14,98,115,116]

  [Level of evidence – C.]
- Discussion of IBD cases with clinicians helps reduce the risk of inaccurate classification and misunderstandings.[14,60,61]

- The acronym ‘PAID’ (pattern, activity, interpretation, dysplasia) can be a useful aide-memoire for the structure of the conclusion of an IBD biopsy report.[14]
- Immunohistochemistry for CMV is a consideration when there is severe refractory disease, severe activity/ulceration, or when inclusions are suspected in H&E-stained sections.[12]

  [Level of evidence – GPP.]

Microscopic colitis

- Classification as ‘collagenous colitis’ or ‘lymphocytic colitis’ is usually preferable to the term ‘microscopic colitis’. However, overlap is frequent and many experts regard the distinction as unnecessary.[106,117,118]
- Diagnosis of collagenous colitis requires a thickened subepithelial collagen band (>15 micrometres).
- Diagnosis of lymphocytic colitis requires an intraepithelial lymphocyte count of >20 per 100 epithelial cells. A similar increase can occur in collagenous colitis. If there is a thickened collagen band, the diagnosis defaults to collagenous colitis.
- Both forms of microscopic colitis may show degenerative surface epithelial changes and lamina propria lymphoplasmacytosis. Neutrophils do not exclude the diagnosis but raise the possibility of other entities, particularly if numerous.
- The differential diagnosis of collagenous colitis includes amyloidosis. Examination of blood vessels and muscularis mucosae for evidence of amyloid is advisable, with Congo Red staining where appropriate.

Drug effect

- Drugs can cause a variety of patterns of GI tract inflammatory change. Most histological patterns can occur as a result of diverse drug types. In addition, many drugs can cause a wide range of abnormalities. Unfortunately, there are few drugs that cause specific patterns of change. This is a complex topic, reviewed elsewhere.[119–121]
- NSAID-induced colitis is worth considering if features do not conform to a recognised pattern, but the histology is not specific.[119,120] Ileal erosion is probably common.
- ICI drugs are effective for the treatment of cancer. Their use is increasing steadily. They commonly cause side effects and can produce a wide variety of patterns of colitis including a microscopic colitis appearance, acute neutrophilic colitis, chronic or active

chronic inflammation resembling IBD, a GvHD-like appearance with crypt epithelial cell apoptosis, or crypt epithelial cell apoptosis only. Mixed patterns are common. A full drug history is essential.[122,123] ICIs can also cause upper GI tract toxicity.

- Mycophenolate mofetil damage may mimic GvHD histologically and can share some features with IBD but rarely resembles IBD closely.[124]

Comments on other forms of colitis

- Radiation colitis, diversion colitis, diverticular colitis and GvHD: reliable diagnosis depends on clinical details.[10]
- Diverticular colitis can resemble IBD clinically and histologically; there may be some overlap.[125]
- Ischaemia and rectal mucosal prolapse are also common causes of lower GI tract mucosal abnormalities. Mucosal prolapse sometimes produces alarming histological changes that may suggest neoplasia to the unwary.
- Acute changes, sometimes resulting in the pattern of 'focal active colitis', are the result of diverse causes but in particular raise the possibility of infection and drugs.[126]

Polyp biopsies/dysplasia

- Polyp biopsies are usually from adenomas, hyperplastic polyps, sessile serrated lesions (SSLs) or inflammatory polyps. Native lymphoid tissue, particularly lymphoid follicles or mucosal folds may mimic a polyp endoscopically. Deeper levels are appropriate if initial H&E-stained slides show no features of a polyp.[48,50,51]

  [Level of evidence – C.]

- In the setting of IBD, it is often difficult to distinguish a sporadic adenoma from IBD-related dysplasia on the basis of histology. The distinction is not relevant to clinical management.[127] However, recognition of new forms of IBD-related dysplasia are emerging and may require new approaches to interpretation and management by pathologists.[128,129]
- Serrated epithelial change is a poorly defined entity, apparently related to longstanding IBD. There is little consensus about definitions and clinical implications.[130]

Hirschsprung's disease

- Ideally, specialist pathologists will report these specimens. In a general setting, examination of multiple serial H&E sections of a deep mucosal biopsy from the

submucosal aspect towards the mucosal aspect will usually reveal ganglion cells if they are present, thus (according to most guidelines) allowing exclusion of Hirschsprung's disease. A positive diagnosis of Hirschsprung's disease requires specialist input.

Colorectal biopsy: recommendations

If there is inflammation, categorise it as IBD type, microscopic colitis, acute or another type where possible. Consider drugs and infection.

State the probability of IBD if this is a clinical consideration, especially in initial biopsies. The features that favour IBD over other causes most strongly are basal plasmacytosis and mucosal architectural changes.

[Level of evidence – A.]

If IBD is definite or very likely, state the probability of UC or Crohn's disease. The microscopic features that are most useful for distinguishing UC and Crohn's disease from each other include non-cryptolytic granulomas, architectural changes and distribution of disease.

[Level of evidence – A.]

The Nancy histological index may be useful for grading severity of inflammation in IBD.

The term 'indeterminate colitis' is not applicable to biopsy reporting. If a term is necessary, the clinicopathological term 'IBD unclassified' is appropriate.

The acronym 'PAID' (pattern, activity, interpretation, dysplasia) is an aide-memoire for the structure of the conclusion of an IBD biopsy report.

Record microscopic colitis as collagenous colitis or lymphocytic colitis if possible.

Avoid the terms 'non-specific chronic colitis' and 'non-specific colitis'.

Clinical details are essential for accurate diagnosis and assessment of most types of colitis.

[Level of evidence – D.]

2.7 Anal biopsy: additional comments

2.7.1 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and assessment of wart virus change, AIN/squamous intraepithelial lesion (SIL) and malignancy.

General

- The description of squamous epithelium should include a record of wart virus change and AIN (classified as AIN 1, AIN 2, or AIN 3 and as LSIL or HSIL [see above]). Immunohistochemistry for p16 is increasingly popular as a surrogate marker for high-risk types of human papillomavirus (HPV) infection and/or to help confirm high risk lesions but is not reliable for determining grade of dysplasia. There is variation in practice and in interpretation.[131,132]
- Immunohistochemistry or in situ hybridisation for HPV, if available, help to confirm a HPV-related pathogenesis but are not often necessary clinically.
- Additional details are available in the College dataset on anal cancers.[133]

2.8 Ileoanal pouch biopsy: additional comments

2.8.1 Report and microscopic description

Indications for biopsy: examples

- Assessment of inflammation/pouchitis.
- Exclusion of other inflammatory conditions.
- Surveillance for dysplasia and carcinoma.

Pouchitis

- Adaptive changes, e.g. villous atrophy and ‘colonisation’ of ileal mucosa (metaplasia to a colonic phenotype), may occur in the ileal mucosa of a pouch.
- Diagnosis of pouchitis depends on a combination of clinical, endoscopic and histological findings and is not precise in terms of histological criteria. Pouch inflammatory scores exist, are in use in some centres and can act as an aide-memoire to the pathologist.[134–138]
- The features of pouchitis may mimic those of UC or Crohn’s disease. Comments on the presence of IBD in a pouch biopsy should be cautious.[134,139,140]

[Level of evidence – C.]

