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

Tissue pathway for histopathological examination of the placenta

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INVESTOR IN PEOPLE

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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.

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Foreword

The tissue pathways published by The Royal College of Pathologists (RCPath) are guidelines that should assist pathologists in providing a high standard of care for patients. 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 document was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be carefully considered by the reporting pathologist; just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

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

This tissue pathway has been developed in consultation with the following stakeholders:

- the British Paediatric Pathology Association (BRIPPA)
- The Royal College of Obstetrics and Gynaecology (RCOG)
- The Royal College of Paediatrics and Child Health (RCPCH)
- The Royal College of Midwives.

The information used to develop this tissue pathway was collected from electronic searching of the medical literature, previous recommendations of the RCPath, RCOG and local guidelines and protocols from perinatal pathology units in the United Kingdom. Published evidence was evaluated using modified SIGN guidance. The level of evidence was either grade C or D, or met the GPP/good practice point criteria. Consensus of evidence in the tissue pathways was achieved by expert review. Gaps in the evidence were identified by College Fellows via feedback received from consultation.

Implementation of the tissue pathway to its full extent may have some cost implications or require some local organisational changes, as the delivery of placental pathology services varies widely between hospitals and is not available to all obstetric units in the United Kingdom.

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 or not the document needs to be 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 one month for Fellows' attention. If Fellows 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 publications page of the College. All changes will be documented in the data control section on the front page of the relevant pathway.

This pathway has been reviewed by the Working Group on Cancer Services and was placed on the College website for consultation with the membership from 13 July to 1 September 2011. All comments received from the Working Group and membership were addressed by the author(s) to the satisfaction of the Chair of the Working Group and the Director of Communications.

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Director of Professional Standards and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 General introduction

Histopathological examination of the placenta following a pregnancy affected by medical complications, pregnancy loss or neonatal death may provide an explanation of the pregnancy complications, pregnancy loss or neonatal death and may also provide information relevant to the management of the current infant and/or subsequent pregnancies and medicolegal litigation.[1, 2]

This document is intended as a guide to reasonable practice, rather than a policy statement. It also attempts to provide information that might be useful when dealing with different types of placenta. Where possible, references are provided, but it is inevitable that many of the suggestions are based on common UK practice rather than on published evidence, as the latter is often non-existent or sparse. Many laboratories have adopted approaches based on their own experience, evidence and resources, which may differ from these guidelines but which achieve the same outcome. This document does not aim to change such approaches. In addition, the document is not intended as a replacement for standard textbooks, but highlights the principles of handling and reporting placental specimens. For detailed guidance on examination of the placenta in specific circumstances, the reader is referred to the 'Further reading' list in Section 5.1.

This tissue pathway aims to provide guidance on the range of indications for referral of a placenta for histopathological examination and minimum standards for pathologists undertaking placental examinations. Variations to the standard pathway for singleton placentas, relating to pregnancies from multiple gestations, are also included. Please note that products of conception (1st trimester) have been included in the tissue pathways for gynaecological pathology.

This pathway will be of use to consultants and trainees in general histopathology and subspecialist paediatric and perinatal pathologists, obstetricians and midwives and those commissioning perinatal pathology services.

2 Generic considerations

2.1 Staffing and workload

In general pathologists should:

- participate in audit
- participate in The Royal College of Pathologists' Continuing Professional Development (CPD) scheme
- participate in relevant external quality assessment (EQA) schemes of a general or specialist nature. Although there is currently no EQA scheme solely for placental pathology, placental pathology does form part of the Paediatric and Perinatal Pathology EQA scheme organised by the British Paediatric Pathology Association (BRIPPA) and is undertaken by all subspecialist paediatric and perinatal pathologists. General pathologists undertaking perinatal autopsies or paediatric surgical pathology, in addition to placental pathology, should participate in this scheme
- have access to specialist referral opinions on a local/regional network or national basis. For general pathologists, this will usually mean access to a subspecialist perinatal pathologist at a regional centre.

