Standards and datasets for reporting cancers

Dataset for gastrointestinal stromal tumours (GISTs)

February 2011, amended February 2012

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Comments

In accordance with the College’s pre-publications policy, this document was put on The Royal College of Pathologists’ website for consultation from 23 August to 17 September 2010. Twenty-six items of feedback were received and the authors considered them and amended the document as appropriate. Amendments were then suggested, to clarify the requirement for mitosis counting. This was to take into account the fact that the exact area of a microscopic high-power field may vary greatly from microscope to microscope. A further online consultation was held from 16 November to 14 December 2011. Forty-six items of feedback were received and the authors again considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments.

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.
Foreword

The cancer datasets are guidelines. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the dataset was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed a failure of duty of care.

This dataset was reviewed by the Cancer Services Working Group and was placed on the College website for consultation with the membership between 23 August and 17 September 2010. All comments received from the Working Group and College members were addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Communications.

Each year, the authors of the dataset, in conjunction with the sub-specialty advisor to the College, will consider whether or not the dataset needs to be revised.

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

This dataset was developed without external funding to the dataset writing group or lead author. The remit of The Royal College of Pathologists is to promote the quality of pathology services through training and education. It has no remit to negotiate the terms and conditions of employment for pathologists.

The College requires the authors of datasets to provide a list of potential conflicts of interest and intellectual property deed of assignment; these are monitored by the Professional Standards Unit and are available on request. The authors of this document have declared that there are no conflicts of interest.

This document has been devised to include the data required for a careful and thorough assessment of specimens resected for gastrointestinal stromal tumours (GISTs). Where possible, it is evidence based. The document has been reviewed by stakeholder groups: The British Society of Gastroenterology (GI section) and the UK GIST group. Panels of specialist and general histopathologists acting on behalf of the College have also reviewed it. We strongly recommend its use as a dataset.

1 Introduction

The diagnosis and management of GISTs is best accomplished within the multidisciplinary team environment. The pathologist has a key role within this framework to provide accurate and comprehensive diagnostic and prognostic information.1 These guidelines describe the core and non-core data that should be recorded in histopathological reports from GIST resection specimens to facilitate this process. The information within histopathology reports not only allows formulation of the definitive management plan but is also used to:

- provide accurate and complete data for cancer registration
- provide feedback to the other clinical specialties, including surgery, radiology and oncology
- allow for high-quality clinical audit and research.

Gastro-intestinal stromal tumours (GISTs) are the most common connective tissue tumour of the gastrointestinal tract. They have been the subject of great interest over the past decade as a much deeper understanding of the underlying molecular biology of this tumour type and the consequent therapeutic options, principally the use of tyrosine kinase inhibitors, have
emerged. Until the early 1980s, most tumours now recognised to be gastrointestinal stromal tumours were regarded as smooth muscle tumours, namely leiomyomas, leiomyosarcomas and epithelioid smooth muscle tumours or leiomyoblastomas. It was well recognised that prognostication in any individual case was difficult and that no clear criteria existed to distinguish benign tumours from malignant tumours with certainty. With the advent of electron microscopy and subsequently immunohistochemistry, it became apparent that many of these tumours did not show evidence of smooth muscle differentiation but rather of neural, including autonomic nerve sheath, differentiation or no specific differentiation. For this reason, the generic term ‘gastro-intestinal stromal tumour’ was introduced. Later, the demonstration of CD34 expression in many GISTs and the observation that both they and the interstitial cells of Cajal (ICC) expressed CD117, the product of the receptor tyrosine kinase KIT indicated that GISTs should now be regarded as a specific tumour type, probably with a close histogenetic relationship to ICCs. The demonstration of mutations in the c-kit gene in many GISTs opened the way to the use of tyrosine kinase inhibitors in the treatment of irresectable or metastatic tumours. These mutations are an early event and are seen in very small lesions. Subsequently, it was shown that a minority of GISTs contained mutations not of c-kit but of a gene encoding a related tyrosine kinase, platelet-derived growth factor alpha (PDGFRα).

Recent epidemiological studies have shown that the incidence of GISTs is higher and the morphological spectrum of GISTs wider than previously recognised. The estimated incidence of GISTs is around 15 per million of population per annum, implying approximately 900 new cases per year in the UK. Most patients are adults with a median age of 50–60 years and perhaps a slight male predominance; they are rare in childhood. While GISTs can occur anywhere in the GI tract, from the oesophagus to the rectum, most arise in the stomach (60–70%) or small intestine (20–30%); a few appear to arise primarily within omentum, but it is important to be sure that these do not represent spread from a primary lesion in the gut.