- The endoscopist may take biopsies from columnar mucosa at the distal end of the pouch originating in the anal canal, from specific locations within the pouch itself, or from the pre-pouch ileum. The endoscopist should specify clearly their site of origin. This permits discrimination of ‘cuffitis’ (inflammation of residual rectal mucosa of the distal pouch) from ‘pouchitis’ and ‘pre-pouch ileitis’, a distinction that may be clinically important but may be impossible to make histologically because of adaptive and inflammatory changes.[12]
- Further details are available in standard textbooks.[138,141]

2.9 Ampulla of Vater biopsy: additional comments

2.9.1 Report and microscopic description

Indications for biopsy: examples

- Exclusion of neoplasia.
- Characterisation of focal lesions.
- For IgG4 immunohistochemistry.

Report

The term ‘ampulla’ is sometimes not precise and may refer to the true ampulla and/or the periampullary duodenal mucosa.[142–144] A report of dysplasia or carcinoma in this area may have profound implications for clinical management, including radical surgery. Interpretation of histology should consider the clinical and imaging findings and past history. Atypical epithelial changes are not uncommon if there is ulceration, inflammation or a history of intervention (sphincterotomy, stenting). Inflammatory-type polyps can mimic neoplasia.[145] Double reporting or involvement in reporting by a specialist pathologist is usually appropriate.

[Level of evidence – GPP.]

IgG4 immunohistochemistry can be performed on biopsies from the ampulla of Vater (as a surrogate diagnostic sample) to support a diagnosis of autoimmune pancreatitis.[146] A ratio of IgG4 to IgG higher than 40% or absolute numbers (>10 IgG4+ plasma cells per high power field in a biopsy) may be used to support the diagnosis.[147,148] IgG4 +ve plasma cells can accumulate in other settings. The diagnosis is clinicopathological.

[Level of evidence – D.]

2.10 Pancreatic biopsy: additional comments

2.10.1 Macroscopic description of needle core biopsies: additional considerations

- Record the length of each core (millimetres). Note obvious focal changes, e.g. haemorrhage.

2.10.2 Sections and stains from needle core biopsies: additional considerations

- Additional unstained sections from needle core biopsies at initial processing may be useful as the amount of tissue is often small and immunohistochemistry may be necessary. Furthermore, repeat biopsy is not always easy.

2.10.3 Clinical

- Ideally, processing and reporting of pancreatic biopsies will take place in specialist centres with access to appropriate clinical, imaging and histopathological expertise. Details of the indication(s) for biopsy, imaging results, operative findings and previous histology are important.

  [Level of evidence – GPP.]

2.10.4 Sections and stains

Immunohistochemistry

- Immunohistochemistry can help characterise pancreatic tumours and in some cases is essential.[7,17,148] IgG4 staining may be useful if type 1 autoimmune pancreatitis is suspected.[147,148,150] Elastic stains may help to highlight obliterative phlebitis in type 1 autoimmune pancreatitis.

2.10.5 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and characterisation of neoplasia.
- Confirmation or exclusion of inflammatory conditions.

Report

- Chronic pancreatitis can be difficult to distinguish from carcinoma, especially in frozen sections.[149,151] Double reporting may be appropriate.

  [Level of evidence – GPP.]

- Autoimmune pancreatitis may mimic carcinoma clinically and radiologically.[152] The histological changes may suggest or support the diagnosis.[153] Histological peritumoral

inflammation can have features that overlap with autoimmune pancreatitis. IgG4 immunohistochemistry may be helpful in this situation.[149] A ratio of IgG4+ to IgG+ plasma cells higher than 40% and/or >10 IgG4+ plasma cells per high power field in a pancreatic biopsy may support a diagnosis of type 1 autoimmune pancreatitis.[147,148,154]

[Level of evidence – C.]

- Unusual tumours and difficult cases may require correlation with imaging findings and discussion at a multidisciplinary meeting, preferably by a histopathologist familiar with pancreatic pathology.[149,152] Referral of the histology material to a specialist centre may be appropriate.

  [Level of evidence – GPP.]

2.11 Endoscopic ultrasound-guided fine needle biopsies: additional comments

2.11.1 Macroscopic description of endoscopic ultrasound-guided biopsies: additional considerations

- The approach is similar to that described above for needle core biopsies. There may be considerable fragmentation. Input from cytopathologists may be helpful.

2.11.2 Sections and stains from needle core biopsies: additional considerations

- Serial sections or unstained sections at initial processing may be useful (see section 2.10).

2.11.3 Clinical

- Pancreatic and bile duct biopsies, as noted above, should ideally be reported in specialist centres.

2.11.4 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and characterisation of GI and pancreatobiliary neoplasia.

3 Small gastrointestinal resection specimens

3.1 Appendicectomy

3.1.1 Preparation, dissection and blocks

Sampling and processing

- Bisect the tip longitudinally.[24] Serially slice the remaining appendix transversely or bisect the proximal end (base) and slice the intervening tissue between the base and tip transversely or longitudinally.
- Sample the surgical margin (base), either longitudinally or transversely. This section should be identifiable microscopically (e.g. coloured ink/a nick in the relevant section/a section of a different shape/use of a separate cassette). Other blocks should include at least 1 longitudinal half of the tip (with mesoappendix) and at least 1 more section, plus representative blocks from abnormal areas.[24]
- Process the entire appendix if neoplasia is likely (see below).
- Process the entire appendix if it is dilated or contains obvious mucin or has other macroscopic or histological features of a mucinous neoplasm (see below).
- Process the entire appendix if there is dysplasia or a serrated lesion.[5]
- Process the entire appendix if there is acute serositis or other evidence of inflammation that does not fulfil the criteria for a diagnosis of acute appendicitis.
- Diverticula can cause focal appendicitis. Regenerative changes in association with diverticula can resemble low grade appendiceal mucinous neoplasm.[155]
- 'Interval' appendicectomy may show mainly chronic changes with little or no residual acute inflammation.
- Many pathologists advise sampling the entire appendix when initial histology is normal. There is evidence both to support this approach and to show that this approach has no clinical value.[156,157]
- If the appendix looks normal at initial cut-up, it may be worth submitting in its entirety at this stage.

  [Level of evidence – GPP.]

3.1.2 Specimen description

- Dimensions (millimetres): length and diameter.[24]
- External surface: perforation, peritonitis, congestion, abscess, mucin. Always inspect the unopened appendix for external mucin and evidence of mucin leakage, especially if the appendix is dilated.[158]
- Cut surface: luminal contents, mucin, diverticula, nodules, possible neuroendocrine neoplasm. The latter is most often at the tip but can be elsewhere.
- Refer to College guidelines on appendiceal neoplasia if low grade appendiceal neoplasm or malignancy is suspected.[5]

3.1.3 Report and microscopic description

Indications

Indications include confirmation or exclusion of acute appendicitis or of neoplasia.

Report

- Appendicitis: ulceration or transmural acute inflammation are necessary for diagnosis. Mucosal inflammation alone is not sufficient.

  [Level of evidence – GPP.]

- Appendiceal serosal inflammation in the absence of transmural inflammation may reflect extra-appendiceal pathology. In this circumstance, the entire appendix should be sampled to demonstrate or exclude acute appendicitis.

  [Level of evidence – GPP.]

- There may be features suggesting Crohn's disease, e.g. granulomas or transmural chronic inflammation. However, they are more likely to reflect delayed resection of acute appendicitis (interval appendicitis). Crohn's disease accounts for a minority of granulomatous appendicitis.[155,159]

  [Level of evidence – D.]

- UC may involve the appendix, and the changes can occur in the absence of caecal involvement.[160,161]

  [Level of evidence – D.]

- Distinction between hyperplastic polyps, other serrated lesions and adenomas is often not easy in the appendix.[162,163] If examination shows a serrated lesion, epithelial

dysplasia, or any feature suggestive of carcinoma, sampling of the entire appendix is advisable.[5]

[Level of evidence – GPP.]