2.2 Laboratory facilities and generic laboratory requirements

Placental examination should be undertaken in an appropriate laboratory environment. Provision should be made for macroscopic and microscopic photography as placentas from

pregnancy losses may be discussed at local perinatal mortality meetings and visual information may assist the discussion. If injection studies are to be undertaken on monochorionic twin placentas, a microwave oven to make agar solution and coloured tissue-marking dyes, syringes and cannulae should be available.

The laboratory should:

- be equipped to allow the recommended technical procedures to be performed safely
- be enrolled with Clinical Pathology Accreditation (UK) Ltd
- participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique
- participate in the UK National External Quality Assurance Scheme for Immunocytochemistry
- have access to light microscopy and common special stains
- have access to immunohistochemistry
- have access to genetics services
- have access to microbiology and virology services
- have access to photographic equipment.

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 Clinical Terms* (SNOMED) T, M and P codes. It is acknowledged that existing laboratory information systems may not meet this standard; however, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.

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

3 Tissue-specific pathway: placenta

3.1 General issues

3.1.1 Staffing and workload

In hospitals with specialist(s) in perinatal pathology, placental examination may be undertaken by the specialist. However, in many departments, placental examination is undertaken as part of a general rota. In either circumstance, there must be sufficient pathologists to provide cover and to conform to The Royal College of Pathologists' (College) guidance on staffing and workload levels.[3]

3.1.2 Specimen submission

The decision regarding the indications for referral of a placenta for histopathology should be agreed with local obstetricians and neonatologists. A suggested list of indications for referral is shown in Appendix A.[4] As a minimum, all placentas from stillbirths,[5] intrauterine growth restriction (below 3rd centile),[6] immaturity,[7] cases of severe fetal distress requiring admission to a neonatal intensive care unit (NICU)[4] (evidence level C) and late miscarriages (evidence level D) should be referred. Consideration may be given to providing an urgent placental examination service for infants in NICU. Submission of placentas following other pregnancy complications may depend on local resources and the value placed on placental examination in these situations by the local obstetricians[8] (evidence level D, GPP).

Full details of the patient (mother), clinical consultant and date of delivery should be provided on the request form. As a minimum, the gestational age, birth weight and the indication for referral should be stated. Details of previous pregnancy complications and relevant maternal disease should also be provided. It may be appropriate to develop a simple placental referral proforma for use by clinicians, e.g. Appendix B.

The specimen container must be labelled with the patient details. Placentas may be submitted to the laboratory in the fresh state or formalin-fixed as per local protocols. If submitted in formalin, the container should be of sufficient size to minimise distortion of the specimen and formalin should be of adequate volume to cover the specimen entirely to ensure proper fixation. Any samples for cytogenetic testing should be taken prior to fixation. The specimen should not otherwise be disrupted prior to receipt in the histopathology laboratory, unless this has been agreed upon previously.

Submission of the unfixed placenta may be preferable for identification of macroscopic changes. However, formalin fixation may be preferred if there is likely to be a delay in undertaking the examination following submission or when refrigerated storage is not available. It may also be desirable to fix the placenta in potentially high-risk infective cases or where there is a risk of congenital infection being transmitted to a vulnerable member of staff. For adequate fixation, the placenta must be placed in a container of adequate size, containing at least 3 times the tissue volume of formalin.

3.1.3 Specimen dissection and block selection

Sampling of the placenta for histology should be undertaken from sufficient areas to provide a representation of the pathology present.[4,8] Each cassette must have a unique identifying number or letter. A record of the number of pieces of tissue in each cassette is desirable for audit purposes. Specific details of dissection and block selection relating to singleton and multiple pregnancy placentas are detailed in Sections 3.2–3.4 below.

In a small number of clinical situations, it may be appropriate for the examination to be limited to a macroscopic description, without sampling for histology (Appendix C). In this case, the placenta should be retained for at least 2 weeks in case the baby or mother becomes ill and placental histology becomes necessary.

