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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of tumours of the central nervous system in adults, including the pituitary gland

March 2020

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Unique document number	G069
Document name	Dataset for histopathological reporting of tumours of the central nervous system, including the pituitary gland
Version number	5
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Date active	March 2020 **(to be implemented within 3 months)**
Date for full review	March 2023
Comments	This document will replace the 4th edition of *Dataset for tumours of the central nervous system, including the pituitary gland* published in January 2016. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 20 November to 18 December 2019. Responses and authors' comments are available to view on publication of the final document. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

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Registered charity in England and Wales, no. 261035

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NICE has accredited the process used by the Royal College of Pathologists to produce its cancer datasets. Accreditation is valid for five years from 25 July 2017. 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 published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices C and F–J) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders groups were contacted to consult on this document:

- British Neuropathological Society (www.bns.org.uk)
- Society of British Neurosurgeons (www.sbns.org.uk)
- British Neuro-Oncology Society (www.bnos.org.uk)
- International Brain Tumour Alliance (IBTA) (www.theibta.org).

Recommendations in this dataset are based on:

- factors used in clinical management as reported in the literature
- *WHO classification of tumours of the central nervous system*[1]
- *Brain tumours (primary) and brain metastases in adults* (NICE)[2]
- *Tumours of the central nervous system (CNS) reporting guide* (International Collaboration on Cancer Reporting [ICCR])[3,4]
- Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy – Not Official WHO (cIMPACT-NOW)[5-8]
- consensus and clinical practice guidelines on neuroendocrine and non-neuroendocrine tumours of the pituitary gland, including *WHO classification of tumours of the endocrine organs.*[9-12]

The level of evidence for the recommendations has been summarised (Appendix N). Unless otherwise stated, the level of evidence corresponds to 'Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group'. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix O.

Implementation of the dataset to its full extent may have some cost implications or require some local or regional organisational changes.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items 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 two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation with the membership from 20 November to 18 December 2019. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review (Cellular Pathology).

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors have declared that they have previously received payment for advisory work for commercial organisations involved in molecular testing and treatment of CNS tumours. They give their assurances that these conflicts of interest have not influenced the content of this dataset.

1 Introduction

Central nervous system (CNS) tumours have an estimated incidence of around 20/100,000 per year,[13] with approximately 10,000 new brain tumours diagnosed every year in the UK. Brain tumours represent 3% of all cancer cases and they cause morbidity and mortality that is disproportionate to the incidence.[14] Reported brain tumour incidence varies across different regions in the world, reflecting different methods of ascertainment, with 5.74 per 100,000 person-years in the USA, 6.95 in northern Europe and 2.55 in south-east Asia.[14] Brain metastases are seen in 2.0% of all patients with cancer and in 12.1% of those patients with metastatic disease. The estimated annual incidence of identified brain metastases in the US among patients with newly diagnosed cancer is approximately 23,000.[15]

Brain tumours form a large and heterogenous group of neoplasms affecting the brain and spinal cord and their coverings.[1] Intra-axial tumours, such as gliomas, arise from within the CNS parenchyma whilst extra-axial tumours such as meningiomas or schwannomas arise from coverings and adjacent structures. Pituitary tumours arise in close proximity to the brain and may impinge upon diencephalic structures and cranial nerves. Brain tumours also comprise metastases originating from tumours outside the CNS.

Brain tumours are best managed by referral to a specialist multidisciplinary centre with expertise in neuroimaging, neurosurgery, neuro-oncology and neuropathology. These centres should have access to molecular genetic diagnostic services. The pathological assessment of all CNS tumours should be dealt with by neuropathologists or histopathologists with expertise in neuropathology. This is recommended in the NICE guidelines *Improving outcomes for people with brain and other central nervous system tumours: Cancer service guideline [CSG10].*[16]

1.1 Purpose of these guidelines

These guidelines are intended to assist pathologists in the provision of the core data that should be included in histopathology reports from biopsy and resection specimens of CNS and related tumours in adults. Separate guidelines deal with non-neoplastic CNS lesions and with paediatric CNS tumours.

The guidelines are intended to assist pathologists in reporting CNS tumours and gather data to:

- allow accurate histological and molecular typing of CNS tumours according to a recognised, up-to-date system, which provides essential information for clinical management, including prognostication, risk stratification and treatment
- encourage consistency of reporting and terminology
- provide information for clinical audit
- potentially allow stratification of patients for clinical trials
- provide accurate data for cancer registration through organisations such as the National Cancer Registration and Analysis Service (NCRAS; www.ncin.org.uk/home).

1.2 Target users and health benefits of these guidelines

The target primary users of the dataset are histopathologists and neuropathologists at trainee and consultant level and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and NCRAS. Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists, and it facilitates international benchmarking and research.

1.3. Who reports CNS tumours?

CNS tumours are most commonly reported in specialist centres by neuropathologists. For the purposes of reporting CNS tumours, the NICE guidance on *Improving outcomes for people with brain and other CNS tumours* defines a neuropathologist as “an accredited pathologist who is registered as a neuropathologist or histopathologist, has specialist expertise in neuro-oncology, and takes part in the national External Quality Assurance (EQA) scheme for neuropathology organised by the British Neuropathological Society”. NICE guidelines also emphasise the central role of the MDT meeting in the management of CNS tumours.[16] Pathologists reporting CNS tumours should attend these meetings and participate in the relevant EQA scheme.

2 Clinical information required on the specimen request form

Clinical details, as provided by the submitting clinician on the request form, should be recorded on the pathology report. Relevant clinical history is essential to provide adequate interpretation of the histological findings.

In addition to essential demographic data, such as sex and age, which are part of the mandatory dataset, relevant clinical information may include location and focality of the tumour, neuroimaging findings and history, including previous relevant diagnoses, biopsies or therapies.

Location and focality of the tumour
Neuroradiological findings and neurosurgical intraoperative information provide important information helpful for the diagnostic interpretation of the histology. They can be essential for appropriate diagnostic work-up, for example the close association of histone H3.3 K27M mutations with midline gliomas, or the correct risk stratification of ependymomas. They can also signal potential discrepancies in the histological interpretation.

Neuroimaging findings
Certain imaging appearances in conjunction with the histological appearance of a low-grade, IDH-wildtype astrocytoma may prompt consideration and appropriate work-up to identify an infiltration zone or early stages of a high-grade glioma. Access to a picture archiving and communication system (PACS) during intraoperative diagnosis can provide additional essential information, including location, growth pattern and evidence of contrast enhancement.

History: previous relevant diagnoses, biopsies or therapies
Radiotherapy, radiosurgery or some forms of chemotherapy or immunotherapy may modify histological appearances. Knowledge of prior therapies is essential for a correct interpretation of histological findings and assignment of WHO grade. Preoperative embolisation of meningiomas may produce necrosis and increased proliferation, features that are used in tumour grading, and therefore could lead to an incorrect grade if this information is not known. Radiotherapy can change cytoarchitecture in recurrent gliomas and the long-term effects of radiotherapy include increased risk of cavernous haemangioma or meningioma development. Duration and nature of clinical symptoms can also point towards relevant differential diagnoses.

3 Preparation of specimens before dissection and frozen archiving

In many centres, specimens are received in standard fixative (usually 10% neutral buffered formalin). Specimens should be stored in an adequately sized specimen pot. Fixatives that may lead to a degradation of nucleic acids such as Bouin and Carnoy should not be used as they hinder downstream molecular studies.

Large samples may require up to 24 hours' fixation before dissection. Some very large or encapsulated specimens may benefit from incision or slicing prior to dissection to allow adequate penetration of fixative. However, overfixation impacts on subsequent molecular genetic tests and may also denature some antigens, in particular nuclear markers (e.g. transcription factors) or cell surface antigens (e.g. CD [cluster of differentiation markers), resulting in potential difficulties in detecting these markers with diagnostic antibodies.

There are advantages to specimens being received in a fresh state (see points below in this section). This requires good communication between the operating theatre and laboratory to ensure that the fresh specimen is delivered to the laboratory and dealt with promptly.

Submission of a fresh specimen is necessary in cases for which intraoperative diagnosis is requested (see section 10). Residual tissue from the intraoperative assessment should be fixed in formalin for subsequent conventional paraffin histology, and frozen archiving of a proportion should be considered (see below).

When possible, frozen material should be archived routinely and the availability of frozen tissue recorded, as it will allow future molecular genetic studies for diagnostic or research/clinical trials purposes. As there is an increasing drive from NHS England to offer whole genome sequencing (WGS), the routine archiving of frozen tissue should become standard of care. (WGS is already offered as a diagnostic test to paediatric and soft tissue tumours from 2020 onwards.)

Importantly, the archiving of frozen diagnostic material does not require additional ethical approval. The use of frozen tissue for research and clinical trials is subject to appropriate ethical, clinical and research governance frameworks.

Frozen tissue is required for some types of molecular genetic analysis (in particular WGS) in clinical trials. Following the successful conclusion of the Genomics England (GeL) 100,000 genomes project, WGS has been commissioned for some CNS tumours, e.g. paediatric neoplasms. One of the missions of GEL and its follow-up initiatives is to improve cancer care for NHS patients. It aims to return WGS results to people in time to help with their care.[17]

Biobanking is recommended in the recent *Criteria for the Definition of Pituitary Tumour Centers of Excellence* published by the Pituitary Society.[18] In addition to local research initiatives, this will become increasingly important as national initiatives for adult and paediatric brain tumours continue to develop (e.g. Children's Cancer and Leukaemia Group, National Cancer Research Institute). Systematic frozen CNS tumour tissue banking can also be an important contributor to national resources, for example through BRAIN UK, a national virtual neuropathology brain bank (www.southampton.ac.uk/brainuk/index.page).