- Appendiceal mucinous neoplasms require sampling of the entire appendix.[5,164]

  [Level of evidence – D.]

- Incidental neuroendocrine neoplasms may be inconspicuous. They are often at or near the tip.
- Record the status of the base (proximal resection margin) if dysplasia or malignancy are present.
- Report neoplasia according to standard guidelines and texts.[3,5,7]

Appendix: recommendations

Sample the tip, the resection margin and at least 1 transverse section.

Process the entire appendix in the following settings:

- serositis with no transmural inflammation
  - serrated lesion
  - atypical epithelial changes that are difficult to classify, particularly in association with a diverticulum
  - dysplasia
  - mucinous neoplasm
  - malignant tumour.

Consider processing the entire appendix if macroscopy is normal.

Consider processing the entire appendix if initial histology is normal.

3.2 Polyps (oesophageal, gastric and intestinal)

3.2.1 Preparation, dissection and blocks

Opening and fixation

If the polyp is large, slicing prior to fixation may be necessary.

Sampling

- Identify and ink the resection margin (base) if possible.[24]
- Submit all tissue.
- Embed small fragments or small polyps (<5 mm in diameter) whole.
- Bisect or serially slice a polyp if 5 mm or more in diameter. If orientation is possible, slice it in the axial plane. Preserve the stalk with the body of the polyp in at least 1 block if possible. Please note that further details are available in relevant guidelines.[6,15,16]

  [Level of evidence – D.]

- Local mucosal resections, e.g. endoscopic submucosal dissection or endoscopic mucosal resection, require serial slicing after inking of deep and lateral margins. Deeper levels on each block are ideal. However, an initial single level on each block may be appropriate for larger resections to avoid the generation of an unmanageably large number of slides. Ideally, the endoscopist or surgeon pins the resection to a corkboard for optimal fixation and orientation.

  [Level of evidence – GPP.]

3.2.2 Macroscopic description

- Nature of specimen, e.g. polypectomy/fragments.
- Number of fragments.
- Dimensions: maximum dimension of polyp; length of stalk and/or diameter of base.
- External surface: e.g. ulcerated/smooth/lobulated/villous/fronded.
- Cut surface: cysts, mucus, haemorrhage, necrosis.

3.2.3 Sections and stains

Deeper levels

- Routine multiple levels (ideally at least 3) are advisable.
- Further levels may assist with distinction between invasion and gland displacement (‘pseudoinvasion’).

  [Level of evidence – GPP.]

3.2.4 Report and microscopic description

Indications for polypectomy: examples

These include: symptom management, characterisation of polyps, documentation of dysplasia and malignancy, the BCSP.[15]

- Adenoma (intestinal/conventional):
  - classify architecture as tubular, tubulovillous or villous. A tubulovillous adenoma should be at least 20% villous and a villous adenoma at least 80% villous. However, definitions vary.[165] For example, suggested figures for the minimum villous component in a tubulovillous adenoma include 20% and 25%, and for the minimum villous component in a villous adenoma 75% and 80%.[15] Furthermore, interobserver variability for this classification is so high that many experts cast doubt on its clinical value.[33]
  - classify dysplasia as low grade or high grade, based on architectural and cytological changes.[7,15] Use the terms '[architectural type] adenoma with low grade dysplasia' or '[architectural type] adenoma with high grade dysplasia', avoiding the incorrect terms 'low grade [architectural type] adenoma' and 'high grade [architectural type] adenoma'.[15] Interobserver variation is high.[166]
- Traditional serrated adenoma (colorectal):
  - traditional serrated adenomas (TSA) are considerably less common than conventional adenomas. They have specific features such as slit-like spaces/serrations, ectopic crypts, abundant eosinophilic cytoplasm, small pencillate nuclei, and complex tubulovillous and fronded architectural appearances.[7,167] They usually show very mild epithelial nuclear atypia. Some pathologists would classify the atypia as low grade dysplasia and others would require the presence of obvious conventional low grade dysplasia before diagnosing dysplasia, but this is a topic of controversy.[167]
- Hyperplastic polyps and SSLs:
  - SSLs usually occur in the right colon (75%). They have a low prevalence in the sigmoid colon and a very low prevalence in the rectum. They have diagnostic features such as L-shaped or inverted T-shaped crypts (horizontal branching), asymmetric dilation of crypts, serration that extends deeply, exaggerated serration

and vesicular nuclei. A small minority show low grade or high grade dysplasia.[7,167] Assessment of completeness of excision can be difficult.

  - hyperplastic polyps in the large bowel are very common and require distinction from SSL. Although they are most common in the left colon, they also occur in the right colon. Therefore, classification of all right-sided serrated polyps as SSL is not appropriate.[167] Deeper levels may be useful if initial levels from a right-sided serrated polyp show no features of SSL. Sometimes, especially in small samples, the distinction is not possible.
  - hyperplastic polyps with serration, analogous to their colorectal counterparts, occur very rarely in the duodenum.[168]

- Gastric and duodenal adenomas:
  - intestinal type adenomas of stomach and duodenum: classify as for intestinal type colorectal adenoma
  - other types of adenoma in the upper GI tract include pyloric gland adenoma, foveolar adenoma and oxyntic gland adenoma. Distinction from hyperplastic and inflammatory polyps can be difficult. Criteria for grading dysplasia in these polyps may differ from those for intestinal-type adenoma.[7,169]

Adenomas and serrated lesions: macroscopic description

- If the sample is an excision (although this detail can be difficult to determine), record completeness of excision or record the inability to determine completeness of excision.
- If carcinoma is present within an adenoma, record precise distance from margin, vascular invasion, grade and other features according to formal guidance.[2,6,15]

  [Level of evidence – D.]

- Misplaced glands/'pseudoinvasion' can mimic carcinoma. This is particularly common in sigmoid colon adenomas. Deeper levels may be very useful. Immunohistochemistry for desmin to define the muscularis mucosae and lymphovascular markers, e.g. CD31 and D2-40, may be helpful in making the distinction between invasive adenocarcinoma and displacement. Pathologists should have a low threshold for performing additional work and seeking colleagues' opinions in this setting. Occasionally, there is perhaps no 'correct' answer.[15,170]
- Inflammatory polyps:

  - inflammatory-type polyps of the GI tract may occur in apparently non-inflamed mucosa
  - in the stomach, the terms inflammatory polyp, regenerative polyp and hyperplastic polyp are generally synonymous. Many pathologists favour the term inflammatory polyp over other terms.

- Other common GI polyps:
  - in the oesophagus, squamous papillomas and squamous epithelial hyperplastic polyps can show overlapping features. Usually, a papilloma has a distinctive endoscopic appearance and shows papillomatous change histologically. The role of HPV in the pathogenesis of papillomas is controversial.[171]
  - fundic gland polyps of the stomach (body and fundus mucosa) are very common, can be single or multiple and may be syndromic or non-syndromic. Dilated glands are characteristic. Dysplasia can occur in syndromic forms and, rarely, in non-syndromic forms.[169]
  - gastric heterotopia manifests as specialised gastric-type tissue outside the stomach, most commonly in the first part of the duodenum (D1) or in the upper oesophagus (inlet patch)
  - pancreatic heterotopia can produce a polyp, particularly in the stomach or duodenum, and histologically may include any admixture of islets, acini and ducts[172]
  - gastric xanthelasma shows characteristic foamy macrophages in the lamina propria
  - inflammatory fibroid polyp is most often gastric, includes variable proportions of spindle cells, blood vessels, eosinophils and inflammatory cells, and may harbour a PDGFRA mutation.[173]

- Hamartomas
  - juvenile polyp can occur as a sporadic lesion or in a syndrome. Sporadic lesions occur most commonly in children who are less than 10 years of age. Features include expanded lamina propria, variably dilated crypts, inflammation and ulceration.[167,174] Reliable distinction from an inflammatory polyp is usually not possible on the basis of histology alone.[175]

    [Level of evidence – D.]

