# Guidelines on Autopsy Practice

## Autopsy in sickle cell disease and persons with sickle cell trait

**April 2017**

**Series authors:** Dr Michael Osborn, Imperial College Healthcare NHS Trust  
Professor Jim Lowe, Nottingham University Hospitals NHS Trust

**Specialist authors:** Professor Sebastian Lucas, Guy's & St Thomas' NHS Trust  
Dr Juliet Raine, Guy's & St Thomas' NHS Trust

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<td>The specialist content of this guideline has been produced by Professor Sebastian Lucas (Consultant Histopathologist at Guy’s and St Thomas’ NHS Foundation Trust and Emeritus Professor of Pathology at King’s College London School of Medicine) and Dr Juliet Raine (Specialty Trainee in Histopathology, Guy’s and St Thomas’ NHS Foundation Trust)</td>
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**Comments**

In accordance with the College’s pre-publication policy, this document was on The Royal College of Pathologists’ website for consultation from 22 February to 22 March 2017. Seventeen items of feedback were received and the document was amended as appropriate. Please email publishing@rcpath.org if you wish to see the responses and comments.

This document replaces earlier editions and is part of the Guidelines on autopsy practice series.

Dr Lorna Williamson  
Director of Publishing and Engagement

The Royal College of Pathologists  
4th Floor, 21 Prescot Street, London E1 8BB  
020 7451 6700  
www.rcpath.org

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

The autopsy guidelines published by The Royal College of Pathologists (RCPPath) are bench-top guidelines for pathologists to deal with non-forensic consent and Coroners' post-mortem examinations in a consistent manner and to a high standard. They may contain some distressing information and as such are not intended for the lay audience.

The guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. Given that much autopsy work is single observer and one-time only in reality, it has to be recognised that there is no reviewable standard that is mandated beyond that of the FRCPath Part 2 examination. Nevertheless, much of this can be reviewed against ante-mortem imaging and/or other data. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The medicolegal risk of departing from the guidelines should be assessed by the autopsy 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.

There is a general requirement from the General Medical Council to have continuing professional development (CPD) in all practice areas and this will naturally encompass autopsy practice. Those wishing to develop expertise or specialise in pathology are encouraged to seek appropriate educational opportunities and participate in the relevant External Quality Assurance (EQA) scheme.

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

The stakeholders consulted for this document were the:

- Sickle Cell Society, through their consultant clinician Dr David Rees
- Human Tissue Authority (HTA) and its Histopathology Working Group, which includes representatives from the Association of Anatomical Pathology Technology, Institute of Biomedical Science, The Coroners Society of England and Wales, the Home Office Forensic Science Regulation Unit and Forensic Pathology Unit and the British Medical Association.

The information used to develop this document was derived from practical experience, current medical literature and a previous version of this guideline. Much of the content of the document represents custom and practice, and is based on the substantial clinical experience of the authors. All evidence included in this guideline has been graded using modified SIGN guidance see Appendix A. As with much of autopsy practice, the evidence level for the majority of the material in this text is Grade D. Nonetheless, many of the clinicopathological scenarios that occur in sickle cell disease and persons with sickle trait have been investigated in Coroners' courts, along with clinical expert witness contributions, and several have gone to High Court litigation for resolution on causality. Thus the following guidelines represent current thinking and practice among the interested parties.

No major organisational changes or cost implications have been identified that would hinder the implementation of the guideline. However, as sepsis has to be considered in all sickle cell disease patients who die, there must be facilities in mortuaries to undertake routine blood cultures and organ cultures, and a pathway for the material to be analysed subsequently. If these are not available, then the case should be transferred to another more appropriate mortuary. As with other uncommon and potentially complicated autopsy scenarios, such as maternal deaths, it is preferable that all sickle cell disease autopsies are performed by pathologists with an interest and suitable expertise in such matters. This does not apply to sickle cell trait (unless it is thought to directly relate to the death), the gene being frequent in the general population and sickle trait-related complications being uncommon.
A formal revision cycle for all guidelines takes place on a five-year cycle. The College will ask the authors of the guideline to consider whether or not the guideline needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the College’s Clinical Effectiveness Department, Death Investigation Group, Lay Governance Group and Specialty Advisory Group. It was placed on the College website for consultation with the membership from 22 February to 22 March 2017. All comments received from the membership were addressed by the author to the satisfaction of the Director of Publishing and Engagement.

This guideline was developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request. The authors of this document have declared no conflicts of interest.