For molecular analysis, the specimen should be received fresh so that tumour (and sometimes non-tumour) tissue can be frozen for WGS. Formalin-fixed paraffin-embedded (FFPE) tissue is usually adequate for many other molecular tests, such as fluorescent in situ hybridisation, sequencing, MGMT promoter methylation, copy number assays, DNA methylation arrays and even RNA sequencing.

To ensure long-term stability, the tissue should be snap frozen and stored at a temperature of –70°C or below. Nitrogen storage (liquid phase at –196°C or vapour phase at –140 to –180°C) can be considered as an alternative.

In cases where it is suspected that ultrastructural examination of the specimen is likely to be required, a small sample of the tumour should be placed in glutaraldehyde. However, this is of decreasing relevance as molecular profiling, both for viral pathogens and neoplastic lesions, can provide more informative results.

Bony and heavily calcified specimens may need to be placed in a decalcifying solution following fixation prior to dissection. An attempt should be made to remove some softer tissue pieces for histology prior to decalcification, in particular bearing in mind that the acid used for decalcification depurinates DNA and makes it unsuitable for molecular tests. For optimal tissue decalcification procedures, please refer to the RCPath's *Tissue pathways for bone and soft tissue pathology* guideline.[19]

4 Specimen handling and block selection

4.1. General comments

There is a limited evidence base for the macroscopic handling of specimens from CNS tumours, although there are some published guidelines.[20, 21] The specimen should be measured in three dimensions and/or weighed. In many cases, CNS tumour specimens will be in the form of multiple fragments and in these instances an aggregate measurement should be taken. In particular, collections of surgical aspirate may be difficult to assess in three dimensions and weighing may give an additional useful quantitative value.

The specimen should be described fully, including the following features: recognisable anatomical structures; colour, consistency and dimensions/weight of the tumour; and macroscopically visible presence of calcification, necrosis, haemorrhage or cystic change. A template recording should be attempted to standardise recording of macroscopic features and measurements (appendices C and F).

4.2 Biopsies

Stereotactic biopsies should be embedded in their entirety for processing into a paraffin block (see further information below in section 4.6). Larger biopsies are usually completely embedded in paraffin. Local arrangements should be made to receive fresh tissue for frozen archiving of a proportion of the sample. Levels (step sections through the paraffin block) may be considered if the initial section is non-informative, and it is best practice to retain all unstained serial sections between the levels for immunohistochemistry (IHC) and/or molecular analysis.

Surgical ultrasonic aspirates (e.g. Cavitron Ultrasonic Surgical Aspirator [CUSA]) may provide additional diagnostically important information,[22] and may be particularly useful if the biopsy is otherwise small. If available, the aspirate should be embedded for histology, processed to a cytology preparation or frozen, depending on its consistency and the clinical context. Even where cytology and architecture are poorly preserved in aspirated material, it may be suitable for IHC and if the sample contains predominantly viable tumour it is potentially very useful for molecular genetic tests.

4.3 Intra-axial tumour resections, including lobectomy specimens

Resection specimens may be received as anatomically intact lobectomy specimens or fragmented specimens removed piecemeal. For diffuse gliomas, complete resection is, with only rare exceptions, precluded because of their infiltrative nature, and a resection is therefore subtotal.

When possible, the specimen should be orientated and any anatomical structures identified. Lobectomy specimens may be sliced at approximately 5 mm intervals, generally perpendicular to the long axis of the specimen and through the pial surface.[23]

The tumour should be described with particular attention to foci of macroscopically visible necrosis, which may be of prognostic significance. Gross extension of tumour into leptomeninges or to resection margins should be noted.

In a number of studies, including the NICE guidelines,[2] the extent of resection has been shown to be a prognostic factor.[2, 24-27] Neuroradiological assessment from postoperative imaging/computer-assisted volumetric studies is a much better measure of this than pathological measures. Nevertheless, pathological assessment of tumour volume removed provides some indication of the extent of excision and so an approximate measurement of tumour size in three dimensions should be given.

Photography may be helpful in selected cases to confirm the orientation of the specimen with the neurosurgeon, assess resection margins histologically and to demonstrate the tumour extent at MDT meetings.

While it may be good practice to describe tumour extent and distance from the edge of the specimen when possible, assessment of margins by pathology is not of prognostic/diagnostic relevance for CNS tumours, and assessment of extent of resection is generally by postoperative neuroimaging. In lobectomy specimens, assessment of margins may be possible. However, for diffuse gliomas (both low and high grade), because of their infiltrative nature and often piecemeal resection, histological evaluation of resection margins is not meaningful. Furthermore, the margin of the lobectomy may not be a true margin because of additional ultrasonic aspiration (CUSA) of the tumour bed after lobectomy. Resection margins therefore do not require formal assessment in CNS tumour diagnostics.[21]

Although evidence-based guidelines are not available, it would seem reasonable to conclude that the presence of heterogeneity within tumours requires that multiple blocks should be taken to allow for adequate sampling. The entire specimen should be blocked out on serial faces,

unless the tissue is very large, in which case enough blocks must be taken to avoid a sampling error. Evidence-based guidelines for the number of blocks to be taken are not available.

Similar principles of thorough sampling apply to piecemeal resections. Embedding of surgical aspirates helps to reduce sampling bias and can change WHO grading.[22] Furthermore, owing to the nature of this material, it can contain a variety of tissues, including normal or infiltrated CNS, and thus can generate valuable tissue for future studies, including control sections for antibody tests.

In some cases, gliomas may involve multiple lobes or may be multifocal, and this information from neuroimaging and the request form should be recorded. If two samples from separate sites are submitted, histology blocks should be made from both to allow a separate histological assessment of these areas and ensure that the area of highest histological grade is represented.

4.4 Extra-axial tumours

The most common tumour at this site is meningioma followed by schwannoma, but a range of other tumours may occur. As for intra-axial tumours, specimens are often resected piecemeal, making assessment of anatomical extent and margins difficult. The approach to specimen handling and block selection will need to be modified according to the limits imposed by the specimen type. The following paragraphs focus on meningioma, but similar issues related to infiltration of local structures apply to other extra-axial tumours.

The tumour should be orientated and measured together with the distance to the nearest radial dural resection margin. The tumour should be sampled generously; although there is no strict evidence base for sampling, many neuropathologists use one block per centimetre diameter of tumour and this seems a reasonable, pragmatic approach to ensure that any higher grade areas are not missed.

Blocks for histology should include tumour, including from the brain interface (generally the smooth surface), dura and radial margin. In the case of meningiomas, the cortical interface should be sampled as brain invasion, defined as a breach of the pial barrier, which is a critical prognostic factor affecting WHO grade.[28] It is considered unnecessary to mark the surface of tumours with ink.

If bone and other samples from adjacent anatomical structures accompany the specimen, these should be separately described and sampled (decalcification may be required). It is helpful to orientate and ink the margins of any infiltrated bone. In the case of meningiomas, infiltration through the dura, into skull and into extra-cranial tissues occurs with tumours of all histological grades. Thus, even a WHO grade I tumour may show this type of infiltrative behaviour. It is not considered to be a prognostic factor in the WHO grading scheme; however, particularly in the skull base, infiltration may make surgical resection more difficult and affect recurrence. Therefore, invasion of extra-dural structures should be included in the report when this can be assessed.

Sampling of frozen tissue for molecular genetics should always be considered. It may aid classification in difficult cases. Even though advanced molecular diagnostics can be carried out on FFPE material (exome sequencing, RNA sequencing, panel sequencing, or methylation arrays), some tests (e.g. WGS) may require frozen material. Frozen material can be stored as part of the diagnostic tissue archive (also see section 3).

Resection margins are often difficult to assess in specimens of extra-axial tumours and it is usually not possible to comment on the completeness of surgical resection using histological methods. Rather, this is assessed using radiological methods. This is therefore not included as a core data item, but under some circumstances it may be possible to comment on margins;

a comment on a specific margin may be requested by the surgeon. Sampling of margins should therefore be carried out where this is possible.

4.5 Neuroendocrine and non-neuroendocrine pituitary tumours

In most cases, these specimens are small. The tissue, including CUSA specimens, should be blocked for histology, sparing a fragment for biobanking when the tissue is submitted fresh. Electron microscopy is now less likely to be required for diagnosis and can be performed if necessary from FFPE. For pituitary tumours, invasion of surrounding structures (i.e. dura mater, sphenoid sinus, bone and cavernous sinuses) may be associated with a higher risk of tumour recurrence and should be commented upon whenever possible, although it is recognised that the dura mater and other surrounding structures are not always submitted for histological examination.[29, 30]

If specimens are submitted from areas suspected of being infiltrated, these should be blocked separately to allow comment on infiltration and correlation with neuroimaging features and help guide postoperative treatment.

4.6 Section staining

Haematoxylin and eosin (H&E)-stained sections remain the gold standard for the initial assessment of histological material. Following the identification of a presumed or definite neoplasm of the CNS or its coverings, the diagnostic process will depend on the histological type, location and size of the neoplasm.

The classification and prognostication of many intrinsic tumours requires immunohistochemical staining, for example to detect mutations (using mutation-specific antibodies, e.g. IDH1 R132H,[31] Histone H3.3 K27M[32] or BRAF V600E[33]), a loss of expression (e.g. INI1,[34] ATRX,[35] Histone K27me3[36]) or pathological translocation of a protein (nuclear expression of STAT6[37, 38] or p65 RELA[39]).

For neuroendocrine tumours of the pituitary gland, the immunopanel should cover anterior pituitary hormones and, where necessary, pituitary transcription factors and pan-cytokeratin. For non-endocrine pituitary tumours, the immunopanel should include TTF1 and, depending on histology, additional epithelial, neuronal and glial markers. Immunostaining for Ki67 allows the proliferation fraction to be estimated in both neuroendocrine and non-endocrine tumours. Immunostains for SMARCB1 (INI1, BAF47), SMARC A4 (BRG1) and brachyury are recommended for poorly differentiated lesions. For the use of level sections, see section 9.