- Peutz-Jegher polyps may include characteristic arborising smooth muscle. In the colon, differentiation from mucosal prolapse is important.[167] GI tract Peutz-Jegher polyps are rare outside the setting of a syndrome.[174]

Gastric and intestinal polyps: recommendations

All tissue from oesophageal, gastric and intestinal polyps requires processing (unless the polyp is very large).

Deeper levels on each section are appropriate, except when the number of blocks is 4 or more from a non-screening case.

The resection margin (base) requires identification and inking where appropriate, especially if adenoma, sessile serrated lesion, carcinoma or another neoplasm is likely.

Colorectal adenomas are classified as tubular, tubulovillous or villous, and as having low grade dysplasia or high-grade dysplasia. A tubulovillous adenoma should be at least 20% villous and a villous adenoma at least 80% villous. Interobserver variation for these classifications is consistently high.

Juvenile polyps and inflammatory polyps have similar histological appearances.

[Level of evidence – D.]

3.3 Anal polyps

3.3.1 Preparation, dissection and blocks

Sampling

- All tissue from polyps should be embedded when there is a risk of dysplasia and/or when a polyp is not very large.
- If a polyp is very large and there is minimal risk of dysplasia (e.g. haemorrhoid), representative blocks are sufficient. In general, there is no need to sample more than 6 blocks from a low-risk lesion.

  [Level of evidence – GPP.]
- Polyps or fragments >5 mm in maximum dimension should ideally be sliced. Fragments 5 mm or less in maximum dimension may be submitted whole.

3.3.2 Specimen description

- Specimen type: polypectomy/fragments.

- Dimensions (millimetres): maximum dimension of polyp or range of dimensions if multiple fragments are present.
- Appearance: luminal surface and cut surface; focal changes, e.g. ulceration, haemorrhage, thrombosis.

3.3.3 Report and microscopic description

Indications

These include management of symptoms, characterisation of polyp and exclusion of dysplasia and malignancy.

Report

- Haemorrhoid: vascular ectasia, congestion, haemorrhage, thrombosis. Rarely, AIN is present.[176] Reactive hyperplasia and atypia, particularly in the squamous epithelium adjacent to columnar/transitional epithelium, is frequent and can mimic AIN. Rectal mucosal prolapse changes are also common.
- Fibroepithelial polyp. Inflammation can cause considerable epithelial hyperplasia.
- Mucosal prolapse shows crypt angulation, lamina propria smooth muscle fibres and fibrosis and may show erosion or ulceration. The changes can mimic adenocarcinoma.[167]

  [Level of evidence – GPP.]

3.4 Other anal lesions (e.g. fissure, fistula, sinus)

3.4.1 Preparation, dissection and blocks

Sampling

A resection specimen should be sliced in the plane most likely to demonstrate the lesion, if applicable. Representative samples of any track, abscess or other focal changes should be taken.[24] 1 block should include skin and any possible opening (punctum) of a sinus or fistula and at least 1 block should include the deep margin (if identifiable) and the lesion.

[Level of evidence – GPP.]

3.4.2 Specimen description

- Dimensions (millimetres): specimen dimensions; skin dimensions.
- Appearances: record the presence and appearance of skin/mucosa; describe tracks and abscesses and their contents; note the state of the adjacent tissue; and record the

presence of dye. Note distance of lesion from deep and lateral margins, where appropriate.

3.4.3 Report and microscopic description

Indications

These include management of symptoms, identification of cause, exclusion of neoplasia.

Report

- Describe skin and/or squamous mucosa.
- Describe track/abscess, including contents (e.g. hair shafts).
- Exclude recognisable causes of sinuses/fistulas/fissures, e.g. Crohn's disease, tuberculosis, hidradenitis suppurativa, pilonidal sinus and neoplasia.[24,177] Seek granulomas. In most cases, the cause is not obvious.

  [Level of evidence – GPP.]
- Granulomas raise the possibility of Crohn's disease, particularly if numerous. However, they are less specific for Crohn's disease in this setting than in the GI tract mucosa.

3.5 Ileostomy/colostomy

3.5.1 Preparation, dissection and blocks

Opening and fixation

The stoma and bowel may require opening and further fixation.

Sampling/blocks

Sample mucocutaneous junction and margin(s). Take further representative sections as appropriate.

3.5.2 Specimen description

- Dimensions: record the length of skin and of bowel.
- Specimen type and appearances: type of stoma; note focal lesions.

3.5.3 Report and microscopic description

Indications for procedure

These include symptom management, loss of stomal function, inflammatory changes and re-anastomosis.

Report

- Confirm the presence of skin.
- Ulceration and inflammation (and mucosal prolapse changes) are frequently present near a stoma.
- Features suggestive of IBD, e.g. granulomas and chronic inflammation, require cautious interpretation in this setting as they may be secondary to foreign material or other causes.

3.6 Omentum and omental biopsy

3.6.1 Preparation, dissection and blocks

Sampling

Core biopsy: embed whole.

Larger samples: serially slice if large, sample any focal changes and take representative sections. If there is no macroscopic abnormality, the clinical indication for the procedure can guide sampling. 2 or 3 blocks is usually sufficient.

[Level of evidence – GPP.]

3.6.2 Specimen description

- Specimen type: needle core biopsy, omentectomy or fragments.
- Dimensions (millimetres): core biopsy (length), omentectomy (maximum dimension), fragments (maximum size of each or a range of sizes).
- Appearances: note nodules/necrotic foci/abscesses/cysts/fibrosis/probable tumour.[24]

3.6.3 Report and microscopic description

Indications

These include characterisation of focal lesions, confirmation or exclusion of tumour, technical reasons, reduction of tumour burden.

Report

Malignancy in the omentum is usually carcinoma. Immunohistochemistry may help to elucidate the site of origin of a tumour. Exclude other pathologies, e.g. tuberculosis.

4 Large gastrointestinal resection specimens

4.1 Preparation, dissection and blocks

4.1.1 Opening and fixation of GI resections

- A large resection specimen should be unopened on receipt to allow orientation.[22,42,178] It should be in a volume of formalin at least sufficient to cover it completely.
- Ideally, open the stomach along the greater curvature and the intestine along the antimesenteric border, unless this approach disrupts a focal lesion; open the oesophagus longitudinally along the anterior border or leave intact, depending on local preference.[22]
- Wash out luminal contents gently with tepid or cold water.[22] Excess washing, trauma from handling, or the use of hot water can damage the mucosa and interfere with subsequent histological assessment.
- If there is thickening of the wall or narrowing of the lumen, serial transverse slices before further fixation are often preferable to opening.
- Serial transverse slicing (before or after fixation) may facilitate the examination of focal abnormalities of the wall, e.g. diverticula, endometriosis.[24]
- Infarcted tissue may be friable, thin-walled and unsuitable for opening.
- Ink relevant margins if there is a possibility of neoplasia.[179]

  [Level of evidence – D.]

- The specimen should be pinned to a corkboard or stabilised in another way and fixed in a volume of formalin that is at least sufficient to cover it.[24] Fixation for 48 hours after opening is generally recommended, but adequacy of fixation can be estimated by visual inspection.[22,24]
- Photographs may be useful, particularly for tumours or IBD or to facilitate subsequent discussion at meetings.[22,24] They are appropriate in cases of trauma.