1 Introduction

The sickle gene is common in the UK population. Genotypically, there are three main types of sickle cell disease (SCD): the HbSS, HbSC & HbS-beta thalassaemia genotypes. HbSS is the most common. Currently, the birth rate for SCD is about 1 in 2000 births, with more than 15 000 patients living with SCD. Additionally, about 1% of all births have the HbAS genes, giving them sickle cell trait (SCT).\(^1,2,3\) Demographically, these people are concentrated in and around metropolitan areas such as London, Birmingham and Manchester.

This document was created to address the needs of the autopsy pathologist dealing with deaths in persons with the sickle cell diseases and sickle cell trait, and indicates a technical approach and investigations that should prevent criticism of case analysis in medicolegal environments. The limitations of local coronial practice and permissions are often unique to different cases and various parts of the UK, but this documentary guidance should be satisfactory for all cases. The document is designed to be a focused bench-top guide with step-by-step examination suggestions. It highlights matters for consideration and applies to both children and adults.

The levels of evidence reflect published case reports and series, and the small number of systematic analyses of sickle cell disease and sickle trait morbid anatomy. The importance of autopsy pathology in advancing our understanding of the pathogenesis of severe sickle cell disease cannot be overstated. All our pathological knowledge of the brain, lung, cardiovascular and splenic syndromes can only come from autopsy, as these organs are not biopsied in life, and in-life imaging is ambiguous.

1.1 Target users of this guideline

The target primary users of this guideline are consultant pathologists performing coronial and hospital/consented post-mortem examinations. The recommendations will also be of value to trainee pathologists, especially those considering Certificate of Higher Autopsy Training.

2 Role of the autopsy

- To determine the pathologies that led to death and the contribution of the SCD\(^1,2\) to death.
• Deaths in SCD occur in the community, in hospital after admission in crisis, in intensive care and peri-operatively.
• The gross autopsy findings are often minimal, and case evaluation requires careful macroscopic examination, almost always a range of histopathological samples, and usually microbiological cultures, to determine what took place.
• Where the sickle genotype has not been confirmed before death or autopsy findings suggest its presence, autopsy blood electrophoresis will determine the precise genotype.
• SCT (HbAS genotype) is common in the UK but is rarely a significant contributor to death. However, the possibility of SCT contributing to death is relatively often raised in forensic autopsies on persons with SCT, particularly when it is a death in state custody. The autopsy and histopathology can assist in this evaluation.

[Level of evidence: GPP.]

3 Pathology encountered at the autopsy

As with all systemic diseases, having the sickle gene or disease does not necessarily mean that death resulted because of that. The main causes of death and clinical pathologies in the three sickle cell disease genotypes include those listed below. Some entities may be grossly evident at autopsy, but most require histopathological analysis for identification.

The following pathologies have been broadly grouped into those that are common causes of death in sickle patients, common pathologies found in sickle patients and less common pathologies. This is based on our own experience and several case series. Needless to say, coincidental pathologies may be present and their relative importance must be evaluated when establishing the events that led to death.

Common causes of death:

• bacterial sepsis: pneumonia, meningitis, septic shock, osteomyelitis; pneumococcal, Haemophilus influenza and non-typhoid Salmonella infections
• acute chest syndrome (ACS) due to pulmonary arteriolar obstruction by sickled red cells and/or bone marrow embolism with thrombotic microangiopathy
• chronic pulmonary vascular arteriopathy, pulmonary artery hypertension and cor pulmonale
• cerebrovascular accident infarction, intracerebral haemorrhage and subarachnoid haemorrhage
• acute hepato-splenic sequestration
• acute and chronic renal failure due to glomerulosclerosis, pyelonephritis and papillary necrosis
• multi-organ failure following pan-body sickle crisis
• deep vein thrombosis and pulmonary thromboembolism
• dural venous sinus thrombosis and brain haemorrhage
• aplastic marrow crisis from parvovirus B19 infection (in children and less commonly in adults).