5 Core data items

5.1 Summary of core data items

The dataset for brain tumours is based on recommendations made by the ICCR's *Tumours of the central nervous system (CNS) – Histological assessment reporting guide*, published in 2018.[3] Proforma reporting will assist in future data collection strategies, but it is also important to retain free text comment. The collection of itemised data is mandated as part of the COSD version 8. Appendix D provides a list of core and non-core items as specified in the ICCR guidelines and the COSD dataset. The COSD dataset was created to provide a comprehensive dataset for all histopathology subdisciplines while the 2018 edition of the ICCR guidelines was tailored specifically for tumours of the CNS.

Separate proformas are provided for:

- intra-axial CNS tumours (Appendices C and D)
- extra-axial CNS tumours (Appendix F)
- pituitary tumours (Appendix G).

5.2 Clinical and radiological core items

Core items include:

- site of lesion
- tumour laterality
- focality
- tumour dimensions
- operative procedure.

5.3 Macroscopic core data items

Core items include:

- specimen dimensions (mm x mm x mm)
- estimated tumour dimensions or weight (g).

5.4 Pathological core items

Core items include:

- specimen description
- histological appearance
- WHO 2016 tumour grade

  [Level of evidence A–D – Tumour type, subtype and WHO grade are important prognostic indicators. The evidence level varies from A to D depending on the tumour type. The WHO grading of astrocytomas has been reproduced in multiple large studies, while for other entities, definitions are based on case reports or small series.]

- integrated diagnosis

  [Level of evidence A–D – Molecular characteristics are important diagnostic and prognostic indicators. The evidence level varies from A to D depending on the tumour type. The relevance of histone or IDH mutations as diagnostic and prognostic factors has been reproduced in many large studies (level A), while other, rare entities require larger cohorts to reach levels A or B.]

- presence of brain invasion for extra-axial tumours (particularly meningiomas).

  [Level of evidence B – The presence of brain invasion is an adverse prognostic indicator for extra-axial tumours. The stated evidence level relates to meningiomas. For other tumour types, there is less evidence available owing to smaller cohorts.]

5.5 SNOMED codes

- SNOMED T and M codes.

6 Histological classification and novel molecular approaches

Primary tumours of the nervous system are classified and graded according to the WHO grading scheme – currently the 2016 update of the WHO classification for CNS tumours.[1] This scheme is used in all neuropathology centres in the UK and its use is endorsed by the British Neuropathology Society and its national EQA scheme (NEQAS). The WHO scheme is also widely used internationally, allowing comparison of data from European and North American centres. This provides a uniform system of nomenclature, essential for comparative studies and multicentre trials.

The present update has moved on from a long tradition of classification and grading of tumours solely based on the concept of histogenesis, i.e. a classification according to the microscopic similarities with putative cells of origin and their developmental differentiation states.[40, 41] Instead, the 2016 WHO classification incorporates well-established molecular parameters into the classification of a number of brain tumours. It is recognised that changing the classification to include diagnostic categories that depend on genotype may create certain challenges with respect to accessibility to such testing (e.g. mutation-specific antibodies, surrogate immunostains, gene sequencing and copy number assays) and, consequently, reporting. Nevertheless, the advanced immunohistochemical work-up complemented by molecular analysis (DNA or RNA based) of brain tumours now has a firm place in the diagnostic work-up of many intrinsic tumours.[42, 43]

A fundamentally different approach to CNS tumour classification is the determination of methylation classes of brain tumours. This has been established by a number of international centres, using methylation arrays that determine the methylation status of selected CpG sites, followed by a computer-based algorithmic classification.[44] This classification is based on patterns of methylation of tumour DNA caused by a combination of factors, such as the cell of origin and a mutation or pattern of mutations, rather than identifying the mutations themselves. This approach can help in diagnosing neoplasms that are histologically indistinct and may have an inconclusive molecular test.

The use of IHC and molecular genetic techniques should always be subject to appropriate internal and external quality controls. This should involve the use of appropriate controls for all techniques and the laboratory should be accredited and a participant in the appropriate UK NEQAS schemes.

6.1 Adopting the concept of integrated diagnosis

Originally, the WHO classification was devised as a malignancy scale covering a wide variety of intracranial neoplasms in the context of no, or limited, effective therapy. This grading scheme formed the cornerstone of the WHO grading.

For some tumour entities, the relevance of this grading scheme has been gradually eroded by the advancements in understanding of tumour pathogenesis, which led to the discovery of prognostically relevant markers. For example, the IDH-wildtype astrocytoma, which histologically corresponds to WHO grade II or III, may in fact reflect either incompletely sampled, or early manifestation of, IDH-wildtype glioblastoma.[45] Likewise, midline gliomas correspond to WHO grade IV when a histone K27M mutation is present, even in the absence of histological high-grade features.[1] Recently, the relevance of certain histopathological features in IDH-mutant astrocytomas has been challenged in that, for example, microvascular proliferations have much less significance than a *CDKN2A/B* homozygous deletion.[46] The IHC test for histone K27me3 in ependymomas of the posterior fossa[36] and the detection of RELA

fusion (or surrogate IHC markers L1CAM and p65)[39] in supratentorial ependymomas has much greater prognostic value than the identification of mitotic figures or assessment of cellularity.[47] To aid the diagnostic process and provide an algorithm for diagnosing adult brain tumours, the most commonly encountered brain tumour classes are discussed below and in Appendices K and L.

6.2 Molecular biomarkers

The molecular genetic and epigenetic analysis of brain tumours has made considerable progress towards improved understanding of the pathogenesis of brain tumours and contributes to evidence-based and homogeneous classification of brain tumours. An increasing number of molecular markers continue to be discovered. It is not the purpose of these guidelines to review these comprehensively, but to summarise and provide guidance for the use and integration of clinical parameters (age, location) with the histology and molecular tests.

While the primary histological classification should be based on the histological findings, it is important to recognise early during the diagnostic process the most appropriate choice for molecular tests (either IHC based or nucleic acid based) and to integrate this in the preliminary report with subsequent integration of the molecular test results in the final diagnostic report. It is, therefore, likely that in some instances (and in particular for diffuse gliomas) there will be several iterations of reports, to reflect additional evidence gained through subsequent and increasingly advanced molecular methodologies. It is essential that in such cases the planned diagnostic work-up is discussed in the preliminary reports and with the oncology MDT to manage expectations and guide treatment decisions.

6.3 Application of molecular markers in adult diffuse gliomas

6.3.1 IDH-mutant gliomas

Oligodendrogliomas
Oligodendrogliomas are defined by the combined presence of an *IDH1* or *IDH2* mutation and a codeletion of the chromosomal arms 1p and 19q. The presence of an *IDH* mutation is mandatory to diagnose oligodendroglioma. The use of antibodies against the ATRX protein is useful in the initial decision-making process, in particular in gliomas with astrocytic and oligodendroglial features on H&E-stained sections. All IDH-mutant and 1p/19q codeleted oligodendrogliomas retain nuclear *ATRX* expression. An additional useful marker that can help identify oligodendroglioma in cases where the 1p/19q test is ambiguous is the *TERT* promoter mutation,[48] which is nearly always mutually exclusive with ATRX loss. The loss of the histone H3 trimethylation at position K27 has been identified as a further useful surrogate marker for 1p/19q codeletion. It is lost in a large proportion of 1p/19q codeleted oligodendrogliomas. Therefore, IDH-mutant gliomas with retained ATRX expression and a robust loss of H3 K27me3 can be discriminated from IDH-mutant astrocytomas, which usually retain K27me3 expression (see below), early during the diagnostic process by immunohistochemical stains.[49]

Astrocytomas
Astrocytomas are defined by an *IDH* mutation that is usually combined with a loss of nuclear *ATRX* expression. However, a small proportion of IDH-mutant astrocytomas have silent *ATRX* mutations with retained *ATRX* expression.[48] These tumours require further testing for 1p/19q to exclude an oligodendroglial tumour. Concomitant testing for a *TERT* promoter mutation, present in nearly all oligodendrogliomas,[50] may help to further clarify the molecular profile. An improved classification scheme for IDH-mutant astrocytomas has been proposed that allows much better prognostication of these tumours by a combination of histological features and molecular profiles. According to this study,[46] IDH-mutant astrocytomas with histological low-grade features, no copy number variation and absence of *CDKN2A/B* homozygous deletion have the best prognosis. Tumours with absence of *CDKN2A/B* deletion but high copy number variation and/or presence of necrosis (irrespective of other histological features of malignancy)

have an intermediate prognosis, and IDH-mutant astrocytomas with a *CDKN2A/B* homozygous deletion, regardless of the presence of necrosis, have the worst prognosis. According to this study, microvascular proliferation has no significant prognostic value. A diagram summarising these findings has been published elsewhere.[50]

6.3.2 IDH-wildtype astrocytomas and glioblastomas

It is important that pathologists convey information about IDH-wildtype gliomas clearly and consistently to clinical teams. IDH-wildtype glioma encompass low-grade gliomas but can also represent an under-sampled or a precursor of IDH-wildtype glioblastoma (glioblastoma multiforme [GBM]). All IDH-wildtype gliomas require adequate histological and/or molecular work-up to differentiate between these biologically distinct entities.