  [Level of evidence – GPP.]

4.1.2 Sampling: margins

- Sampling of proximal and distal resection margins can be parallel or perpendicular to the margin, depending on the site and nature of the lesion. Perpendicular blocks allow the distance from the lesion to be determined when the lesion is nearby.
- In some circumstances, there is no evidence that sampling of proximal and distal margins of intestinal resections has any value. In other situations (e.g. Crohn's disease) the evidence conflicts.[22,45,180] Nevertheless, margins may be worth taking as they represent background mucosa.
- If doughnuts are present, these often represent the true proximal and/or distal margins.[24] There are exceptions, e.g. a doughnut does not necessarily include the entire gastric margin of a partial gastrectomy.
- Staples and sutures are unsuitable for processing. If sutures are present at the margin, removal before sampling is important. Stapled tissue requires removal before sampling.
- Mesenteric and/or circumferential margins are sometimes relevant and are necessary if malignancy is present or suspected.[22,24]
- A more detailed description of the approach to the colorectal and oesophagogastric mesenteric/circumferential margins is available in the College datasets for colorectal and upper GI cancers.[2,6]

  [Level of evidence – GPP.]

4.1.3 Sampling: adherent organs

- Sample to show any connection between organs, e.g. around a fistula or diverticulum.
- A large (whole mount) block may occasionally be useful and may help to show the anatomical relationships more clearly.

4.1.4 Sampling: lymph nodes

- Retrieve at least 3 representative lymph nodes if possible, as they may add useful information.[24] Extensive lymph node sampling is not necessary or advisable for non-neoplastic disease.
- If malignancy is a possibility, retrieve all regional nodes.

- A bisected or serially sliced lymph node cannot share a cassette with another node if neoplasia is a consideration.

4.1.5 Specimen description

- For lymph nodes, record the number of lymph nodes and the number of pieces in each cassette.
- State whether the blocks of the proximal and distal margins are parallel (transverse) or perpendicular (longitudinal).
- Consider a corresponding line diagram or annotated photograph in complex cases.

4.2 Oesophagectomy/gastrectomy for non-neoplastic disease

4.2.1 Preparation, dissection and blocks

Sampling: lesions

- Representative samples of focal lesions, e.g. ulcer, haemorrhage, abscess, fistula.
- Additional blocks from any lesion with features suggesting neoplasia.
- At least 1 block should show the relationship with the circumferential margin/serosal surface if malignancy is a possibility.
- Longitudinal blocks may help to show the relationship with oesophagus or stomach proximal to and distal to the lesion.
- Sleeve/partial gastrectomies for obesity may harbour gastritis or incidental lesions. Assuming that there is no focal abnormality, a maximum of 2 blocks is appropriate.
- If tumour is suspected or present, the College dataset for oesophageal and gastric cancer is applicable.[2,24]

4.2.2 Specimen description

Specimen type

- Oesophagectomy/total gastrectomy/distal gastrectomy, sleeve gastrectomy.

Dimensions of specimen (millimetres)

- Lengths of oesophagus, greater curve of stomach, lesser curve of stomach and duodenum.[42]
- Maximum dimension of attached fat/omentum.

External surface

- Diffuse or variable external changes, e.g. peritonitis, congestion.
- Perforations/defects in wall: number, site, size and distance from nearer margin. Reliable distinction between iatrogenic and pathological defects is often not possible.
- Focal external lesions, e.g. stricture, puckering, haemorrhage: record site, size and distance from nearer margin.
- Seek evidence of trauma.

Opened oesophagus/stomach/duodenum

- Focal lesions, e.g. ulcer, abscess, haemorrhage, stricture, diverticulum, polyp or tumour: record appearance, site, size and, if relevant, relationship with serosal surface/margins.[24,43] If there are multiple lesions, record a range of sizes and the distance from the margin of the nearest lesion.
- Record appearance of background oesophageal, gastric and duodenal mucosa.

4.2.3 Report and microscopic description

Indications for surgery

- These include stricture, ulceration, trauma and perforation. One of the most common specimens is a partial gastrectomy (usually a sleeve gastrectomy) as treatment for morbid obesity.

Report

- Record microscopic appearances of oesophagus, stomach and duodenum.
- Note ulceration, inflammation, abscess, fibrosis, perforation, penetration into other structures, granulomas, foreign bodies.
- Describe polyps (see sections 3.2 and 3.3).
- Record lymph node histology.
- A resection for cancer with no residual macroscopic or microscopic tumour after neoadjuvant therapy requires processing and reporting as a cancer.[2,6]

4.3 Intestinal resections: general considerations

4.3.1 Preparation, dissection and blocks

Sampling: lesions

- Longitudinal blocks (perpendicular to mucosal folds) are usually preferable to transverse, unless serial transverse slicing took place before further fixation.[24]
- Sample focal lesions, e.g. infarcts, perforations, strictures, abscesses, according to their size and number.
- Sample diffuse abnormalities, e.g. erythema, loss of mucosal folds and multiple inflammatory polyps, at intervals of approximately 100 mm.[24] Sample sequentially if possible (i.e. from proximal to distal or distal to proximal).[22]
- Samples of macroscopically normal bowel away from areas of abnormality may be informative, e.g. in Crohn's disease resections.[24]
- Blocks of the junction between normal and abnormal bowel may be informative, e.g. ulcerated or ischaemic mucosa.[24]
- If no macroscopic lesion is present, at least 3 blocks are advisable, depending on specimen size and indication.
- If there is any risk of dysplasia, e.g. in a patient with IBD and no macroscopic lesion is seen, samples at intervals of 100 mm or less are advisable.[22,24]
- Mucosal nodules, polyps or irregular areas that might represent dysplasia merit thorough sampling, especially if the clinical setting carries a risk of dysplasia (e.g. IBD).[24]
- Sampling should demonstrate the deepest extent of a lesion and, if relevant, its relationship with the serosal surface and margins.

Sampling: lymph nodes

- Sample representative lymph nodes, as they may show pathological changes which are absent from, or less obvious in, the alimentary tract itself.[24] For example, granulomas may occasionally be identifiable in lymph nodes when they are not obvious in the bowel or may be more easy to characterise in the lymph nodes than in the bowel.
- If neoplasia is suspected, retrieve all regional nodes.

Sampling: appendix, ileocaecal junction and mesentery

- Sample the tip and body of the appendix as a minimum. If an appendiceal lesion is apparent macroscopically, the best approach is to submit the entire appendix.
- A block of the ileocaecal junction may be informative, particularly in the setting of IBD.
- 1 or more blocks of mesentery, in a plane likely to demonstrate blood vessels, are sometimes useful. They can be very helpful if there is a suspicion of ischaemia or a vascular disorder.[24]

4.3.2 Macroscopic description

Specimen type

- Small bowel resection/right hemicolectomy/subtotal colectomy/total colectomy/sigmoid colectomy/anterior resection/abdominoperineal resection.[24]

Dimensions of specimen (millimetres)

- Length of ileum, appendix, colon, rectum, anal canal.
- Maximum diameter or range of diameters, if appropriate.
- Site of peritoneal reflection in rectum.

Bowel: external surface

- Perforations and defects in wall: record number, location, size and distance from nearer margin. Consider the possibility that these are artefactual or iatrogenic.
- Other focal serosal changes, e.g. puckering, adhesions and strictures; record appearance, size and location.
- Note fat wrapping, exudate, congestion and evidence of pneumatosis (thin-walled cysts or bubbles).[181]
- Seek evidence of trauma.
- Note adhesions to bowel or to other organs.
- Note Meckel's diverticulum (small bowel). This is usually on the antimesenteric border.