Common pathologies that are less often the direct cause of death:

• left ventricular hypertrophy
• bone marrow necrosis from painful bony sickle crisis.
Less common pathologies and scenarios:
- posterior reversible encephalopathy syndrome (PRES)\textsuperscript{17}
- ischaemic heart disease\textsuperscript{16}
- pregnancy-related ì with multi-organ failure and ACS, and sepsis
- hyperhaemolysis (post-transfusion) syndrome in adults\textsuperscript{16}
- multi-organ haemosiderosis ì related to therapeutic/prophylactic blood transfusions; this mainly affects heart, liver, kidney and pancreas
- biliary stone diseases: obstructive jaundice, cholecystitis and pancreatitis
- overdose of opiate pain-killers: morphine/heroin, pethidine (which also causes seizures), fentanyl patches\textsuperscript{19}
- gut ulceration and perforation from NSAID medication
- hydroxy Carbamide ì this drug is the only specific drug treatment for SCD; occasionally it damages the marrow causing pancytopenia and associated complications.

Patients with SCT (HbAS):
- death from acute cardio-respiratory arrest and ACS (type A ì see 9.3 below) is ~30 times more frequent than among persons with normal HbAA; this usually occurs after severe exertion with dehydration. Skeletal muscle rhabdomyolysis is often part of this syndrome.\textsuperscript{5,20} At autopsy, there is grossly little or nothing to see beyond congested lungs
- dehydration and rapid-onset hyperosmolar diabetes can also precipitate the ACS, type A\textsuperscript{21}
- dural venous sinus thrombosis is also associated with SCT and dehydration
- a very uncommon, genetically related, cancer association with sickle trait is medullary carcinoma of the kidney
- some persons labelled as sickle trait ì may actually have the HbSC genotype, not recognised because the laboratory tests were incomplete. If there is a mismatch between apparent sickle-related pathological features and the clinical history of trait, autopsy blood can be tested to evaluate the genotype formally.

[Level of evidence: D.]

4 Specific health and safety aspects

There are no specific health and safety aspects to consider. With current transfusion practice, HIV and hepatitis B and C are no longer inadvertently transmitted to sickle cell patients.

Sickle patients are at no more risk of HIV infection than the general ethnic population.

[Level of evidence: D.]

5 Clinical information relevant to the autopsy

- All the present relevant and past medical history details, particularly the clinical mode of death, recent operation records, drug and pain-relief therapy, current radiology.
• Laboratory results such as blood cultures, recent haematology data (haemoglobin, WBC, platelets, reticulocyte count, clotting studies) and relevant biochemistry, must be gathered, including the specific sickle genotype.
• Discussion with the sickle physicians is always helpful to understand the complex pathophysiological processes taking place.

[Level of evidence: D.]

6 The autopsy procedure

• In all cases, unless the results of recent pre-mortem blood cultures are available, take blood for culture (aerobic and anaerobic bottles) from the neck veins or heart, before any incisions are made into the body.
• Full autopsy according to standard practice, with examination of the brain, and vertebral bone marrow sampling.
• If a long bone sickle crisis has been diagnosed clinically, it may be useful to remove one femur and split it longitudinally. This enables examination of marrow hyperplasia and sampling of old and recent sites of bone infarction. It can be replaced with leg strut during reconstruction.
• Note whether there are skin ulcers on the legs.
• Photography: as in any other disease, significantly abnormal organs can be photographed to show clinical and pathology colleagues.

[Level of evidence: GPP.]

7 Specific organ systems to be considered

All organs are important: the most important in severe sickle cell morbidity and mortality are the lungs, liver and spleen, brain, heart, kidneys and bone marrow.

Specific attention is needed to the vascular and infective pathologies:
• lungs: pulmonary artery hypertension, thrombotic obstruction of arteries, thromboembolism, pneumonic inflammation, generalised congestion
• heart: the coronary arteries, left and right ventricular hypertrophy
• brain: the circle of Willis is a critical indicator of cerebro-vascular disease; new and old ischaemic strokes; intracerebral haemorrhage; subarachnoid haemorrhage; meningitis; dural venous sinus thrombosis
• liver: size, congestion, fibrosis, portal vein thrombosis
• spleen: the size (tiny remnant to massive sequestration enlargement); infarcts and fibrotic nodules
• kidneys: pyelonephritis, papillary necrosis, cortical necrosis
• bone marrow: old and new vertebral/long bone infarcts, extent of haemopoietic marrow (hyperplasia); osteomyelitis
• biliary system: bile stones, cholecystitis, pancreatitis
• pelvic and leg vein thrombosis, if there is pulmonary thromboembolism.

[Level of evidence: D.]
8 Organ retention

In general, whole organ retention is not required; the exception is the brain in cases of cerebro-vascular and haemorrhagic pathology.

[Level of evidence: GPP.]