A large study demonstrated that IDH-wildtype astrocytomas often represent either incompletely sampled, or early stages of, glioblastoma.[45] A common molecular feature of IDH-wildtype GBM (and its precursor forms) is gains in chromosome 7 and losses of chromosome 10.[51] Up to 50% of IDH-wildtype GBM have *EGFR* amplifications, which are exceedingly rare in IDH-mutant astrocytomas or other brain tumours.[51, 52] Therefore, *EGFR* amplification is a useful diagnostic marker, in particular in small, non-representative biopsies or early manifestations of *IDH*-wildtype GBM. Likewise, the *TERT* promoter mutations, while seen in many other tumour entities, can be diagnostically useful when found in combination with *EGFR* amplifications in tumours with astrocytic morphology (a *TERT* promoter mutation occurs in approximately 50% of *EGFR* amplified GBM and in 50% of *EGFR* non-amplified GBM). Centres with access to robust copy number profiling techniques may consider testing for chromosome 7 gains and chromosome 10 losses, in particular in young patients with radiologically diffusely infiltrative gliomas, in which no *IDH* or histone mutations are found.[51]

6.3.3 Midline gliomas

A breakthrough in the understanding of the biology of midline tumours was the identification of histone H3 K27M mutations.[53] This quickly led to the adoption of H3 K27M-mutant diffuse midline glioma as an entity in its own right in the WHO 2016 classification. It corresponds to WHO grade IV irrespective of histological appearances. Even though the stereotypical assignment of a WHO grade IV for these tumours has been challenged by some centres with large case numbers of pontine gliomas,[32] it has provided pathologists with an opportunity to achieve a robust, consistent and reproducible diagnosis with a single, straightforward immunostain using a mutation-specific H3 K27M antibody. The use of mutation-specific antibodies in neuropathology services is affordable and reveals a larger than anticipated number of histone mutant tumours.[52] Any tumour located in, or close to, the midline (spinal cord, brainstem, cerebellum and thalamus) should undergo this robust and affordable IHC test. While the H3 K27M mutation most commonly occurs in the H3F3A gene encoding for the H3.3 histone variant, the K27M mutation does rarely occur in other histone H3.1 and H3.2 variant encoding genes, such as *HIST1H3B*, *HIST1H3C* and *HIST2H3A*. Testing for these mutations is possible by sequencing. Varied frequency of ATRX loss of expression has been reported for H3 K27M tumours, and it has been suggested that ATRX loss in these tumours increases with age.[53] Several paediatric series reported ATRX loss in 10–25% of H3.3 mutant tumours,[32, 53, 54] while ATRX loss was shown in more than 40% of H3 K27M mutant gliomas in an adult series.[52]

6.3.4 Gliomas with *BRAF* mutations and other MAP kinase pathway activation

The family of brain tumours with MAP kinase activation is diverse. Frequently, MAP kinase activation is caused by alterations in the *BRAF* gene, such as point mutations (most commonly V600E) or various fusion mutations. The *BRAF* V600E point mutation is a feature of pleomorphic xanthoastrocytomas, gangliogliomas, a small proportion of pilocytic astrocytomas and a small proportion of IDH-wildtype glioblastomas (including some with epithelioid morphology), indicating that *BRAF* V600E-mutant tumours represent a spectrum of morphologies and malignancies. The assessment of gene mutations in the MAP kinase pathway, in particular the *BRAF* V600E mutation, is important since these mutations represent therapeutic targets.[55] These mutations are detectable with a mutation-specific antibody[33] (but

the robustness of this immunostaining in brain tumours has been debated) and Sanger sequencing.

6.3.5 Ependymomas

There is now strong evidence that the outcome of a consensus treatment decision for ependymoma should not be based on histological grading according to WHO.[56] A number of independently conducted genomic profiling efforts have identified clinically and molecularly distinct subgroups of ependymoma arising from the spinal, posterior fossa and supratentorial CNS compartments.[56, 57] It has been recommended that molecular subgrouping of ependymomas should be part of all clinical trials. Distinct genetic alterations in supratentorial ependymomas include either *RELA* or *YAP* fusions. p65 immunostaining is a useful surrogate marker for identifying *RELA*-fused ependymomas.[39] Infratentorial ependymomas of molecular subtypes A and B can be discriminated with immunostaining for (trimethylated) histone H3 K27me3.[36] Spinal ependymomas usually do not require further molecular work-up, as their outcome is influenced by the extent of the surgery rather than histology. The clinically favourable subependymomas occur in all three compartments. Methylation arrays have been successfully used to determine the molecular subgroups of ependymal tumours[58] and a useful example of a diagnostic decision-making algorithm for ependymomas has been published.[52] Appendix L shows a proposed algorithm for diagnosis of ependymomas.

6.3.6 Other intrinsic tumours with low-grade histology

Many low-grade glial and glioneuronal tumours have distinctive histological features (such as ganglioglioma, dysembryoplastic neuroepithelial tumour and papillary glioneuronal tumour), as well as rarer composite/mixed tumours of different entities (e.g. ganglioglioma plus pilocytic astrocytoma).[59] There are also forms with indistinct, diagnostically uninformative histological features or diffuse growth patterns (*IDH*-wildtype or histone-wildtype), which may harbour *MYB, MYBL1, FGFR1 or BRAF* V600E alterations and overlap with 'paediatric-type' diffuse gliomas. They are considered equivalent to WHO grade I or II.[8] In adults, tumours in this group often present in the setting of long-term (>2 years) focal epilepsy.[60] Owing to the wide differential diagnostic spectrum, these tumours particularly benefit from a diagnostic approach using methylation array technology supplemented by further genetic testing as needed.[59] Molecular characterisation of these tumours is also important to identify high-grade intrinsic tumours (i.e. IDH-wildtype glioblastoma) presenting with low-grade histology.[52] It can also detect unexpected entities,[61] including those that may respond to targeted treatment.[62] Appendix K shows a proposed algorithm for diagnosis of low-grade gliomas.

6.3.7 Other intrinsic tumours with high-grade histology

A proportion of high-grade intrinsic tumours present with poorly differentiated histological features. Although the majority, in particular in the elderly population, represent IDH-wildtype glioblastoma, there is now recognition of a much wider range of high-grade neoplasms. Seminal work originating from the analysis of childhood tumours, previously summarised as primitive neuroectodermal tumours, has identified a wide variety of tumours,[63] of which most are now molecularly defined.[64] Medulloblastomas occur predominantly in children but 'tail off' in the adult population, and adequate profiling can help classify them into molecular subgroups.[65] In children, clinical trials, based on molecular subgrouping, have been published;[66] however, the benefit of enrolling adults with medulloblastoma into such clinical trials has yet to be established.

6.4 Application of molecular markers in adult extrinsic tumours

Meningiomas account for approximately a third of all intracranial and spinal neoplasms, and 80% of meningioma patients can be cured by surgery alone. Some of the WHO grading criteria are prone to intraobserver bias.[28, 67, 68] A number of attempts have been made to better prognosticate the recurrence risk of meningiomas. Mutations in the *TERT* promoter[69] and loss of histone H3 K27me3[70] have been identified as risk factors for accelerated tumour progression and increased risk of recurrence. Recently, a classification tool based on methylation array data identified six molecular subclasses, including meningiomas, which are at a higher risk of

recurrence. Importantly, these methylation subclasses do not entirely overlap with the WHO grade.[71] Clinical trials have yet to establish the utility of these advanced molecular tests for routine diagnostics of meningiomas.[71]

Haemangiopericytomas/solitary fibrous tumours (HPC/SFT) were notoriously difficult to diagnose with certainty, and the lack of robust and discriminatory biomarkers contributed to inter- and intra-observer variability. The discovery of the *STAT6-NAB1* fusion gene product has now practically eliminated these challenges and firmly established the utility of immunostaining for STAT6 protein (specifically its translocation to nucleus in HPC/SFT) in identifying HPC/SFT.[37] Histological grading of HPC/SFT is according to criteria set out in WHO.

6.5 Diagnostic aspects of neuroendocrine and non-neuroendocrine pituitary tumours

The 4th edition of the *WHO Classification of Tumours of Endocrine Organs,*[12] published in 2017, has recommended the adoption of primary adenohypophyseal cell lineages rather than type of hormone produced as a basis for tumour classification. Subtyping according to hormone expression is also encouraged as it may have value in predicting the response to treatment. The concepts of 'null cell adenoma' and 'silent type 3 adenoma' have been redefined and the term 'atypical adenoma' removed. Instead, tumours with uncertain malignant potential are now described as 'high-risk' adenomas. This change has caused considerable controversy that has partially been resolved in the European Association of Endocrinology consensus guidelines for aggressive pituitary tumours.[9] Mitotic count, quantification of MIB-1 (Ki67) and the description of invasion have been recommended in the identification of potentially aggressive tumours. The statement that certain histotypes, such as silent corticotroph and Crooke's cell adenomas, are associated with worse outcomes is not supported by sufficient evidence to be introduced in clinical practice. The definition of plurihormonal adenomas also remains vague as no clear cut-off for each population has been suggested.[72]

More emphasis has been given to the identification of molecular alterations (e.g. *USP8* mutations in Cushing disease) and to adenomas occurring in genetically defined syndromes.

New entities such as pituitary blastoma and sellar ependymoma have been added to the most recent WHO classification. Tumours from the posterior gland (spindle cell oncocytoma, pituicytoma and granular cell tumour) have been unified as TTF1-positive tumours. For spindle cell oncocytoma and granular cell tumour, the terms 'oncocytic pituicytoma' and 'granular cell pituicytoma' have been proposed.[73]

The current WHO classification comprises differentiated neoplasms classified as (pituitary) adenomas or well-differentiated (pituitary) carcinomas based on the presence of distant metastasis. They are subclassified depending on hormone production. A recent consensus of the International Pituitary Pathology Club[11] has proposed that the term pituitary neuroendocrine tumour (PitNET) replace adenoma, since PitNET better reflects the biology of primary adenohypophyseal neuroendocrine tumours and conforms with the classification of neuroendocrine tumours from other sites of the body. See Appendix G for a reporting proforma. A diagnostic scheme of neuroendocrine pituitary tumours is in Appendices M. According to the recommendations of the European Society of Endocrinology, the case must be discussed at the MDT meeting.[9]

The diagnosis of tumours of the posterior lobe requires the expression of TTF1. GFAP, EMA and S100 protein help differentiated spindle cell oncocytoma (EMA+ membranous, S100+, GFAP-), pituicytoma (EMA-, S100+, GFAP+), granular cell tumour (EMA-, S100+, GFAP-) and sellar ependymoma (EMA+ mostly dot-like, S100 +/-, GFAP focal).