It is important to be aware of the wide differential diagnosis of mesenchymal tumours of the GI tract, including true smooth muscle tumours, gastro-intestinal schwannomas and intra-abdominal fibromatosis, among others.

While most cases of GIST are sporadic, there are four important settings in which they arise. These are Carney’s triad, in association with paraganglioma and pulmonary chondroma, as well as Carney Stratakis syndrome, an association of GIST with paraganglioma alone. Third, there are rare familial GISTs that are associated with germline mutations of the c-kit and PDGFRα genes. There is also an increased incidence in type 1 neurofibromatosis (NF-1) — these tumours often being multiple.

2 Clinical information required on specimen request form

As GISTs may occur anywhere within the gastrointestinal tract, as well as outwith it (extra gastrointestinal stromal tumour [EGIST]) clinical information regarding the nature of the surgical resection and the site of the tumour is useful in optimising specimen handling; in addition, prognosis is related to site.

While there is little published information specifically relating to EGIST, it is generally presumed that most of the basic principles and features of GIST apply to these tumours. The size of the tumour on radiology is helpful. The surgeon’s impression of the completeness of excision and the presence of peritoneal seedlings or liver metastases is also valuable. It is essential that a history of previous medical treatment, e.g. imatinib, is given as this may well modify the size, the histological appearances and assessment of proliferation. In addition, radiological assessment using Choi criteria is a helpful predictor of response.
3 Specimen preparation before dissection

Due to the varied anatomic sites from which GISTs arise, a wide array of specimen types may be encountered. Endoscopic biopsies are common, while practices vary as to whether percutaneous biopsies are carried out or the surgeon immediately proceeds to removal.

An exception is those tumours, for example in low rectum, which would necessitate abdominoperineal resection, and in the area of the duodenum, in which neo-adjuvant tyrosine kinase inhibitors may allow less radical surgery.

Specimen preparation and handling is therefore somewhat dependent on site, although general principles apply. Ideally, and assuming the theatre and laboratory are well connected by a rapid delivery system, resection specimens should be received fresh (unfixed) as soon as possible after resection. The specimen is then inspected externally to locate the tumour and identify any serosal involvement. The circumferential resection margin may be marked with ink. The specimen is then opened in a manner appropriate for the anatomic location. The specimen is pinned out, if suitable or required, and fixed in the manner most appropriate for the anatomic site. If the tumour mass is very large, fixation will be facilitated by serial sectioning. The specimen should then be allowed to fix in an adequate volume of formalin for 24–48 hours.

4 Specimen handling and block selection

After adequate fixation, the specimen should be examined to locate the site of the tumour. The maximum tumour diameter should be measured, as should the distance to the closest surgical and circumferential resection margins. Evidence of extension into mucosa, ulceration and depth of invasion are all noted. The length of gastrointestinal tract including the tumour should then be serially sectioned at 5–10 mm intervals. Areas of necrosis, haemorrhage or myxoid change should be noted. The slices may then be laid out and examined.

A permanent photographic record of the macroscopic specimen may then be made for presentation at the subsequent multidisciplinary team meeting.

The following tissue blocks should then be taken.

- Margin – surgical and circumferential resection margin.
- Tumour – sufficient blocks of the tumour are taken to ensure that all macroscopically different areas are sampled (e.g. areas of haemorrhage or myxoid change). The number of blocks will depend on tumour size and heterogeneity. One block per cm of tumour diameter is recommended. These tumour blocks should include suspected mucosal infiltration/ulceration, possible blood vessel invasion, the closest circumferential margin, and involvement of any adjacent organs. A block containing tumour and adjacent mucosa/muscularis propria is often useful in serving as an internal control for immunohistochemistry.
- One block of normal background mucosa.
- Any lymph nodes identified, although involvement is seldom seen.
- Blocks from any other co-existing macroscopic abnormality in the resected specimen or organ.
5 Core data items

Summary:

Macroscopic

- Specimen type
- Site of tumour
- Tumour size, maximum diameter measured in cm
- Resection margins – distance of tumour to nearest surgical and circumferential resection margins.