9 Histological examination

Histological studies are essential to diagnose and to understand the pathogenesis of sickle-related death. Gross observation, and pathological guesswork only, will fail to provide the correct cause of death within the sickle cell complex of disorders; this will not satisfy the clinicians or help them with clinical governance issues, and will certainly not satisfy the relatives of the deceased.

9.1 Tissue sampling

The following represents best practice for all cases; this is the recommended minimum if histology is to be sent for expert review:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Recommended sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Five blocks from a mid-horizontal slice: anterior and posterior RV, and the four quadrants of the LV</td>
</tr>
<tr>
<td></td>
<td>Epicardial coronary arteries, if stenosed</td>
</tr>
<tr>
<td>Lungs</td>
<td>One sample per lobe and arterial emboli/thrombi, if present</td>
</tr>
<tr>
<td>Spleen</td>
<td>As per usual protocols</td>
</tr>
<tr>
<td>Liver</td>
<td>As per usual protocols</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Sample if it appears fibrosed/possible haemosiderosis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Include cortex, medulla, pyramid and calyx</td>
</tr>
<tr>
<td>Brain</td>
<td><strong>Circle of Willis</strong>: sample any aneurysm, if present. If not, and in all cases with cerebral or subarachnoid haemorrhage, dissect off the CoW, fix it entire, embed in a medium-large size block and cut step sections</td>
</tr>
<tr>
<td></td>
<td><strong>Brain</strong>: If there is cerebral haemorrhage, ischaemic stroke, meningitis or venous sinus thrombosis, sample as usual</td>
</tr>
<tr>
<td></td>
<td>If <strong>PRES</strong> was suspected in life, sample the occipital lobes</td>
</tr>
<tr>
<td>Bone</td>
<td>Lumbar vertebral bone in all cases</td>
</tr>
<tr>
<td></td>
<td>Femoral bone and marrow if it has been examined</td>
</tr>
<tr>
<td>Other</td>
<td>Deep vein thrombosis, if present, with the vein wall</td>
</tr>
<tr>
<td></td>
<td>Recent operation sites</td>
</tr>
<tr>
<td></td>
<td>Septic foci not already sampled (e.g. gall bladder)</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle if rhabdomyolysis is relevant, particularly in persons with SCT dying following exertion</td>
</tr>
</tbody>
</table>
Formalin fixation: ideally use buffered formalin, to reduce artefactual post-mortem sickling of red cells in sickle disease and persons with sickle trait. Thereafter, routine processing to paraffin is appropriate.

[Level of evidence: D.]

9.2 Bacteraemic sepsis

For the evaluation of bacteraemic sepsis, the following tissue samples and special stains are essential:22

<table>
<thead>
<tr>
<th>Tissue</th>
<th>IHC</th>
<th>Pathology seen in sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen, liver and bone marrow</td>
<td>CD68 IHC</td>
<td>Macrophage haemophagocytosis</td>
</tr>
<tr>
<td>Lung and heart</td>
<td>CD54 IHC</td>
<td>Up-regulation of endothelial cell intercellular adhesion molecule (ICAM-1)</td>
</tr>
<tr>
<td>Lung and kidney</td>
<td>CD61 IHC Fibrin</td>
<td>Staining of fibrin and platelets to demonstrate thrombotic microangiopathy (DIC)</td>
</tr>
<tr>
<td>Spleen and lymph nodes</td>
<td>CD68 IHC</td>
<td>Lymphoid atrophy; haemophagocytosis</td>
</tr>
</tbody>
</table>

[Level of evidence: GPP.]

9.3 Specific points on interpretation of histology

Lungs

- ACS has a clinical not pathological case definition,1,2,14 but histopathology can support or refute the diagnosis. The broadest depiction is: rapid development of respiratory signs and symptoms and a new infiltrate on chest X-ray. There are at least two pathogenetic and histopathological versions:23
  - type A: severe distension of arterioles, capillaries and venules by packed sickled red cells (i.e. a pan-lung sickle crisis); there may also be local infarction; if there is no distension by sickled red cells present, it is not the ACS
  - type B: embolism of necrotic bone marrow to small pulmonary arteries, prompting local thrombosis, intravascular sickling and acute cor pulmonale.
- Chronic sickle cell pulmonary arteriopathy is the cause of pulmonary artery hypertension and chronic cor pulmonale in SCD; it is a progressive intimal thickening of medium and small size pulmonary arteries; there may be associated episodes of local thrombosis contributing to the stenosis.24
- Pulmonary fat embolism is always present in persons who have cardiopulmonary resuscitation (CPR) before death.25 Distinguish this phenomenon from marrow tissue embolism which, in sickle cell disease, usually represents pre-mortem marrow necrosis.