A comment should be made for tumours showing aggressive microscopic features (high mitotic count >2 x 10 high power fields; Ki67 labelling index >3%). The current WHO classification suggests the term 'high-risk adenoma' for these tumours.

7 Non-core data items

Non-core data items (see Appendix D) comprise preferences of individual laboratories, items for clinical research and supplementary information that may contribute to prognosis, management or treatment decisions in individual cases.

8 Diagnostic coding and staging

TNM staging is not applicable. The use of SNOMED T and M codes or equivalent codes in SNOMED CT is recommended.

It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and Public Health England of SNOMED CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

A list of applicable T and M SNOMED and SNOMED CT codes is provided in Appendices A and B. Mapping SNOMED CT terminology is provided.

Histological grading of all tumours from the CNS and its coverings is as per criteria set out in the 2016 WHO classification.

The final report should include a date when the report was authorised (usually automatically assigned by the reporting database) and a SNOMED code for statistical purposes. It is acknowledged that many of the SNOMED codes do not reflect the molecular entities of brain tumours.

9 Reporting of small biopsy specimens

For any sample, but in particular for small targeted biopsies from critical regions such as eloquent areas in the cerebral hemispheres, intramedullary spinal cord, brainstem, thalamus and optic nerve, the diagnostic approach needs to be carefully planned. The value of an intraoperative smear and portioning tissue for this purpose should be discussed with the surgical team in individual cases prior to sample preparation. It is advisable to limit the number of immunostainings (see also section 4.6),[52] so as not to exhaust the material and preserve it for relevant molecular studies. Advanced molecular testing of small samples with methylation arrays[44, 74] should be considered early during the diagnostic process. Careful consideration of the necessity of ancillary markers such as MAP2, vimentin, neuron-specific enolase (NSE) and often even GFAP, synaptophsin or chromogranin A is essential when dealing with small biopsies, where preservation of tissue for molecular tests is paramount.

Level sections of stereotactic biopsies should only be considered in exceptional circumstances. If level sections are performed, it is essential to mount all sections on glass slides and retain all sections between levels for potential molecular tests. While DNA in tissue sections mounted on slides is reasonably stable, RNA degrades within weeks at room temperature.

10 Reporting of frozen sections

Either smear preparations and/or frozen sections may be used intraoperatively.[75] Intraoperative diagnosis helps to guide the surgical approach, but it may use up precious tissue. Although the evidence base for the benefit of this technique is limited in the current imaging era and its use varies according to local protocols and preferences, it is a well-

established procedure that is valued by neurosurgeons. It can be an important addition that complements preoperative imaging, in particular for ring-enhancing lesions where the differential diagnosis may include high-grade glioma, metastasis, lymphoma or abscess. In addition to guiding ongoing surgical treatment intraoperatively, it has also been used to determine whether intraoperative adjuvant therapy is appropriate, with the placement of chemotherapy wafers. NICE therefore recommends its availability in neurosurgical centres.[2] It should be noted, however, that final diagnosis, treatment planning and patient counselling should be based on the final report of the paraffin histology and an integrated molecular diagnosis were appropriate. Any diagnostic information present in the intraoperative preparations should be included in the final analysis. The fact that an intraoperative diagnosis has been carried out should be recorded for audit purposes but as the findings from any intraoperative preparations are included in the total evaluation of the specimen, it is not recorded as a separate dataset item.

11 Specific aspects of individual tumours not covered elsewhere

Specific information on issues related to diagnosis, subtyping and grading of individual tumours is provided in the WHO classification[1] (see Appendix B).

12 Criteria for audit

The following are recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, www.rcpath.org/profession/guidelines/kpis-for-laboratory-services.html):

- cancer resections must be reported using a template or proforma, including items listed in the English COSD, which are by definition core data items in RCPath cancer datasets. English Trusts were required to implement the structured recording of core pathology data in the COSD by January 2016 and to update their systems in line with subsequent COSD updates.
  - standard: 95% of reports must contain structured data
- histopathology cases should be reported, confirmed and authorised within seven to ten calendar days of the procedure
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

Potential audits should include the completeness of provision of core dataset items:

- 100% of reports should contain the basic demographic patient identification data.
- 100% of cases should indicate tumour type using WHO categories and subtype if relevant.
- 100% of tumours should be reported with their WHO grade (where a grading is applicable).
- 100% of cases should include core clinical information.

The dataset may also be audited for provision of molecular data for specific tumour types. In Scotland, it is recommended that results of molecular tests be available by 21 days post-neurosurgery.[33]

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Appendix A SNOMED topography codes

SNOMED topography should be recorded for the site of the tumour.

Note: Versions of SNOMED prior to SNOMED CT have ceased being licenced by the International Health Terminology Standards Development Organisation from 26 April 2017. It is recognised that versions of SNOMED 2, SNOMED 3/RT and SNOMED CT are in use in the UK; these are therefore currently considered acceptable.

SNOMED Procedure codes (P codes in SNOMED 2/3/RT) should be recorded for the procedure. P codes vary according to the SNOMED system in use in different organisations, therefore local P codes should be recorded and used for audit purposes.

Topography codes

Tumour	SNOMED RT	SNOMED CT CONCEPT ID	Fully specified name
Brain	T-A0100	12738006	Brain structure (body structure)
Cerebellum	T-A6000	113305005	Cerebellar structure (body structure)
Cerebral hemisphere	T-A2000	11628009	Structure of telencephalon (body structure)
Choroid plexus	T-A1900	80621003	Structure of choroid plexus (body structure)
Cranial nerve	T-A8000	25238003	Cranial nerve structure (body structure)
Meninges NOS	T-A1110	1231004	Meninges structure (body structure)
Pineal gland	T-B2000	45793000	Pineal structure (body structure)
Pituitary gland	T-B1000	56329008	Pituitary structure (body structure)
Skull	T-11100	89546000	Bone structure of cranium (body structure)
Spinal cord NOS	T-A7010	2748008	Spinal cord structure (body structure)
Spinal nerve root	T-A7160	69733000	Spinal nerve root structure (body structure)
Spine	T-11500	44300000	Entire vertebral column (body structure)

Appendix B SNOMED morphology codes

SNOMED morphology codes should be recorded for the diagnosis/tumour morphology.

Morphology codes and WHO grade (according to WHO 2016 classification of CNS tumours)

Entities	WHO grade	ICD-O code
Diffuse astrocytic and oligodendroglial tumours		
Diffuse astrocytoma, IDH-mutant	II	9400/3
Gemistocytic astrocytoma, IDH-mutant	II	9411/3
Diffuse astrocytoma, IDH-wildtype	*	9400/3
Diffuse astrocytoma, NOS	*	9400/3
Anaplastic astrocytoma, IDH-mutant	III	9401/3
Anaplastic astrocytoma, IDH-wildtype		9401/3
Anaplastic astrocytoma, NOS		9401/3
Glioblastoma, IDH-wildtype	IV	9440/3
Giant cell glioblastoma	IV	9441/3
Gliosarcoma	IV	9442/3
Epithelioid glioblastoma	IV	9440/3
Glioblastoma, IDH-mutant	IV	9445/3*
Glioblastoma, NOS	IV	9440/3
Diffuse midline glioma, H3 K27M-mutant	IV	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	IV	9450/3
Oligodendroglioma, NOS	*	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III	9451/3
Anaplastic oligodendroglioma, NOS	*	9451/3
Oligoastrocytoma, NOS	*	9382/3
Anaplastic oligoastrocytoma, NOS	*	9382/3
Other astrocytic tumours		
Pilocytic astrocytoma	I	9421/1
Pilomyxoid astrocytoma	*	9425/3
Subependymal giant cell astrocytoma	I	9384/1
Pleomorphic xanthoastrocytoma	II	9424/3
Anaplastic pleomorphic xanthoastrocytoma	III	9424/3
Ependymal tumours		
Subependymoma	I	9383/1
Myxopapillary ependymoma	I	9394/1
Ependymoma	II	9391/3
Papillary ependymoma	II	9393/3

Entities	WHO grade	ICD-O code
Clear cell ependymoma	II	9391/3
Tanycytic ependymoma	II	9391/3
Ependymoma, RELA fusion-positive	**	9396/3*
Anaplastic ependymoma	III	9392/3
Other gliomas		
Chordoid glioma of the third ventricle	II	9444/1
Angiocentric glioma	I	9431/1
Astroblastoma	*	9430/3
Choroid plexus tumours		
Choroid plexus papilloma	I	9390/0
Atypical choroid plexus papilloma	II	9390/1
Choroid plexus carcinoma	III	9390/3
Neuronal and mixed neuronal-glial tumours		
Dysembryoplastic neuroepithelial tumour	I	9413/0
Gangliocytoma	I	9492/0
Ganglioglioma	I	9505/1
Anaplastic ganglioglioma	III	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	I	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	I	9412/1
Papillary glioneuronal tumour	I	9509/1
Rosette-forming glioneuronal tumour	I	9509/1
Diffuse leptomeningeal glioneuronal tumour	**	
Central neurocytoma	II	9506/1
Extraventricular neurocytoma	II	9506/1
Cerebellar liponeurocytoma	II	9506/1
Paraganglioma	I	8693/1
Tumours of the pineal region		
Pineocytoma	I	9361/1
Pineal parenchymal tumour of intermediate differentiation	II or III	9362/3
Pineoblastoma	IV	9362/3
Papillary tumour of the pineal region	II or III	9395/3
Embryonal tumours		
Medulloblastomas, genetically defined	IV	
Medulloblastoma, WNT-activated	IV	9475/3*
Medulloblastoma, SHH-activated and TP53-mutant	IV	9476/3*
Medulloblastoma, SHH-activated and TP53-wildtype	IV	9471/3
Medulloblastoma, non-WNT/non-SHH	IV	9477/3*