Microscopic

- Tumour type: spindle/epithelioid/mixed
- Mitotic count per 5 mm²
  (The total area to be counted should amount to 5 mm². With older microscopes, 50 high-power fields (HPF) may be equivalent to 5 mm². However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for his or her microscope.)
- Mucosal invasion
- Resection margins
- In tumours treated with imatinib or other tyrosine kinase inhibitors, presence of response to treatment.

Other

- Immunohistochemistry for CD117 and DOG1
- Prediction of tumour behaviour (prognostic index)
- Metastatic spread.

Macroscopic assessment

Specimen type

The type of resection specimen should be recorded, e.g. oesophagectomy, gastro-oesophagectomy, partial or total gastrectomy, small intestine resection, left or right hemicolecstomy, anterior resection, abdominoperineal resection. Gastrectomy specimens may vary from sleeve type gastrectomy specimens to partial or total gastrectomies with omental tissue. The presence of other resected organs, e.g. partial hepatectomy, must be recorded.

Site of tumour

The site of the tumour must be recorded. The most common sites are stomach and small intestine. Extra-gastrointestinal sites of origin are also encountered and this should be noted. Gastric GISTs generally have a better prognosis than small intestinal GISTs of similar size and mitotic activity. Oesophageal GISTs tend to be diagnosed at a late stage and have a poor prognosis.

Maximum tumour diameter

There is a well-established relationship between maximum tumour diameter measured in cm and tumour behaviour, when taken together with mitotic count (see below).
Resection margins
The principal treatment for GISTs is surgery with wide local resection including a margin of 10–20 mm for most tumours. Radical resection such as total gastrectomy with lymphadenectomy is not required. Involvement of surgical margins indicates a higher likelihood of local recurrence and therefore poorer outcome.

Microscopic assessment

Tumour type
GISTs may be of spindle cell type (70%), epithelioid type (20%) or mixed type (10%). Epithelioid and mixed types are much more common in the stomach.

Mitotic count
Taken together with maximum tumour dimension, mitotic count is used to predict tumour behaviour (see below). Mitotic count should be expressed as the number of mitoses per 50 high power fields. The count should be done from the areas with the highest mitotic activity. Atypical mitotic figures are uncommon in GISTs. The proliferation marker Ki67 may be useful in assessing proliferation rate, but has not been proven superior to mitotic count.

Mucosal invasion
Mucosal invasion, characterised by diffuse spread of tumour cells in a ‘lymphoma-like’ pattern, has been associated with an adverse prognosis. This is not common.

Resection margins
The presence or absence of histological involvement of the circumferential and surgical margins should be recorded as histologically proven margin involvement is associated with poorer outcome. Should the distance measured histologically be more accurate than that measured macroscopically, it should be recorded instead.

Response to treatment
While surgery is the mainstay of treatment of resectable GISTs, imatinib may be used in a neoadjuvant manner in an attempt to render large or strategically placed tumours, e.g. those adjacent to the anal sphincter, resectable. The changes associated with a response to therapy include loss of cellularity, with the formation of a loose, rather myxoid stroma and a reduction in mitotic activity or Ki67 proliferation index.

Increasingly, it is apparent that acquired secondary resistance to tyrosine kinase inhibitors is seen, and in patients in whom there is focal clinical or radiological progression, surgical excision is appropriate therapy. In these specimens, there may be evidence of previous responsive therapy as well as fully viable and proliferating tumour.

Other

Immunohistochemistry
Immunohistochemistry for CD117 and DOG1 must be performed on every case. A block of well-fixed tumour without necrosis or haemorrhage is selected. The following immunohistochemical panel is recommended as good practice, but only CD117 and DOG1 are regarded as core data items:

- KIT (CD117) .................. Almost 95% positive
- DOG1 ........................ > 95%
- CD34 ........................ 65% positive (40–72%)
- Desmin ......................... Negative (0.2%)
- Smooth muscle actin .... Variably positive (34%)
- S100 ............................ Variably positive (14%)
- Cytokeratin ........................ Very rarely positive.

The problem of CD117 negative GISTs: tumours morphologically typical of GISTs may be KIT negative by immunohistochemistry, and some of these do harbour mutations of the c-kit gene. Another one-third are due to mutations of PDGFRα. The antibody DOG1 is a useful addition to the immunohistochemistry panel as a significant proportion of around one-half of KIT negative tumours are positive for this marker. Even when both CD117 and DOG1 are negative (approximately 2% of tumours), it is legitimate to make the diagnosis of GIST on morphological grounds, but this is a very strong indication to refer paraffin blocks to a centre capable of mutational analysis.