Opened bowel

- Luminal contents, e.g. blood, foreign material.
- Diffuse mucosal changes, e.g. erythema, cobblestoning, loss of mucosal folds, pseudomembranes. Record extent and relationship with nearer margin.

- Note evidence of trauma, e.g. perforation, foreign objects. Take photographs if appropriate.
- Focal mucosal lesions, e.g. nodules, ulcers, haemorrhage, polyps: record number, size, appearance, distance from nearer margin and the state of the adjacent wall/circumferential margin/serosal surface.[24]
- Stricture, fibrosis, diaphragms: number, location, length, degree of narrowing of lumen, distance from nearer margin.
- Diverticula: location, approximate number, perforation, abscess.
- Ischaemia: length of the affected segment(s) and distance from longitudinal resection margins. Seek underlying lesions, e.g. adhesion, extrinsic compression, diverticular disease, intussusception, tumour.
- Obstructive colitis occurs at a variable distance proximal to an obstructing lesion.[7,182–184] The causative lesion may remain within the patient.
- Volvulus: this has usually already been corrected surgically before receipt of the resection specimen. Signs of ischaemia may be apparent.[24]
- Diversion proctocolitis: may show diffuse mucosal erythema, haemorrhage, nodularity, granularity and flattening. A clinical history is necessary.[185,186]
- Fistula/abscess: record location and relationship with external surface or with attached organ.
- Appendix: describe external and cut surfaces, or appendix stump.
- Attached organs: describe appearance, relationship with bowel and presence of fistula, diverticulum, abscess or tumour.
- Mesentery: note haemorrhage, fat necrosis, cystic change, tumour.

4.3.3 Report and microscopic description

Indications for surgery

- These are numerous and include: ulceration, haemorrhage, stricture, obstruction, perforation, trauma, ischaemia, intussusception, volvulus, vascular anomaly, diverticular disease and IBD (e.g. if severe, refractory to treatment, or complicated by dysplasia).

Report

- Proximal and distal margins: record all abnormalities at margins, particularly ischaemia. If there is an abnormality close to a margin, record the approximate distance from the margin.
- Lymph nodes: record histology, especially specific features such as granulomas.
- Appendix: describe histology, including involvement by IBD and incidental lesions.
- Mesenteric vessels: note thrombosis, vasculitis, abnormalities of wall.

Specific conditions

- Diverticula: confirm diverticula. Record complications of diverticula, e.g. peridiverticular fibrosis, abscess, perforation. Crohn's-like transmural changes can occur. Diverticular colitis may mimic IBD (especially UC).[187,188]
- Meckel's diverticulum: describe lining (small intestinal/gastric/pancreatic).[24,63]
- Volvulus: note associated ischaemia, perforation, melanosis and fibrosis.
- Diversion proctocolitis: diagnosis requires the clinical history. The pathology may mimic that of IBD. Granulomas can occur. Inflammation tends to be more severe in the setting of UC than in other settings.[181,185,186]
- Obstructive colitis occurs as a response to a more distal obstructing lesion. Often, there is intervening unaffected bowel. Ischaemia probably plays a role in some cases.[182]
- Motility disorders: exclude other common causes of similar symptoms. Assess myenteric and submucosal ganglion cells, myenteric plexus, muscularis propria/muscularis mucosae, vasculature. Choice of special stains and immunohistochemistry depends on local experts. Possible myopathies and neuropathies merit referral to a specialist pathologist, e.g. a neuropathologist.

Large GI resection specimens: recommendations

Pin the opened specimen to a corkboard or stabilise in another way and then fix in a volume of formalin at least sufficient to cover it for at least 48 hours.

Serial transverse slices may identify focal mural lesions, e.g. diverticula, and allow sampling. Otherwise, longitudinal blocks are usually more appropriate than transverse.

Sample the proximal and distal margins.

[Level of evidence – GPP.]

If malignancy is a consideration, include the circumferential (non-peritonealised) margin in samples of the lesion and ink relevant margins.

Sample lymph nodes if they are present. This is particularly important if there is any suspicion of neoplasia.

4.4 Ischaemic bowel: additional comments

4.4.1 Report and microscopic description

Indications for surgery

- These include removal of non-viable tissue and management of symptoms.

Considerations

- The cause of the ischaemia may already be apparent. Occasionally, pathological examination reveals the cause, e.g. vasculitis.[189] There may be an underlying contributory condition, e.g. IBD, diverticular disease, neoplasia or an obstructing lesion. The status of the resection margins is worth recording, although in practice it may not predict clinical outcome.

Report

- Evidence of acute ischaemia (e.g. haemorrhage, necrosis) or chronic changes (e.g. fibrosis).[189]
- Severity and depth of acute ischaemic changes/infarction (e.g. mucosal, transmural).
- Abnormalities of mesenteric vessels, e.g. thrombus, atheroma, vasculitis.
- Status of resection margins.

4.5 Vascular malformation and angiodysplasia: additional comments

4.5.1 Preparation, dissection and blocks

Opening and fixation

- If the specimen is fresh at receipt, it may be possible to inject the vasculature with a contrast medium, e.g. barium sulphate, before opening. Distention with formalin,

fixation and X-rays is then possible.[189] However, the specimen is usually received fixed and there is rarely a need or opportunity to take these steps.

Sampling

- Sample areas of erythema, haemorrhage, mucosal flattening and discoloration, because macroscopic changes may be focal or subtle.[189]

4.5.2 Report and microscopic description

Indications for surgery

- These include GI haemorrhage and its consequences (e.g. anaemia). Pre-operative imaging may suggest angiodysplasia.

Report

- Confirm the diagnosis if possible.
- Other lesions may be associated with angiodysplastic changes, especially diverticula. Secondary 'angiodysplasia' is more common than primary vascular anomalies.[190]
- Exclude other causes of bleeding.
- Describe vascular abnormalities. Note depth and extent of vascular changes.
- Record evidence of ischaemia.

4.6 Inflammatory bowel disease (large intestinal resections): additional comments

4.6.1 Macroscopic description

Opened bowel

- Consider whether the macroscopic changes favour UC (e.g. continuous disease from rectum proximally, sharp transition between abnormal and normal mucosa) or Crohn's disease (e.g. discontinuous disease, cobblestoning, strictures, fat wrapping). A discontinuous caecal 'patch' of disease can occur in new or established UC.[98,191–193] Treated chronic disease, especially UC, may fail to conform to classical patterns.[1,14,110–114] Usually, there is a longstanding clinical history of 1 or other condition.

  [Level of evidence – C.]

4.6.2 Report and microscopic description

Indications for surgery

- These include refractory disease, severe acute disease, dysplasia or carcinoma.