Entities	WHO grade	ICD-O code
Medulloblastoma, group 3	IV	
Medulloblastoma, group 4	IV	
Medulloblastomas, histologically defined	IV	
Medulloblastoma, classic	IV	9470/3
Medulloblastoma, desmoplastic/nodular	IV	9471/3
Medulloblastoma with extensive nodularity	IV	9471/3
Medulloblastoma, large cell/anaplastic	IV	9474/3
Medulloblastoma, NOS	IV	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	IV	9478/3*
Embryonal tumour with multilayered rosettes, NOS	IV	9478/3
Medulloepithelioma	IV	9501/3
CNS neuroblastoma	IV	9500/3
CNS ganglioneuroblastoma	IV	9490/3
CNS embryonal tumour, NOS	IV	9473/3
Atypical teratoid/rhabdoid tumour	IV	9508/3
CNS embryonal tumour with rhabdoid features	IV	9508/3
Tumours of the cranial and paraspinal nerves		
Schwannoma	I	9560/0
Cellular schwannoma	I	9560/0
Plexiform schwannoma	I	9560/0
Melanotic schwannoma	I	9560/1
Neurofibroma	I	9540/0
Atypical neurofibroma	*	9540/0
Plexiform neurofibroma	*	9550/0
Perineurioma	I	9571/0
Hybrid nerve sheath tumours	*	
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV	9540/3
Epithelioid MPNST	II, III or IV	9540/3
MPNST with perineurial differentiation	II, III or IV	9540/3
Meningiomas		
Meningioma	I	9530/0
Meningothelial meningioma	I	9531/0
Fibrous meningioma	I	9532/0
Transitional meningioma	I	9537/0
Psammomatous meningioma	I	9533/0
Angiomatous meningioma	I	9534/0
Microcystic meningioma	I	9530/0

Entities	WHO grade	ICD-O code
Secretory meningioma	I	9530/0
Lymphoplasmacyte-rich meningioma	I	9530/0
Metaplastic meningioma	I	9530/0
Chordoid meningioma	II	9538/1
Clear cell meningioma	II	9538/1
Atypical meningioma	II	9539/1
Papillary meningioma	III	9538/3
Rhabdoid meningioma	III	9538/3
Anaplastic (malignant) meningioma	III	9530/3
Mesenchymal, non-meningothelial tumours		
Solitary fibrous tumour/haemangiopericytoma**		
Grade 1	I	8815/0
Grade 2	II	8815/1
Grade 3	III	8815/3
Haemangioblastoma	I	9161/1
Haemangioma		9120/0
Epithelioid haemangioendothelioma		9133/3
Angiosarcoma		9120/3
Kaposi sarcoma		9140/3
Ewing sarcoma/PNET		9364/3
Lipoma		8850/0
Angiolipoma		8861/0
Hibernoma		8880/0
Liposarcoma		8850/3
Desmoid-type fibromatosis		8821/1
Myofibroblastoma		8825/0
Inflammatory myofibroblastic tumour		8825/1
Benign fibrous histiocytoma		8830/0
Fibrosarcoma		8810/3
Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma		8802/3
Leiomyoma		8890/0
Leiomyosarcoma		8890/3
Rhabdomyoma		8900/0
Rhabdomyosarcoma		8900/3
Chondroma		9220/0
Chondrosarcoma		9220/3
Osteoma		9180/0

Entities	WHO grade	ICD-O code
Osteochondroma		9210/0
Osteosarcoma		9180/3
Melanocytic tumours		
Meningeal melanocytosis		8728/0
Meningeal melanocytoma		8728/1
Meningeal melanoma		8720/3
Meningeal melanomatosis		8728/3
Lymphomas		
Diffuse large B-cell lymphoma of the CNS		9680/3
Immunodeficiency-associated CNS lymphomas		
AIDS-related diffuse large B-cell lymphoma		9680/3
EBV-positive diffuse large B-cell lymphoma, NOS		9680/3
Lymphomatoid granulomatosis		9766/1
Intravascular large B-cell lymphoma		9712/3
Low-grade B-cell lymphomas of the CNS		
T-cell and NK/T-cell lymphomas of the CNS		
Anaplastic large cell lymphoma, ALK-positive		9714/3
Anaplastic large cell lymphoma, ALK-negative		9702/3
MALT lymphoma of the dura		9699/3
Histiocytic tumours		
Langerhans cell histiocytosis		9751/3
Erdheim–Chester disease		9750/1
Rosai–Dorfman disease		
Juvenile xanthogranuloma		
Histiocytic sarcoma		9755/3
Germ cell tumours		
Germinoma		9064/3
Embryonal carcinoma		9070/3
Yolk sac tumour		9071/3
Choriocarcinoma		9100/3
Teratoma		9080/1
Mature teratoma		9080/0
Immature teratoma		9080/3
Teratoma with malignant transformation		9084/3
Mixed germ cell tumour		9085/3
Tumours of the sellar region		
Craniopharyngioma	I	9350/1

Entities	WHO grade	ICD-O code
Adamantinomatous craniopharyngioma	I	9351/1
Papillary craniopharyngioma	I	9352/1
Granular cell tumour of the sellar region	I	9582/0
Pituicytoma	I	9432/1
Spindle cell oncocytoma	I	8290/0
Metastatic tumours		

*WHO grade may change following molecular characterisation.
**Molecularly defined entity with no accurately corresponding WHO grade.

Appendix C Reporting proforma for intra-axial tumours

Surname……..… Forenames…… Date of birth……..… Sex…..
Hospital……..……..… Hospital no……..... NHS/CHI no……....
Date of surgery…..……..… Date of report authorisation……. Report number……....
Date of receipt…….…… Pathologist……..... Surgeon……

CLINICAL DETAILS

Site of lesion

Skull □ Dura □ Leptomeninges □ Brain □ Cerebral lobes □

Deep grey matter □ Ventricle □ Pineal □ Brainstem □ Cerebellum □

Sellar/supersellar/pituitary (specify anterior/posterior) □ Spine/vertebral column □

Spinal cord □ Spinal nerve roots □ Peripheral nerve □

Other (specify) □ ……

Details of location …….

Laterality: Left □ Right □ Midline □ Bilateral □

Not specified □ Other (specify) □ ……

Focality: Unifocal □ Multifocal □ Indeterminate □

If multifocal: Number of lesions ……

Relationship of tumour to adjacent tissue

Well demarcated □ Diffuse/infiltrative □ Mixed □ Indeterminate □

Peritumoural oedema: Absent □ Present □ Contrast enhancement □

Operative procedure

Biopsy □ Resection □ Not provided □

Other, specify (total macroscopic, extent uncertain) □ ……

MACROSCOPIC ITEMS

Specimen dimensions (mm x mm x mm) …… or weight (g) ……

Specimen description …….

MICROSCOPIC ITEMS

Adequacy of specimen for histological assessment

Adequate □ Adequate but limited by (specify) □ ……

Inadequate (specify) □ ……

Adequacy of specimen for diagnostic purposes

Adequate □ Adequate but limited by (specify) □ ……

Inadequate (specify) □ ……

Histological appearance (see non-core dataset)
See ICCR dataset for guidance: www.iccr-cancer.org/datasets/docs/iccr-cns-histo-appear

Histological grade WHO grade

I □ II □ III □ IV □ N/A □ Cannot be determined □

Integrated final diagnosis (see core dataset)

See ICCR dataset for guidance: www.iccr-cancer.org/datasets/docs/iccr-cns-integrated-finaldx

Molecular parameters (see non-core dataset)

See ICCR dataset for guidance: www.iccr-cancer.org/datasets/docs/iccr-cns-mole-overview and Appendix E (COSD dataset)

Signature …… Date ……

SNOMED† codes: T …… M ……

†Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 8.

Appendix D COSD and ICCR data elements

The following includes COSD Version 8.0 – Pathology v3.0.1 and ICCR *Tumours of the Central Nervous System (CNS) Reporting Guide (1st edition, 2018).*[3,4]

Element name	COSD v8	ICCR 1st edition (2018)
Patient identity details		
NHS number	Core	N/A
Local patient identifier	Core	Core
NHS number status	Core	N/A
Birth date	Core	Core
Provider code	Core	N/A
Demographics		
Surname (family name)	Core	Core
Given name (forename)	Core	Core
Patient address	Core	N/A
Postcode	Core	N/A
Stated sex	Core	N/A
Pathology details		
Date and time of surgery/request	Core	Core
Date and time of receipt	Core	N/A
Date of report authorisation	Core	N/A
Report reference number	Core	Core
Pathologist	Core	N/A
Clinician	Core	N/A
Clinical information[a]		
Prior therapy-not administered[a]	Core	Non-core
Prior treatment not known[a]	Core	Non-core
Prior therapy administered (specify)[a]	Core	Non-core
Relevant patient family history: not provided	Core	Non-core
Relevant patient family history: previous history of cancer (specify)	Core	Non-core
Relevant patient family history: specify	Core	Non-core
Duration of symptoms	Core	Non-core
Site of lesion[b] (radiological information)		
Skull, specify precise location, if known	Core	Non-core
Dura, specify precise location, if known	Core	Non-core
Leptomeninges, specify precise location, if known	Core	Non-core
Brain	Core	Non-core
Cerebral lobes, specify precise location if known	Core	Non-core
Deep grey matter, specify location	Core	Non-core
Ventricle, specify precise location if known	Core	Non-core
Pineal, specify	Core	Non-core
Sellar/suprasellar/pituitary, specify anterior or posterior	Core	Non-core
Brainstem, specify precise location, if known	Core	Non-core
Cerebellum, specify site, if known	Core	Non-core
Spine/vertebral column, specify precise location if known	Core	Non-core
Spinal cord, specify precise location, if known	Core	Non-core