Lumbar vertebral bone

- Note the cellularity of haematopoietic lines, haemophagocytosis, zones of infarction and viral inclusion bodies (B19 parvovirus).

Spleen22

- Gamna-Gandy nodules: these represent recurrent intrasplenic vascular crises with small infarctions and fibrosis. They are foci of fibrosis with iron and calcium deposition. They
accumulate over decades, resulting in the tiny (5 gm or less) non-functioning splenic remnant.

- Splenic sequestration: expansion of the red pulp, with aggregates of tightly packed sickled red cells.

Liver

- Hepatic sequestration manifests as severe congestion and expansion of the sinusoids, packed with sickle red cells.
- Haemphagocytosis by Kupffer cells.

Circle of Willis\textsuperscript{11,26}

- Chronic sickle cell arteriopathy is the major cause of stroke and haemorrhage; histologically it is a combination of non-atherosclerotic intimal thickening and fibrosis, and regions of artery wall degeneration with disintegration of the elastic.\textsuperscript{11}

[Level of evidence: D.]

10 Toxicology and other tests

- Toxicology screen in SCD patients (peripheral blood, urine, vitreous) is required in the usual circumstances of suspicion of illicit drug or alcohol-related death.
- A drug screen is essential for persons with sickle trait dying under exertion, where a positive drug test reduces the likelihood that SCT contributed to the death, but does not eliminate that possibility. Myoglobin can also be tested for in the urine.
- If opiates were administered during the final medical management, and there are questions over the dosage, measuring morphine is important.
- Note: fentanyl is not detected by routine screening for drugs of abuse; it must be specified (fentanyl patches are a commonly-used pain-killer in sickle cell patients).
- Mast cell tryptase levels are required only if there is suspicion of acute anaphylaxis.

[Level of evidence: D.]

11 Other samples required

- Bacterial infection: blood cultures in most cases (see above); focal sepsis cultures if grossly evident.
- Spun blood for serology, e.g. B19 virus infection.
- Whole blood if the red cell sickle status had not been evaluated pre-autopsy but is suspected clinically or morbid anatomically.

[Level of evidence: D.]

12 Imaging

Imaging-based post-mortem examination should never be undertaken without an expert external examination of the body having first been performed by an appropriately trained and experienced individual. In principle, all cadavers for autopsy should have been scanned during hospital admission or in the mortuary. However, the clinical pathology of sickle cell
disease mortality is subtle and there is no role for CT or MRI scanning as an alternative to formal autopsy examination.

[Level of evidence: D.]

13 Clinicopathological summary

- Determine whether sickle cell disease is the underlying factor in the cause of death sequence, played a contributory role or was irrelevant to the cause of death.
- Consider whether drug overdose caused fatal respiratory depression or seizures.
- Lay out the pathological sequence logically. The clinicians and relatives are going to study the autopsy report closely, as may the lawyers.
- In sickle trait deaths, consider whether a cardio-pulmonary collapse could have resulted from a sickle chest crisis under stress.
- Consult a more experienced pathologist to review the case and histology, if the pathology and cause of death are not clear.

[Level of evidence: GPP.]

14 Examples of cause of death opinions/statements

1a. Acute cardio-respiratory failure
1b. Acute chest syndrome following painful crisis
1c. Sickle cell disease

1a. Anaemia
1b. Hepato-splenic sequestration
1c. Sickle cell disease

1a. Severe sepsis
1b. Pneumococcal bacteraemia
1c. Sickle cell disease

1a. Cardiopulmonary failure/cor pulmonale
1b. Chronic sickle pulmonary arteriopathy
1c. Sickle cell disease

1a. Subarachnoid haemorrhage
1b. Chronic sickle cerebral vasculopathy
1c. Sickle cell disease

1a. Acute cardio-respiratory failure
1b. Exertion and sickle cell trait (HbAS)

15 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure a post mortem report for coronial autopsies conducted at an institution complies with the national recommendations provided by the 2006 NCEPOD study (www.ncepod.org.uk/2006Report/Downloads/Coronial%20Autopsy%20Report%202006.pdf).
• Supporting documentations:
  – standards: 95% of supporting documentation was available at the time of the autopsy
  – standards: 95% of autopsy reports documented are satisfactory, good or excellent.