**Prediction of tumour behaviour (prognostic index)**

With the exception of very small tumours, all GISTs have the potential to become malignant. A scheme proposed under the aegis of the National Institutes of Health (NIH) defined the risk of aggressive behaviour using the twin criteria of tumour size and mitotic activity count irrespective of tumour location. A significant body of opinion holds that the NIH scheme underestimates the risk of small bowel tumours and overestimates those of gastric origin. It is now widely held that this scheme should be replaced by one derived from the data collected by Lasota and Miettinen (see Table 1). This scheme requires validation on independent data. It is based on tumour size (maximum dimension in mm) and mitotic activity (the total area to be counted should amount to 5 mm²). (With older microscopes, 50 high-power fields (HPF) may be equivalent to 5 mm². However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for his or her microscope.)

<table>
<thead>
<tr>
<th>Tumour parameters</th>
<th>Risk of progressive disease (metastasis or tumour-related death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic index</td>
<td>Size</td>
</tr>
<tr>
<td>≤5 (in 5 mm²)*</td>
<td>≤2 cm</td>
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<tr>
<td></td>
<td>&gt;2–≤5 cm</td>
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</table>

* (With older microscopes, 50 high-power fields (HPF) may be equivalent to 5 mm². However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for his or her microscope.)
Metastatic spread
Lymph node involvement by metastatic GIST is rare, but it is good practice to submit any identified lymph nodes from resection specimens for histology. In particular, GISTs which arise in association with Carney's triad are more likely to produce lymph node metastases.\textsuperscript{23}

Direct extension of tumour into other organs is also rare but must be recorded, especially with regard to margins.

Separately submitted specimens of peritoneal deposits of tumour and resected metastatic lesions (e.g. liver metastases) must be examined and recorded.

6 Non-core data items

Macroscopic
\begin{itemize}
\item Evidence of extension into mucosa, presence of mucosal ulceration and depth of invasion may be recorded
\item Presence of necrosis.
\end{itemize}

Microscopic
\begin{itemize}
\item Presence of haemorrhage
\item Presence of necrosis
\item Presence of ulceration
\item Lymphovascular space invasion
\item Lymph node status (the presence of lymph node metastases, especially with gastric epithelioid GISTs, is important in raising a suspicion of Carney's triad or Carney Stratakis syndrome)
\item Other histological patterns, e.g. myxoid, nested, prominent giant cells
\item Adjacent cell of Cajal hyperplasia, which may indicate that investigation for germ cell mutation of the c-kit gene or raise the possibility of NF-1.
\end{itemize}

Other

Mutational analysis
It is now clear that the precise mutation in a case of GIST is of prognostic and therapeutic importance.\textsuperscript{23} While it is fully recognised that mutational analysis of gastrointestinal stromal tumours is not yet within the repertoire of most departments and probably is performed on a very small proportion of currently diagnosed tumours, the spread of availability of such techniques and the value in terms of diagnosis, prediction of response to therapy and assessment of acquired resistance to such therapies, make it likely that this will be generally available in the lifetime of this dataset. Indeed, the UK guidelines now recommend mutational analysis for all small bowel GISTs and all intermediate-risk and high-risk GISTs, regardless of location.

As has been indicated, mutations of c-kit are detectable in over 80% of GISTs – both larger symptomatic tumours and the common small incidental tumourlets.

The largest group, of around two-thirds, involve exon 11, which encodes the intracellular juxtamembrane domain, and are a heterogeneous group of deletions, substitutions and insertions. These correlate with the best response to imatinib. A further 15% or so affect exon 9, encoding the extracellular domain; these mainly are in frame tandem duplications. While they respond less well to imatinib, they do respond, notably with dose escalation, and
respond well to sunitinib in those tumours resistant to imatinib. Much smaller numbers occur in exons 13 and 17.

Some GISTs express CD117, but do not contain mutations of the gene, and some which do not stain for CD117 nevertheless have mutations of c-kit.

Of those with wild type c-kit gene, about one-third have mutations in the platelet-derived growth factor receptor α gene (PDGFRA), which encodes a related tyrosine kinase inhibitor. Immunohistochemistry for this protein is unreliable, emphasising the value of mutational analysis. The majority of the 5–10% of GISTs containing PDGFRA mutations affect exon18 especially within gastric tumours, and the most common (D842V) responds poorly to imatinib. Mutations have also been found in exons 12 and 14.