Element name	COSD v8	ICCR 1st edition (2018)
Spinal nerve roots, specify precise location, if known	Core	Non-core
Peripheral nerve, specify site, if known	Core	Non-core
Other, specify	Core	Non-core
Tumour laterality		
Right	Core	Non-core
Left	Core	Non-core
Midline	Core	Non-core
Bilateral	Core	Non-core
Other (specify)	Core	Non-core
Not applicable/Not specified	Core	Non-core
Focality		
Unifocal	Core	Non-core
Multifocal (specify number of lesions)	Core	Non-core
Indeterminate	Core	Non-core
Tumour dimensions		
(Largest/dominant lesion) (mm x mm x mm)	Core	Core
Weight	Core	Non-core
Relationship of tumour to adjacent tissue[c]		
Well demarcated	N/A	Non-core
Diffuse/infiltrative	N/A	Non-core
Mixed (both well demarcated and diffuse in different areas)	N/A	Non-core
Indeterminate	N/A	Non-core
Peritumoural oedema: absent/present	N/A	Non-core
Contrast enhancement		
Non-enhancing	N/A	Non-core
Enhancing	N/A	Non-core
Diffuse/solid	N/A	Non-core
Patchy/heterogeneous	N/A	Non-core
Ring/rim	N/A	Non-core
Information not available	N/A	Non-core
Operative procedure[d]		
Biopsy	Core	Non-core
Resection	Core	Non-core
Other, specify (total macroscopic, extent uncertain)	Core	Non-core
Not provided	Core	Non-core
Pathological information		
Specimen description		
Macroscopic description (including other characteristics: e.g. cystic, nodular, necrotic, haemorrhagic)[e]	Core	Non-core
Adequacy of specimen for histological assessment[f]		
Specimen is adequate for analysis	N/A	Non-core
Specimen is adequate but limited by, specify	N/A	Non-core
Specimen is inadequate for analysis (crush, autolysis, cautery, necrosis, other [specify])	N/A	Non-core
Adequacy of specimen for diagnostic purposes[g]		
Specimen is adequate for diagnostic purposes	N/A	Non-core

Element name	COSD v8	ICCR 1st edition (2018)
Specimen is adequate but limited by, specify	N/A	Non-core
Specimen is inadequate for diagnostic purposes (e.g. not representative of likely clinical and radiological diagnosis), specify	N/A	Non-core
Histological appearance/pathology report text		
Describe the appearance from the WHO 2016 entities and variants based on histological appearance only	Core	Non-core[h]
Other, specify	Core	Non-core[h]
Cannot be determined	Core	Non-core[h]
Grade of differentiation (COSD); histological grade (ICCR)		
WHO grade I, II, III, IV	Core[i]	Core
Not applicable	Core	Core
Cannot be determined, specify	Core	Core
Diagnosis		
Integrated final diagnosis (see Appendix C)	Core	Core
Integrated diagnosis based on histology; integrated diagnosis based on molecular information[j]	Core	Core
Diagnosis not elsewhere classified[k]	Core	Core
Invasion		
Not identified (i.e. tumour is well demarcated from surrounding brain or other tissues)	Core	Non-core
Cannot be assessed (e.g. only tumour is present)	Core	Non-core
Present, specify type	Core	Non-core
Histological evidence of prior therapy		
No evidence of prior therapy	N/A	Non-core
Positive response, specify type of response (vascular changes, radiation type necrosis). Granulation and/or scar tissue, ischemic type of necrosis, foreign material (e.g. embolisation/procoagulant material), reactive glial changes, inflammatory changes, other (specify).	N/A	Non-core

[a] Corresponds to item CR1000 in the COSD dataset ('neoadjuvant therapy indicator'), which is a core item.
[b] Corresponds to topography in the COSD (CR6410) dataset, which is a core item. Site of lesion corresponds to ICCR dataset, and is a non-core item.
[c] This item is listed in the COSD dataset (CR0879) under the more generic data item name 'cancer vascular or lymphatic invasion' and therefore not applicable to intrinsic CNS tumours.
[d] This item is listed in the COSD dataset (CR0760) under 'pathology investigation type'.
[e] The description of resection margins is generally not applicable for intra-axial CNS tumours as the surgical technique usually results in fragmented specimens. Diffusely infiltrative tumours have often invaded well beyond designated surgical margins, even when tumour cells are not evident at that margin. Description should also include the presence of other components, such as CNS tissue, dura mater, skin, bone, blood clot and extrinsic components such as haemostatic material, metal clips, synthetic bone, mesh, shunt ducts, etc.
[f] The adequacy of a specimen for histological assessment can be affected by various intraoperative procedures, tissue fixation issues (duration in/volume of fixative) and technical processing issues in the histology laboratory, for example electrocautery/heat/laser treatment intraoperatively, mechanical distortion and fixation delay. If the size of a biopsy is tiny, it can lead to tissue exhaustion during processing. Prior freezing (intraoperative diagnosis) may negatively impact cytological assessment in the fixed, embedded tissues and immunohistochemistry for some antibodies. The pathologist should state which of these conditions make the tissue inadequate/suboptimal for histological assessment.
[g] Many intraparenchymal brain lesions are surgically assessed by either small open excisional biopsy or stereotactic biopsy, which can occasionally be off-target. For example, diffuse infiltrating gliomas taken from the edge of the tumour; biopsies from infections containing only the reactive, but not organism-

containing, edge. The pathologist should specify any, and all, limitations of the tissue in achieving optimal diagnosis.

[h] In nearly all pathology reports of CNS neoplasms, the diagnosis should ideally include one of the over 150 entities and variants listed in the 2016 CNS WHO classification and, when additionally possible, the histological appearance should further be combined with signature molecular alterations to establish a more specific 'integrated diagnosis'. This element should be considered 'core' if it constitutes the final diagnosis. In COSD, this corresponds to data item CR1020.

[i] In COSD (CR0860) these are "Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated/anaplastic", and therefore usually not applicable for CNS neoplasms.

[j] Select all that apply.

[k] In the event that all diagnostic information is present but the tumour still does not meet criteria for an entity defined by the 2016 WHO classification (e.g. a paediatric diffuse glioma that does not harbour IDH or H3 mutations), a 'descriptive' or NEC (not elsewhere classified) diagnosis can be issued, which draws attention to the unusual nature of the lesion. Such designations are distinct from NOS diagnoses, which are included in the 2016 WHO classification and cases in which necessary diagnostic information is not available.[6]

Appendix E Molecular testing and integrated reporting

Please see below a list of genes and alterations reported in the Cancer and Outcomes and Services Dataset (COSD) v8 by Public Health England, National Cancer Registration and Analysis Service (www.ncin.org.uk/collecting_and_using_data/data_collection/cosd_downloads_v8).

A comprehensive molecular information reporting guide has been published by ICCR.[3] All molecular elements are non-core. This dataset is not needed for those tumours in which molecular information is not captured for diagnostic purposes, but this dataset applies to a growing subset of CNS tumours and it is anticipated that its use will increase over time (www.iccr-cancer.org/datasets/docs/iccr-cns-mole-overview).

Molecular testing will be issued in a supplemental report following the histology report. At this point an integrated (or layered) diagnosis can be issued incorporating all data. Suggested report format for integrated diagnosis:[40]

(Layer 1): Integrated histological-molecular diagnosis (if relevant)

(Layer 2): Histological classification

(Layer 3): WHO grade

(Layer 4): Molecular test result(s) (see COSD table below)

COSD code	**Chromosomal or genetic markers associated with the brain tumour**
06	Evidence of *ALK* rearrangement
07	Evidence of native *ALK*
08	Evidence of *ATRX* mutation
09	Evidence of wt *ATRX*
10	Evidence of *BRAF* V600E mutation
11	Evidence of wt *BRAF*
12	Evidence of *KIAA1549-BRAF* fusion
13	Evidence of *BRAF/RAF1* mutations, or fusions involving genes other than *KIAA1549*
14	Evidence of *C11orf95-RELA* fusion
15	Evidence of native *C11orf95* and *RELA*
16	Evidence of amplification or fusion of *C19MC* locus (chr.19q13.42)
17	Evidence of unaltered *C19MC* locus (chr.19q13.42)
18	Evidence of *CDK4/6* amplification
19	Evidence of *CDK4/6* normal copy number
20	Evidence of *CDKN2A* locus homozygous deletion
21	Evidence of *CDKN2A* locus normal copy number
22	Evidence of *CCND1/2/3* amplification
23	Evidence of *CCND1/2/3* normal copy number
24	Evidence of *CTNNB1* mutation
25	Evidence of wt *CTNNB1*
26	Evidence of amplification of *EGFR*
27	Evidence of mutation/rearrangement of *EGFR*
28	Evidence of unaltered *EGFR*

COSD code	Chromosomal or genetic markers associated with the brain tumour
29	Evidence of *EWSR1-FLI1* fusion
30	Evidence of native *EWSR1* and *FLI1*
31	Evidence of *FGFR1* mutation/rearrangement/fusion
32	Evidence of unaltered *FGFR1*
33	Evidence of *H3F3A/H3F3B* (H3.3) K27M mutation
34	Evidence of *H3F3A/H3F3B* (H3.3) wt K27
35	Evidence of *H3F3A/H3F3B* (H3.3) G34R/V mutation
36	Evidence of *H3F3A/H3F3B* (H3.3) wt G34
37	Evidence of *HIST1H3B* K27M mutation
38	Evidence of *HIST1H3B* wt K27
39	Evidence of *HIST1H3C* K27M mutation
40	Evidence of *HIST1H3C* wt K27
41	Evidence of *ID2* amplification
42	Evidence of *ID2* normal copy number
43	*IDH1* (codon 132) or *IDH2* (codon 172) mutation identified
44	*IDH1* (codon 132) and *IDH2* (codon 172) wt confirmed
45	Evidence of *KLF4* K409Q and *TRAF7* mutations
46	Evidence of wt *KLF4* and *TRAF7*
47	Evidence of *MAP2K1* mutation
48	Evidence of wt *MAP2K1*
49	Evidence of *MET* amplification
50	Evidence of *MET* normal copy number
51	Evidence of significant *MGMT* promoter methylation
52	Evidence of unmethylated *MGMT* promoter
53	Evidence of *MYC/MYCN* amplification
54	Evidence of *MYC/MYCN* normal copy number
55	Evidence of *NF1* biallelic loss/mutation
56	Evidence of unaltered *NF1*
57	Evidence of *NF2* biallelic loss / mutation
58	Evidence of unaltered *NF2*
59	Evidence of *NKTR* fusions
60	Evidence of native *NKTR*
61	Evidence of *PTEN* biallelic loss/mutation
62	Evidence of unaltered *PTEN*
63	Evidence of *SDHB* or *SDHD* mutation
64	Evidence of wt *SDHB* and *SDHD*
65	Evidence of *SHH* pathway activation
66	Evidence of normal *SHH* pathway
67	Evidence of inactivation of *SMARCB1* (INI1)
68	Evidence of wt *SMARCB1* (INI1)