In agreement with local clinicians, in some clinical situations it may be appropriate for the placenta to be referred to the pathology department for short-term storage only, in case the baby or mother develops significant complications which placental examination may help to explain or direct treatment. Suggested indications for short-term storage are given in Appendix C. In this situation, a report should be issued, notifying the clinician that the placenta has not been examined, stating the intended period of storage and providing the contact details to initiate examination if this becomes necessary.

3.1.4 Embedding options

Local procedures for processing and embedding tissue samples should be followed. There are no specific requirements for general placental tissue. Samples from the maternal surface, searching for spiral arteries in the decidua, may be embedded either on edge or with the decidual face downwards, depending on local preference and experience.

3.1.5 Sectioning

Tissue sections should be produced as per local protocols.

3.1.6 Staining

In the vast majority of cases, a single haematoxylin and eosin (H&E) stained section of each tissue block is sufficient for diagnosis. It is essential that the sections produced include the fetal and maternal surface of the placenta and that sections of umbilical cord include the complete circumference of the cord.

3.1.7 Further investigations

Additional stains are usually not required. In individual cases, consideration may be given to the use of special stains, immunohistochemistry, genetic analysis, electron microscopy and microbiological samples. Commonly employed special stains include Gram-Twort for bacteria, PAS with diastase predigestion for fungi and Perls' stain for haemosiderin (to distinguish from meconium pigment in the fetal surface). Immunostaining for cytomegalovirus (CMV) and Parvovirus B19 may be useful in the appropriate context. Cytogenetic testing may be indicated if the placenta is being examined following fetal death, where post mortem has been declined and there is a clinical indication (severe IUGR, congenital malformations). Samples should only be sent for cytogenetic analysis if there is documented parental consent. Electron microscopy is rarely indicated, but may be considered in cases of death due to fetal hydrops, when post mortem is declined. Some authors suggest placental bacteriological swabs should be sent in cases of apparent chorioamnionitis. This is of questionable value except in specific circumstances (e.g. suspected listeriosis).

3.1.8 Report content

In general, the report should include, as a minimum, the patient details, the clinical history (summarised or directly transposed from the request form), a macroscopic description of the umbilical cord, membranes, fetal, maternal and cut surfaces of the placenta and a microscopic description of the umbilical cord, membranes, fetal placental surface, villous parenchyma and maternal decidua.[9] The report should conclude with a diagnosis or list of pathological findings and, where appropriate, a clinicopathological comment to assist the clinician in interpreting the significance of the findings. Diagnostic coding of the findings is recommended.

3.2 Tissue pathway: specific considerations for singleton placenta

3.2.1 Dissection and macroscopic description[4,8]

The following measurements should be made in all cases:

- maximum linear dimensions of the placental disc in two perpendicular planes (to nearest 10 mm)
- thickness of disc (to nearest 5 mm)
- length of umbilical cord (to nearest 10 mm) and approximate diameter (to nearest 1 mm)
- weight of placental disc following removal of cord and membranes (to nearest g) and whether this is fresh or fixed.

There should be a systematic description of the umbilical cord, membranes, fetal surface, maternal surface and of the parenchyma. The site of the cord insertion and number of umbilical cord vessels should be recorded. The degree of coiling of the umbilical cord may also be described, either qualitatively or numerically (e.g. *n* coils per 100 mm). The presence and site of true knots in the umbilical cord should be recorded and an assessment should be made regarding whether the knot appears to have occluded flow in the cord vessels. It may be helpful to record the appearance photographically. The appearance of the placental membranes (translucency, colour) and the fetal placental surface (colour, vascular congestion/thrombosis) should be described. The presence and extent of macroscopic pathology in the placental parenchyma should be described and an attempt should be made to assess whether the membranes and parenchyma have been received in their entirety or whether they are incomplete.

Major lesions, particularly in placentas from pregnancy losses, should be recorded photographically, if facilities exist. If the placenta is examined in the fresh state, consideration should be given to sampling the placenta for cytogenetic testing or virology, if clinically indicated. As noted above, cytogenetic analysis should only be undertaken if parental consent has been obtained.