Report

- Chronic inflammation: record extent and distribution and whether transmural or mainly mucosal.
- Acute inflammation, i.e. cryptitis, crypt abscesses: record extent and severity.
- Ulcers: record type and depth (layer affected; for fissure ulcers record depth in terms of superficial half or deep half of muscularis propria, as the latter are very unusual in UC).
- Granulomas: note whether crypt rupture-related (cryptolytic) and whether necrotising or non-necrotising. Request ZN stain if appropriate.
- CMV inclusions may be present. Consider immunohistochemistry for CMV if there is ulceration or severe activity.[52,55]
- Dysplasia: presence or absence; if present, classify as low grade or high grade.[9] Non-conventional types of dysplasia also require recognition and grading.[194]

Classification of inflammatory bowel disease in resections

- Classification of type depends not only on current and preceding histology but also on macroscopic appearances and clinical findings.[14,58,59,98,181,190]
- Crohn's disease, typically showing discontinuous involvement, ileal disease, deep fissure ulcers, non-cryptolytic granulomas, transmural chronic inflammation away from areas of ulceration.[9,56,181,195–197]
- UC, typically showing continuous involvement from rectum proximally, diffusely abnormal mucosal architecture, mucosa-predominant changes.[24,56,181,190]
- 'Indeterminate' colitis refers only to resection specimens with definite IBD in which a diagnosis of either UC or Crohn's disease cannot be made.[56,107,198] It does not mean 'colitis, cause unknown'.[98] Unfortunately, this term has different meanings for different pathologists and clinicians and may cause confusion.[14,197] This is a difficult area of diagnosis, which requires full clinicopathological discussion. Assessment may benefit from the input of more than 1 pathologist. Clinicopathological meetings enhance the

quality of interpretation.[14,60,61] Expression of a preference for UC or Crohn's disease is useful when a definite diagnosis is not possible.

[Level of evidence – D.]

Colorectal resections for IBD: recommendations

The report should include:

- extent and distribution of chronic inflammation
- severity of activity
- greatest depth of ulceration and of inflammation
- presence and characteristics of granulomas
- presence/absence and grade of dysplasia.

Histological features that strongly favour Crohn's disease over UC:

- non-cryptolytic granulomas
- transmural chronic inflammation (latter away from areas of ulceration)
- discontinuous involvement (especially in untreated IBD)
- ileal inflammation
- deep (rather than superficial) fissure ulcers.

Histological features that favour UC over Crohn's disease:

- continuous involvement from the rectum proximally
- diffusely abnormal mucosal architecture
- mucosa-predominant inflammatory changes.

Anatomical discontinuity of disease is not uncommon in longstanding/treated UC.

[Level of evidence – C.]

A periappendiceal/caecal 'patch' of disease separate from more distal colorectal involvement can occur in new or established UC.

IBD that is difficult to classify further in a resection merits the term 'indeterminate colitis', ideally with expression of a preference for UC or Crohn's disease where possible.

Clinicopathological meetings enhance the quality of interpretation.

[Level of evidence – GPP.]

4.7 Small bowel resection for stricture or for Crohn's disease: additional comments

4.7.1 Report and microscopic description

Indications for surgery

- These include relief of symptoms or of obstruction, identification of the cause of the stricture, removal of non-viable bowel, exclusion/treatment of neoplasia.

Considerations

- A small bowel stricture might be a result of ischaemia, Crohn's disease, drugs (particularly NSAIDs), infection, radiation, endometriosis, previous surgery, extrinsic compression, malignancy or other causes.[24,141] Some cases remain 'cryptogenic'.[199]

Report

- Record and describe ulceration, inflammation, fibrosis and granulomas.
- Seek evidence of Crohn's disease.
- Look for evidence of trauma, ischaemia, endometriosis (glands, stroma and haemorrhage), radiation damage (needs appropriate history), NSAID-induced enteritis (including diaphragms) or specific infections.
- Obtain a full clinical history before concluding.

4.8 Intussusception: additional comments

4.8.1 Preparation, dissection and blocks

Sampling

- Demonstrate intussusception if possible. Sample apex of intussusception, including possible causative lesion, and background bowel. Margins are important if there is ischaemia.
- Sometimes there is little or no evidence of intussusception by the time of specimen receipt.

  [Level of evidence – GPP.]

4.8.2 Macroscopic description

Dimensions

- Length of intussusception, distance of apex from distal resection margin, distance of neck from proximal margin, diameter of lumen.

Opened bowel

- Type of intussusception: ileoileal/ileocolic/colocolic.[200]
- Appearance of the mucosa, state of the underlying wall, ischaemia.[24]
- Look for a causative lesion: foreign body, polyp, diverticulum, duplication, neoplasia, ileal lymphoid hyperplasia, appendix.[63,200] A cause is often not apparent, especially in children.

5 Pancreatobiliary resection specimens

5.1 Bile duct resection

5.1.1 Preparation, dissection and blocks

Opening and fixation

- Apply ink to longitudinal margins and external surface if neoplasia is likely. Distinction between circumferential resection margins (posterior and left lateral) and serosal surfaces (anterior and right lateral) is often difficult without assistance from a surgeon.[38,201]

Minimum sampling

- One approach is to take the proximal or distal resection margin *en face* followed by sequential transverse slices as far as the other resection margin, especially if neoplasia is likely. If there is a lesion close to a margin, perpendicular (radial) sections of this margin may be more informative than transverse sections.[38,201]
- Focal lesions require sampling in their entirety, with blocks demonstrating the depth of the lesion and its distance from the external surface.
- Gallbladder (when present): sample lesions fully if present; treat as routine otherwise.
- All lymph nodes should be sampled.[201]

  [Level of evidence – GPP.]

5.1.2 Specimen description

- Specimen type: specify what is included, if possible, e.g. common hepatic duct, cystic duct, common bile duct. Record the presence of a stent.
- Dimensions of specimen (millimetres): length of each portion and total length of specimen; maximum diameter or range of diameters, if appropriate; dimensions of attached organs or tissue.
- Appearances: record any focal lesions (e.g. strictures, perforation, nodules) and their site, size and relationship with margins; note cysts or cystic dilatations.

5.1.3 Report and microscopic description

Indications for surgery

- These include: management of symptoms, removal of stricture or choledochal cyst,[201] abnormal imaging, exclusion of neoplasia.

Report

- Record features suggestive of sclerosing cholangitis or IgG4-associated cholangitis.[202,203]
- Inflammatory epithelial atypia can be severe, especially proximal to an obstruction or after stent insertion.
- Deeply located periductal glands can mimic neoplasia and vice versa.[142] Their lobular arrangement helps to distinguish them from carcinoma.

5.2 Cholecystectomy for non-neoplastic disease

5.2.1 Preparation, dissection and blocks

Opening and fixation

- Open the gallbladder longitudinally along the serosal surface,[24,39] avoiding disruption of the cystic duct margin and gallbladder bed resection margin. Ink the gallbladder bed resection margin (roughened area) if neoplasia is possible or suspected.
- There is emerging evidence that histological examination of gallbladders is not necessary when the macroscopic appearances are not suspicious of neoplasia (in the opinion of the surgeon or the pathology dissection staff). However, this is a controversial topic. We do not currently recommend abandonment of routine

histological examination of submitted gallbladders unless national agreement, with the support of incontrovertible evidence, subsequently emerges.

Sampling

- Cystic duct margin en face.[201] This may be located adjacent to a clip. Ensure that it is identifiable after processing (e.g. histologically distinct section/inked section/section in separate cassette).
- Cystic duct lymph node.[24,] This is often present, but may be small.
- At least 1 section each of neck, body and any focal lesion(s).[201] This might include a full transverse 'ring' of gallbladder before opening.
- Polyps or lesions suspicious of neoplasia: sample thoroughly.[24,201]
- Attached organ(s), to characterise relationship with gallbladder.

[Level of evidence – GPP.]

5.2.2 Specimen description

Dimensions of specimen (millimetres)

- Length and maximum diameter of gallbladder. Dimensions of any attached organs.

Appearances

- Record whether intact, open or fragmented on receipt.
- Note perforations or defects in wall.
- Contents: note stones (number, range of sizes), bile and mucus.
- Record mucosal changes, e.g. cholesterolosis, ulcer, polyp.
- Record thickness of gallbladder wall.[24,38,201]
- Note abscess, fistula and diverticulum. Record site, size and relationship with external surface or attached organ.
- Polyp or suspected malignant tumour: record site, size, depth (if malignant), macroscopic features. For a likely malignancy, describe relationship with peritoneal surface and hepatic gallbladder bed resection margin (see College dataset and WHO classification).[7,39]

5.2.3 Report and microscopic description

Indications for surgery

- These include management of symptoms and characterisation of lesions that were apparent on imaging.
- Some gallbladder neoplastic processes are not apparent clinically or macroscopically and require histology for detection.