There remains a significant and clinically heterogeneous group of around 10% of GISTs lacking mutations in either c-kit or PDGFRA and the underlying oncogenic mechanisms remain obscure.

Some centres now offer mutational analysis on paraffin-embedded tissue blocks and this is subject to an external quality assurance scheme. Mutational analysis should include assessment of primary KIT exons 9, 11, 13 and 17 and PDGFRA exon 12, 14 and 18 mutations.

7 SNOMED coding
GISTs should be coded using the SNOMED system. See Appendix A.

8 Tumour staging
Recently TNM7 has been published by the UICC and includes a staging system for GIST. However, this is not yet in widespread use and is not yet in use in the UK GIST guidelines. It remains to be seen whether TNM staging of tumours confers any further useful information with regard to the treatment of patients when compared to current systems of prediction of tumour behaviour and mutational analysis of this group of tumours.

9 Reporting of small biopsy specimens
The main aim in reporting a biopsy from a suspected (or unsuspected) GIST is to make the diagnosis, and only in unusual circumstances when mitoses may be very prominent would an attempt at prognostication be possible. Clearly, however, imaging of the lesion may give the requisite size which would allow a good estimate of the likely behaviour. With endoscopic biopsies, the difficulties often relate to the biopsy being too superficial, consisting of mucosa or ulcer slough.

10 Multidisciplinary team meetings
All cases of GIST should be discussed at an appropriate multidisciplinary team (MDT) meeting. These are usually the upper GI MDT meetings, but some cases may be discussed at the lower GI or sarcoma MDTs.
Criteria for audit of the dataset

The following are suggested as some of the criteria that might be used in periodic reviews of GIST reporting:

- completeness of histopathology reports expressed as average proportion of the core data items recorded, or as proportion of the reports that successfully include 100% of the items – the standard is that all contain 100% of the items
- the number (or proportion) of cases referred for mutational analysis
- the proportions of GISTs falling into the four prognostic categories, and the proportion of DOG1 or CD117 negative tumours. Although no audit standards are recommended, monitoring this activity will allow standards to be defined in the future.

References


Appendix A  SNOMED codes

SNOMED T codes

T – 62000  Oesophagus
T – 63000  Stomach
T – 64000  Small Intestine
T – 64300  Duodenum
T – 65100  Jejunum
T – 65200  Ileum
T – 66000  Appendix
T – 67000  Colon
T – 68000  Rectum
T – 69000  Anus
T – Y4400  Peritoneum
T – 63850  Omentum
T – 57000  Liver

SNOMED M code

M – 89363  Gastrointestinal stromal tumour

SNOMED P codes

P – 1100  Resection
P – 1101  Local excision
P – 1140  Biopsy
### Appendix B  Proforma for the histological reporting of gastrointestinal stromal tumours (GISTs)

Surname: ...........................................  Forenames: ...........................................  Date of birth: ...........................................

Sex: ...........................................  CHI/NHS no: ...........................................  Hospital: ...........................................

Date of receipt: ...........................................  Date of reporting: ...........................................  Report no: ...........................................

Pathologist: ...........................................  Surgeon: ...........................................

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### Macroscopic

Specimen type ...........................................

Site of tumour ...........................................

Maximum tumour dimension……..cm

Distance of tumour to nearest surgical margin……..mm

Distance of tumour to closest circumferential resection margin……..mm

---

### Microscopic (please circle)

<table>
<thead>
<tr>
<th>Tumour type:</th>
<th>Spindle</th>
<th>Epithelioid</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic count</td>
<td>/5 mm² *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mucosal invasion Y / N  Ulceration Y / N

Necrosis Y / N  Haemorrhage Y / N

Lymphovascular space invasion Y / N

Involvement of surgical margins: Y / N  Involvement of circumferential margins: Y / N

Features indicating a response to treatment: Not applicable / Y / N

Loss of cellularity Y / N  Loose myxoid stroma Y / N  Reduction in mitotic activity Y / N

---

### Metastatic spread

Number of lymph nodes present.............

Number of lymph nodes positive.............

Peritoneal metastasis Y / N

Liver metastasis Y / N

Other (specify)...........................................