3.2.2 Sampling for histology

Histological sampling is indicated in the majority of situations.

It is recommended that the following samples are taken as a minimum:

- one transverse section of umbilical cord
- one roll of membranes (to include the rupture site)
- two full thickness blocks of the placental parenchyma (away from the placental edge) to include the fetal and maternal surfaces
- additional blocks may be required depending on the clinical indications for the examination and macroscopic findings.

Representative samples of macroscopic lesions should be taken as necessary. In cases of severe fetal growth restriction (FGR), maternal pre-eclampsia (PET) or a morbidly adherent placenta (MAP), additional small samples may be taken from the maternal surface to attempt to identify maternal vascular pathology (FGR, PET) or uterine smooth muscle (MAP) 3. In cases of maternal pyrexia or prematurity, additional samples of umbilical cord and membranes and fetal placental surface may be necessary, since chorioamnionitis is often patchy in distribution.

In limited circumstances, with agreement from local obstetricians, macroscopic examination may be performed, without histology[4] (see Appendix C).

When no histology is undertaken, it is advisable to issue a macroscopic report urgently, indicating that histology will only be undertaken if clinically indicated. The placenta should be retained for a short period (1–2 weeks) in case serious neonatal complications occur or further clinical information comes to light necessitating histological sampling.

3.2.3 Report content

See Section 3.1.8 for general comments.

The histological report should be tailored to the specific clinical situation. Key elements to note include: the presence, severity and extent of acute inflammation in the cord, membranes and/or fetal surface; the villous development in relation to the stated gestation and evidence of villous ischaemia; the presence of infarction, chronic inflammation and other parenchymal disease. In cases of FGR and maternal PET, the decidua should be examined for the presence of maternal vascular disease. In case of MAP, the presence of uterine smooth muscle in the maternal surface should be sought.

3.3 Tissue pathway: specific considerations for dichorionic twin placentas

3.3.1 Specimen submission

Dichorionic twin placentas are frequently referred to the pathology laboratory for examination. If the pregnancy and delivery has been uncomplicated, it may be appropriate to undertake macroscopic examination only, with the aim being to confirm chorionicity. The examination may be of limited value in this situation and may equally be undertaken in the delivery suite by an appropriately trained midwife or doctor. If this approach is taken, the clinician should refer the placenta to the pathology for assessment if he/she is uncertain of the chorionicity in the delivery suite. If the pregnancy has been affected by medical complications, the approach to examination should be the same as for singleton placentas.[4]

3.3.2 Dissection and macroscopic description

The first aim of the examination is to confirm that the placenta is dichorionic, by examination of the dividing membrane. A dividing membrane tethered to the placental surface indicates dichorionicity, whilst a mobile dividing membrane is characteristic of a monochorionic placenta. It is usual also to determine whether the placental discs are separate or joined. Otherwise examination assesses the same features as for a singleton pregnancy for each part of the placenta.

3.3.3 Sampling for histology

The pathologist may wish to include a roll of the dividing membrane or a T-block from the insertion of the dividing membrane into the placental surface as histological confirmation of chorionicity. Otherwise the rationale for sampling is the same as for two singleton placentas.

3.3.4 Report content

Apart from a description of the dividing membrane, the report follows the same lines as if for two singleton placentas.

The conclusion or diagnosis should indicate the chorionicity of the placenta. Other relevant pathology should be listed and a clinicopathological comment added as necessary.

3.4 Tissue pathway: specific considerations for monochorionic placentas

3.4.1 Specimen submission

Monochorionic pregnancies are subject to a number of additional pathological disorders, not seen in singleton or dichorionic twin placentas.[10] Rates of complications are also significantly higher. They may also be subject to medical intervention during pregnancy to treat the complications. It is probably advisable for monochorionic twin placentas to be routinely referred for examination by a pathologist.

3.4.2 Dissection and macroscopic description

In general, it is necessary to approach the monochorionic twin placenta as a single entity with regard to weight, measurements and description – the obvious exception being the umbilical cords, which are described separately.