Report

- Chronic cholecystitis/acute cholecystitis/features of both.[24,201]
- Rokitansky–Aschoff sinuses (diverticula) can mimic carcinoma both macroscopically and microscopically.[204]
- Cystic duct lymph node features.
- Describe attached tissue, e.g. liver.
- If low-grade dysplasia (low-grade biliary intraepithelial neoplasia (BilIN)) is present, extra blocks, e.g. 4 additional blocks, are appropriate to exclude high-grade dysplasia or malignancy.[205]
- If there is high grade dysplasia (high-grade BilIN) or carcinoma, the entire gallbladder should be processed and examined.[205]
- Record involvement or absence of involvement of the cystic duct resection margin by dysplasia.

  [Level of evidence – GPP.]

- Intracholecystic neoplasms are polyps/masses with dysplasia (and were previously termed ‘adenomas’). These should be described and classified according to current WHO recommendations, although terminology continues to evolve.[7, 205] If an intracholecystic papillary neoplasm or similar lesion is present, submission of the entire gall bladder for histological examination is appropriate because of the high likelihood of an invasive carcinoma in another part of the gallbladder.
- Carcinoma: see College dataset.[38]

Gallbladder: recommendations

Open along the serosal surface.

Sample cystic duct margin and neck.

Sample cystic duct lymph node (if identifiable).

Sample gallbladder body and any focal lesions.

Sample polyps in their entirety.

If high grade dysplasia or malignancy are present on initial microscopy, examine the entire gallbladder histologically.

If low grade dysplasia is present on initial microscopy, examine additional blocks (e.g. 4).

5.3 Pancreatic resection (non-neoplastic disease)

5.3.1 Preparation, dissection and blocks

Opening and fixation

- Ink resection margins and other external surfaces if neoplasia is suspected.[4,149] Slice the pancreas and open attached bowel (if present) to ensure fixation.

Sampling

- All focal lesions.
- At least 3 representative blocks of pancreas if no focal lesion is present, depending on clinical indication. Usually, more blocks are necessary. They are particularly important if neoplasia is likely or if findings do not correlate with imaging. Large blocks may be useful.

  [Level of evidence – GPP.]
- All peripancreatic lymph nodes, especially if neoplasia is a possibility.
- All margins and surfaces if a suspicious lesion is seen.[4]
- If there is a bile duct lesion, serial sequential bile duct blocks are advisable.
- Ampulla of Vater with adjacent pancreas.
- Beger, Frey or Puestow procedure: embed whole specimen (often received in fragments) to exclude malignancy.[149]

5.3.2 Specimen description

Specimen type

- Pylorus-preserving pancreatoduodenectomy/Whipple's resection (partial gastrectomy also included)/distal pancreatectomy, total pancreatectomy, specimens following Beger, Frey or Puestow procedure.[149]

Dimensions of specimen (millimetres)

- Pancreas in 3 dimensions.
- Extrapancreatic bile duct length.
- Bowel length.

Appearances

- Pancreas: note fibrosis, calcification, fat necrosis, haemorrhage.[4,201]
- Focal lesions (nodules, cysts, abscesses): record location, size and relationship with margins.
- Tumour: refer to College dataset.[4]

5.3.3 Sections and stains

Immunohistochemistry

- IgG4 may be useful for supporting a diagnosis of type 1 autoimmune pancreatitis (see above).

  [Level of evidence – C.]

5.3.4 Report and microscopic description

Indications for surgery: examples

- Chronic pancreatitis.
- To control symptoms or relieve duct obstruction.
- Resection of lesion of uncertain nature.

Report

- Features of chronic pancreatitis, e.g. chronic inflammation, fibrosis and atrophy. These changes can mimic neoplasia.[142,151,152] Consider type 1 autoimmune pancreatitis / IgG4 related disease if pancreatic ducts are narrow with storiform fibrosis, dense lymphoplasmacytic inflammation, obliterative phlebitis and supportive IgG4/IgG

immunohistochemistry and consider type 2 autoimmune pancreatitis if there is duct damage with granulocytic epithelial lesions of duct epithelium.

- Neoplasms: refer to the College dataset for pancreatic cancers and to other standard texts.[4,7,149]

5.4 Pancreatic cyst

5.4.1 Preparation, dissection and blocks

Opening and fixation

- Ink external surfaces, especially if suspicious or focal lesions are present.[4, 24]

Sampling

- 1 block per 10 mm diameter, especially if neoplasia suspected.[24] Sample any focal changes, nodules or more solid areas.[201] Consider sampling the entire wall of the cyst to identify and characterise an epithelial lining.[149]

  [Level of evidence – GPP.]

5.4.2 Specimen description

- Specimen type: distal pancreatectomy/intact cyst/opened cyst/ pancreatoduodenectomy etc.
- Dimensions of specimen (mm) and diameter/maximum dimension of cyst.[24,149] Size of attached pancreas/other tissue.
- Appearances: external surface of cyst (smooth/nodular), contents (mucoid/serous/ haemorrhagic), lining (smooth/ulcers/nodules/papillary areas), wall (consistency, nodules, calcification), attached pancreas (fibrosis, calcification, abscess, relationship with cyst).[24,149]

5.4.3 Sections and stains

Additional stains

- Mucin stains and immunohistochemistry may help characterise the lining. Immunohistochemistry may also help characterise the subepithelial stroma, e.g. confirming ovarian-type stroma in a mucinous cystic neoplasm.[7,149]

5.4.4 Report and microscopic description

Indications for surgery

- These include exclusion of neoplasia and management of symptoms.

Report

- A wide variety of cysts (non-neoplastic versus neoplastic, non-epithelial versus epithelial) arise in the pancreas.[149]
- Describe the cyst lining: epithelium (flat/cuboidal/squamous/mucinous columnar/ non-mucinous columnar), no lining, other.
- Note the presence and grade of dysplasia.
- Look for microorganisms (e.g. Echinococcus in a hydatid cyst).
- Underlying stroma: fibrous/ovarian type/pancreatic tissue/invasive tumour. Ovarian-type stroma is necessary for a diagnosis of mucinous cystic neoplasm.[7]

6 Criteria for audit

As recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation)*:[20]

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

Audits of the value and applicability of this pathway may be useful. A template for audit of colorectal biopsies taken for the diagnosis and assessment of IBD is currently available on the College website. Other possible audits could explore the completeness of recording of data items in histopathology reports, ranges of turnaround times, or compliance with the College's key performance indicators.

Content and timeliness of histopathology reports should be audited against the recommendations in these guidelines.

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Appendix A Summary table – Explanation of levels 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 population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target 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 population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix B AGREE compliance monitoring sheet

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

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Forward, 1
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	N/A
6 The target users of the guideline are clearly defined	Foreword, 1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	1
12 There is an explicit link between the recommendations and the supporting evidence	Throughout
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	1–5
16 The different options for management of the condition or health issue are clearly presented	1–5

17	Key recommendations are easily identifiable	1–5
Applicability		
18	The guideline describes facilitators and barriers to its application	Foreword
19	The guideline provides advice and/or tools on how the recommendations can be put into practice	1–5
20	The potential resource implications of applying the recommendations have been considered	Foreword
21	The guideline presents monitoring and/or auditing criteria	6
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