• Reporting internal examination:
  – standards: 100% of the autopsy report must explain the description of internal appearance
  – standards: 100% of autopsy reports documented are satisfactory, good or excellent.

• Reporting external examination:
  – standards: 100% of the autopsy report must explain the description of external appearance
  – standards: 100% of autopsy reports documented are satisfactory, good or excellent.

A template for coronial autopsy audit can be found on The Royal College of Pathologists’ website (www.rcpath.org/profession/clinical-effectiveness/quality-improvement/clinical-audit-templates.html).

16 References

Note: there is relatively little published on the modern pathology of sickle cell disease. The following are useful clinical and pathogenetic reviews, with some autopsy case reports and series.

1 Howard J, Telfer P. Sickle Cell Disease in Clinical Practice. London: Springer-Verlag, 2015. (The best single-volume overview of sickle cell disease. Mainly clinical, but also includes pathology.)


**Appendix A  Summary table – Explanation of grades of evidence**
(modified from Palmer K et al. BMJ 2008;337:1832)

<table>
<thead>
<tr>
<th>Grade (level) of evidence</th>
<th>Nature of evidence</th>
</tr>
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<tbody>
<tr>
<td>Grade A</td>
<td>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type 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.</td>
</tr>
<tr>
<td>Grade B</td>
<td>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.</td>
</tr>
<tr>
<td>Grade C</td>
<td>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.</td>
</tr>
<tr>
<td>Grade D</td>
<td>Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.</td>
</tr>
<tr>
<td>Good practice point (GPP)</td>
<td>Recommended best practice based on the clinical experience of the authors of the writing group.</td>
</tr>
</tbody>
</table>
Appendix B    AGREE II compliance monitoring sheet

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

<table>
<thead>
<tr>
<th>AGREE II standard</th>
<th>Section of guideline</th>
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</thead>
<tbody>
<tr>
<td><strong>Scope and purpose</strong></td>
<td></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 health question(s) covered by the guideline is (are) specifically described</td>
<td>Foreword, 1</td>
</tr>
<tr>
<td>3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described</td>
<td>Foreword, 1</td>
</tr>
<tr>
<td><strong>Stakeholder involvement</strong></td>
<td></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 views and preferences of the target population (patients, public, etc.) have been sought</td>
<td>Foreword</td>
</tr>
<tr>
<td>6 The target users of the guideline are clearly defined</td>
<td>1</td>
</tr>
<tr>
<td><strong>Rigour of development</strong></td>
<td></td>
</tr>
<tr>
<td>7 Systematic methods were used to search for evidence</td>
<td>Foreword</td>
</tr>
<tr>
<td>8 The criteria for selecting the evidence are clearly described</td>
<td>Foreword</td>
</tr>
<tr>
<td>9 The strengths and limitations of the body of evidence are clearly described</td>
<td>Foreword</td>
</tr>
<tr>
<td>10 The methods for formulating the recommendations are clearly described</td>
<td>Foreword</td>
</tr>
<tr>
<td>11 The health benefits, side effects and risks have been considered in formulating the recommendations</td>
<td>n/a</td>
</tr>
<tr>
<td>12 There is an explicit link between the recommendations and the supporting evidence</td>
<td>Throughout</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><strong>Clarity of presentation</strong></td>
<td></td>
</tr>
<tr>
<td>15 The recommendations are specific and unambiguous</td>
<td>Throughout</td>
</tr>
<tr>
<td>16 The different options for management of the condition or health issue are clearly presented</td>
<td>Foreword</td>
</tr>
<tr>
<td>17 Key recommendations are easily identifiable</td>
<td>3i 14</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td></td>
</tr>
<tr>
<td>18 The guideline describes facilitators and barriers to its application</td>
<td>Foreword</td>
</tr>
<tr>
<td>19 The guideline provides advice and/or tools on how the recommendations can be put into practice</td>
<td>Foreword</td>
</tr>
<tr>
<td>20 The potential resource implications of applying the recommendations have been considered</td>
<td>Foreword</td>
</tr>
<tr>
<td>21 The guideline presents monitoring and/or auditing criteria</td>
<td>15</td>
</tr>
<tr>
<td><strong>Editorial independence</strong></td>
<td></td>
</tr>
<tr>
<td>22 The views of the funding body have not influenced the content of the guideline</td>
<td>Foreword</td>
</tr>
<tr>
<td>23 Competing interest of guideline development group members have been recorded and addressed</td>
<td>Foreword</td>
</tr>
</tbody>
</table>