The fetal surface is of particular interest and usually carries connections between the two fetal circulations. The description of the fetal surface should include the site and distance between the insertion of the two umbilical cords and the relative shares of the placental disc. An assessment of the vasculature in the chorionic plate should be made and the presence, number and size of the three types of interfetal anastomoses – arterioarterial, venovenous and ‘deep’ arteriovenous – should be recorded.[11] Identification of anastomoses may be facilitated by injection of the vasculature. A simple method involves injecting a 1% agar solution, coloured with four tissue-marking dyes, into an artery and the vein of each umbilical cord, after removal of excess blood from the superficial vessels.[11] The resulting preparation can be photographed and is suitable for histological examination. Injection studies are particularly helpful if the pregnancy has been complicated by growth discordance or twin-twin transfusion syndrome (TTTS). Other methods for placental injection to determine vascular anastomoses have been described.[12] These methods are not suitable for formalin-fixed placentas.

If the placenta has been subject to laser coagulation for TTTS, the presence of laser sites and completeness of interruption of interfetal anastomoses should be recorded.

3.4.3 Sampling for histology

In cases where histological examination is undertaken, the approach to histological sampling is the same as for singleton placentas, except that, in complicated MC pregnancies, samples should be taken from the areas supplying each twin for comparison. A roll of the dividing membrane is also usually taken.

3.4.4 Report content

The description of the placenta should include a detailed description of the fetal surface of the placenta, including the site and distance between the insertion of the umbilical cords, the sharing of the placental disc, the types, number and size of interfetal anastomoses and their direction (arteriovenous anastomoses only).

The histological report should include a description of the dividing membrane and should compare the appearance of parenchymal samples from the areas supplying each twin. Otherwise the description follows the same lines as for singleton placentas.

A clinicopathological comment regarding the contribution of the placental findings to the observed clinical complications (if any) should be given.

Note: Placentas from higher multiple pregnancies (e.g. triplets) should be dealt with according to the chorionicity of the placenta. Often this is a combination of monochorionic and dichorionic placentation.

4 Criteria for audit of the tissue pathway

Implementation of this tissue pathway may be monitored by audit of:

- completeness of adherence to referral criteria
- completeness of recording of standard measurements
- inclusion of clinicopathological comment in report
- adherence to minimum histological sampling guidance
- turnaround time for reports.

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5.1 Further reading

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Appendix A Indications for referral of placentas for pathological examination

Referral of placenta for examination is ESSENTIAL for:

- stillbirth (antepartum or intrapartum)
- late miscarriage
- severe fetal distress requiring admission to NNU
- prematurity (less than 30 weeks gestation)
- intrauterine growth restriction (birthweight below 3rd centile)
- fetal hydrops
- maternal pyrexia (>38°C).

Referral of placenta for examination may be DESIRABLE for:

- prematurity (30–36 weeks)
- placental abruption
- fetal congenital malformation
- rhesus (and other) isoimmunisation
- morbidly adherent placenta
- twins or other multiple pregnancy (uncomplicated)
- abnormal placental shape (if clinically relevant)
- two vessel cord, etc.
- prolonged rupture of the membranes (more than 36 hours)
- gestational diabetes
- maternal group B streptococcus
- pre-eclampsia/maternal hypertension
- maternal coagulopathy
- maternal substance abuse.

Referral is NOT indicated in the following conditions as pathological examination is unlikely to provide useful information:

- cholestasis of pregnancy
- pruritis of pregnancy
- hepatitis B, HIV, etc.
- other maternal disease with normal pregnancy outcome
- placenta praevia
- post partum haemorrhage
- polyhydramnios
- normal pregnancy.