---

### Immunohistochemistry

CD117  Positive / Negative / Not done

DOG1  Positive / Negative / Not done
Prediction of tumour behaviour / Prognostic index (please circle)

None / Very low / Low / Moderate / High

<table>
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</table>

Mutational analysis

Tissue block referred Y / N

The result when available will be issued in a supplementary report.

c-kit – exon 9 Yes / No / Unknown  
exon 11 Yes / No / Unknown  
exon 13 Yes / No / Unknown  
exon 17 Yes / No / Unknown  

PDGFRA – exon 12 Yes / No / Unknown  
exon 14 Yes / No / Unknown  
exon 18 Yes / No / Unknown  

Pathologist…………………………..  Date…………/……/……

SNOMED codes T………..  M………..

* (With older microscopes, 50 high-power fields (HPF) may be equivalent to 5 mm². However, 40x lenses in more modern microscopes have a much wider field of view and require far fewer HPFs to be surveyed (20–25) to assess the same area. The exact figure should be established by the individual user for his or her microscope.)
Appendix C  AGREE compliance monitoring sheet

The Cancer Datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

<table>
<thead>
<tr>
<th>AGREE standard</th>
<th>Section of dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOPE AND PURPOSE</td>
<td>Foreword</td>
</tr>
<tr>
<td>1 The overall objective(s) of the guideline is (are) specifically described.</td>
<td>Foreword</td>
</tr>
<tr>
<td>2 The clinical question(s) covered by the guidelines is (are) specifically described.</td>
<td>Introduction</td>
</tr>
<tr>
<td>3 The patients to whom the guideline is meant to apply are specifically described.</td>
<td>Foreword</td>
</tr>
<tr>
<td>STAKEHOLDER INVOLVEMENT</td>
<td>n/a *</td>
</tr>
<tr>
<td>4 The guideline development group includes individuals from all the relevant professional groups.</td>
<td>Foreword</td>
</tr>
<tr>
<td>5 The patients’ views and preferences have been sought.</td>
<td>n/a *</td>
</tr>
<tr>
<td>6 The target users of the guideline are clearly defined.</td>
<td>Foreword</td>
</tr>
<tr>
<td>7 The guideline has been piloted among target users.</td>
<td>Foreword</td>
</tr>
<tr>
<td>RIGOUR OF DEVELOPMENT</td>
<td>Foreword</td>
</tr>
<tr>
<td>8 Systematic methods were used to search for evidence.</td>
<td>Foreword</td>
</tr>
<tr>
<td>9 The criteria for selecting the evidence are clearly described.</td>
<td>Introduction</td>
</tr>
<tr>
<td>10 The methods used for formulating the recommendations are clearly described.</td>
<td>Introduction</td>
</tr>
<tr>
<td>11 The health benefits, side effects and risks have been considered in formulating the recommendations.</td>
<td>Foreword</td>
</tr>
<tr>
<td>12 There is an explicit link between the recommendations and the supporting evidence.</td>
<td>References</td>
</tr>
<tr>
<td>13 The guideline has been externally reviewed by experts prior to its publication.</td>
<td>Foreword</td>
</tr>
<tr>
<td>14 A procedure for updating the guideline is provided.</td>
<td>Foreword</td>
</tr>
<tr>
<td>CLARITY OF PRESENTATION</td>
<td>4–6</td>
</tr>
<tr>
<td>15 The recommendations are specific and unambiguous.</td>
<td>4–6</td>
</tr>
<tr>
<td>16 The different options for management of the condition are clearly presented.</td>
<td>4–6</td>
</tr>
<tr>
<td>17 Key recommendations are easily identifiable.</td>
<td>4–6</td>
</tr>
<tr>
<td>18 The guideline is supported with tools for application.</td>
<td>Appendix B</td>
</tr>
<tr>
<td>APPLICABILITY</td>
<td>Foreword</td>
</tr>
<tr>
<td>19 The potential organisational barriers in applying the recommendations have been discussed.</td>
<td>Foreword</td>
</tr>
<tr>
<td>20 The potential cost implications of applying the recommendations have been considered.</td>
<td>Foreword</td>
</tr>
<tr>
<td>21 The guideline presents key review criteria for monitoring and/audit purposes.</td>
<td>Foreword</td>
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<tr>
<td>EDITORIAL INDEPENDENCE</td>
<td>Foreword</td>
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<tr>
<td>22 The guideline is editorially independent from the funding body.</td>
<td>Foreword</td>
</tr>
<tr>
<td>23 Conflicts of interest of guideline development members have been recorded.</td>
<td>Foreword</td>
</tr>
</tbody>
</table>

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.