Appendix B Sample request form for placental examination

Registration no:	**NHS no:**	**Clinical information:**	
Surname:	**DOB:**	**Date of delivery**	
Forename(s):	**Ward:**	**Live birth / stillbirth / TOP**	
Address:	**Specialty:**	**Sex of baby(babies)**	
	Consultant:	**Gestation at birth (weeks)**	
Alternatively attach patient label		**Birth weight(s) (grams)**	

Indication for referral **(Please tick/delete all relevant)**				***** Delete as appropriate **M** Macroscopic examination only **S** Will be stored for 2 weeks only and will only be examined if requested. Includes births between 34 and 36 completed weeks			
IUGR (birth weight below 2.5 kg or 3rd centile		Maternal pyrexia		2 vessel cord etc. (**M**)		PROM (more than 36 hours) (**S**)	
Abruption		Fetal hydrops		Abnormal placenta shape (**M**)		Gestational diabetes (**S**)	
Morbidly adherent placenta		Isoimmunisation – Rh / ABO / Kell / Other *		Pre-eclampsia (uncomplicated) (**S**)		Maternal Gp B Streptococcus (**S**)	
Prematurity (less than 37/40) (**S** unless<34/40)		Stillbirth – antepartum / intrapartum *		Fetal abnormality (specify)			
Severe fetal distress (requiring admission to NNU) Apgar scores: 1’ 5’ 10’				Other (must specify)			
Twins/other multiple pregnancy (specify) * Monochorionic / Dichorionic / ? * Complications/interventions (specify)							
Relevant previous medical/obstetric history (specify):							

Section to be completed by delivery suite staff		
Placenta request form and specimen checked by:		
Print name:	Signature:	Date:

Section to be completed by mortuary staff		
Placenta received:		
By (initials):	Date:	Time:
Examination type (pathologist to initial):		
Full:	Macro:	Storage:

Appendix C Triage system for placental examination based on clinical situation (with agreement of local clinicians)

Full examination including histology

Stillbirth (antepartum or intrapartum)

Late miscarriage

Severe fetal distress requiring admission to NNU

Prematurity (less than 30 weeks gestation)

Intrauterine growth restriction (birthweight below 3rd centile)

Fetal hydrops

Maternal pyrexia

Placental abruption

Fetal abnormality

Rhesus (and other) isoimmunisation requiring in utero transfusion

Morbidly adherent placenta

Maternal coagulopathy

Maternal substance abuse

Macroscopic examination – no histology (placenta retained for 2 weeks after examination)

Twins or other multiple pregnancy (uncomplicated)

Abnormal placental shape (if clinically relevant)

Two vessel cord, etc.

Storage for 2 weeks (no examination)

A report indicating that the placenta has been received and is being stored without examination may be sent to the referring clinician depending on local agreement/policy.

Prolonged rupture of the membranes (more than 36 hours)

Prematurity (30–36 weeks)

Gestational diabetes

Rhesus negative mother (no fetal anaemia)

Maternal group B streptococcus

Uncomplicated pre-eclampsia/maternal hypertension

Appendix D AGREE tissue pathway monitoring sheet

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

AGREE standard	Section of tissue pathway
SCOPE AND PURPOSE	
1. The overall objective(s) of the guideline is (are) specifically described.	Introduction
2. The clinical question(s) covered by the guidelines is (are) specifically described.	Introduction
3. The patients to whom the guideline is meant to apply are specifically described.	Foreword
STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all the relevant professional groups.	Introduction
5. The patients' views and preferences have been sought.	n/a *
6. The target users of the guideline are clearly defined.	Introduction
7. The guideline has been piloted among target users.	Introduction
RIGOR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence.	Foreword
9. The criteria for selecting the evidence are clearly described.	Foreword
10. The methods used for formulating the recommendations are clearly described.	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	Foreword
12. There is an explicit link between the recommendations and the supporting evidence.	3 and 5
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.	4
16. The different options for management of the condition are clearly presented.	4
17. Key recommendations are easily identifiable.	4
18. The guideline is supported with tools for application.	4
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed.	Foreword
20. The potential cost implications of applying the recommendations have been considered.	Foreword
21. The guideline presents key review criteria for monitoring and/audit purposes.	5
EDITORIAL INDEPENDENCE	
22. The guideline is editorially independent from the funding body.	Foreword
23. Conflicts of interest of guideline development members have been recorded.	Foreword

* 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.