COSD code	Chromosomal or genetic markers associated with the brain tumour
69	Evidence of inactivation of *SMARCA4*
70	Evidence of wt *SMARCA4*
71	Evidence of *TERT* promotor mutation
72	Evidence of wt *TERT* promotor
73	Evidence of *TP53* mutation
74	Evidence of wt *TP53*
75	Evidence of *TSC1* or *TSC2* mutation
76	Evidence of wt *TSC1* and *TSC2*
77	Evidence of *VHL* mutation
78	Evidence of wt *VHL* gene
79	Evidence of *WNT* pathway activation
80	Evidence of normal *WNT* pathway
81	Evidence of *WWTR1-CAMTA1* fusion
82	Evidence of native *WWTR1* and *CAMTA1*
83	Evidence of codeletion of chr.1p and chr.19q
84	Evidence of total chr.1p loss but normal copy number of chr.19q
85	Evidence of normal copy number of both chr.1p and chr.19q
86	Evidence of monosomy chr.6
87	Evidence of chr.6 normal copy number
88	Evidence of polysomy chr.7
89	Evidence of chr.7 normal copy number
90	Evidence of loss of chr.10 or chr.10q
91	Evidence of chr.10 normal copy number
92	Evidence of loss of chr.22 or chr.22q
93	Evidence of chr.22 or chr.22q normal copy number
98	Other
99	Not known (not recorded)

Appendix F Reporting proforma for extra-axial tumours

Surname……..…	Forenames……	Date of birth……..…	Sex…..
Hospital……..…….…..…	Hospital no…….....	NHS/CHI no…….....	
Date of surgery…..……..…	Date of report authorisation…….	Report number…….....	
Date of receipt…….……	Pathologist…….....	Surgeon……	

CLINICAL DETAILS

Site of lesion:

Skull □ Dura □ Leptomeninges □ Brain □ Cerebral lobes □

Deep grey matter □ Ventricle □ Pineal □ Brainstem □ Cerebellum □

Sellar/supersellar/pituitary (specify anterior/posterior) □ Spine/vertebral column □

Spinal cord □ Spinal nerve roots □ Peripheral nerve □

Other (specify) □ ……

Details of location …….

Laterality: Left □ Right □ Midline □ Bilateral □

Not specified □ Other (specify) □ ……

Focality: Unifocal □ Multifocal □ Indeterminate □

If multifocal: Number of lesions ……

Relationship of tumour to adjacent tissue

Well demarcated □ Diffuse/infiltrative □ Mixed □ Indeterminate □

Peritumoural oedema: Absent □ Present □ Contrast enhancement □

Operative procedure

Biopsy □ Resection □ Not provided □

Other, specify (total macroscopic, extent uncertain) □ ……

MACROSCOPIC ITEMS

Specimen dimensions (mm x mm x mm) …… or weight (g) ……

Specimen description……

MICROSCOPIC ITEMS

Adequacy of specimen for histological assessment

Adequate □ Adequate but limited by (specify) □……

Inadequate (specify) □……

Adequacy of specimen for diagnostic purposes

Adequate □ Adequate but limited by (specify) □……

Inadequate (specify) □……

Microscopic invasion of adjacent CNS or other tissues: Present □ Not identified □

Histological appearance (see non-core dataset)
See ICCR dataset for guidance: www.iccr-cancer.org/datasets/docs/iccr-cns-histo-appear

Histological grade WHO grade

I □ II □ III □ IV □ N/A □ Cannot be determined □

Integrated final diagnosis (see core dataset)

See ICCR dataset for guidance www.iccr-cancer.org/datasets/docs/iccr-cns-integrated-finaldx

Molecular parameters (see non-core dataset)

See ICCR dataset for guidance: www.iccr-cancer.org/datasets/docs/iccr-cns-mole-overview and Appendix E (COSD dataset)

Signature …… Date ……

SNOMED† codes: T …… M ……

†Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 8.

Appendix G Reporting proforma for neuroendocrine pituitary tumours

Surname……..… Forenames…… Date of birth……..… Sex…..
Hospital…….……..… Hospital no…….…..... NHS/CHI no……....
Date of surgery…..……..… Date of report authorisation……. Report number……....
Date of receipt……. Pathologist……..... Surgeon……

Summary of clinical and neuroimaging features

Macroscopic description

Specimen dimensions (mm x mm x mm) ……

Microscopic description

Tumour architecture ……

Cytological features (select all that apply):

Nuclear atypia (particular when severe) □

Presence fibrous bodies □

Crooke's hyaline changes □

Cytoplasmic vacuoles □

Ganglion cells or neurones:	Present □	Absent □
Necrosis:	Present □	Absent □
Macrophages and/or lymphocytic infiltrates:	Present □	Absent □
Rathke's rests:	Present □	Absent □
Cavernous sinus, respiratory mucosa and/or bone:	Present □	Absent □
Normal anterior and/or posterior pituitary:	Present □	Absent □

Mitoses should be counted and reported as number per mm^2 or per high power field (x40)

Test type	Explanation	Stain	Test performed	Marker expressed
Immunohistochemistry hormone expression type	Hormone expression by immunohistochemistry (multiple values may be recorded)	ACTH	□	□
		LH	□	□
		FSH	□	□
		Alpha-subunit	□	□
		TSH	□	□
		Prolactin	□	□
		Growth hormone	□	□
		Ki67	□	Labelling index
Proliferation	Proliferation index	Pit-1	□	□
Transcription factors	To refine the diagnosis when immunostaining for pituitary hormones are equivocal or negative. Transcription factors can also help distinguish	T-Pit	□	□
		SF1	□	□

Test type	Explanation	Stain	Test performed	Marker expressed
	different cell populations in the diagnosis of plurihormonal adenoma and double adenomas			
Cytokeratins	Relevant to subtype somatotroph adenoma and help diagnose corticotroph adenoma, particularly silent corticotroph adenoma	Cytokeratin 7 or cytokeratin 8 (CAM5.2)	□	□
Neuronal markers	When immunostains for pituitary hormones and transcription factors are negative to confirm the neuroendocrine lineage of the tumour. After excluding sellar paraganglioma, sellar neurocytoma, low-grade neuroblastoma or metastasis from a neuroendocrine tumour to the pituitary gland, tumours that lack expression of pituitary hormones and transcription factors are defined as 'null cell'	Chromogranin A and/or synaptophysin	□	□
Others	Can be added to the panel in cases of aggressive-looking tumours	p53	□	□

Appendix H Reporting proforma for intra-axial tumours in list format

Element name	Values	Implementation notes
Site of lesion	Single selection value list: • Skull • Dura • Leptomeninges • Brain • Cerebral lobes • Deep grey matter • Ventricle • Pineal • Brainstem • Cerebellum • Sellar/supersellar/pituitary, anterior • Sellar/supersellar/pituitary, posterior • Spine/vertebral column • Spinal cord • Spinal nerve roots • Peripheral nerve • Other	
Site of lesion, Other, specify	Free text	Only applicable if 'Site of lesion, Other' is selected.
Laterality	Single selection value list: • Left • Right • Midline • Bilateral • Not specified • Other	
Laterality, Other, specify	Free text	Only applicable if 'Laterality, Other' is selected.
Details of location	Free text	
Focality	Single selection value list: • Unifocal • Multifocal • Indeterminate	
Number of lesions	Integer	Only applicable if 'Focality, Multifocal' is selected.
Relationship of tumour to adjacent tissue	Single selection value list: • Well demarcated	

	• Diffuse/infiltrative • Mixed • Indeterminate	
Peritumoural oedema	Single selection value list: • Absent • Present • Contrast enhancement	
Operative procedure	Single selection value list: • Biopsy • Resection • Not provided • Other	
Operative procedure, Other, specify	Free text	Only applicable if 'Operative procedure, Other' is selected.
Specimen dimensions	Size in mm x mm x mm	Either estimated tumour dimensions or tumour weight should be given.
Specimen weight	Weight in grams	Either estimated tumour dimensions or tumour weight should be given.
Specimen description	Free text	
Adequacy of specimen for histological assessment	Single selection value list: • Adequate • Adequate but limited by • Inadequate	
Adequacy of specimen for histological assessment, Adequate but limited by, specify	Free text	Not applicable if 'Adequacy of specimen for histological assessment, Adequate' is selected.
Adequacy of specimen for histological assessment, Inadequate, specify	Free text	Not applicable if 'Adequacy of specimen for histological assessment, Adequate' is selected.
Adequacy of specimen for diagnostic purposes	Single selection value list: • Adequate • Adequate but limited by • Inadequate	
Adequacy of specimen for diagnostic purposes, Adequate but limited by, specify	Free text	Not applicable if 'Adequacy of specimen for diagnostic purposes, Adequate' is selected.
Adequacy of specimen for diagnostic purposes, Inadequate, specify	Free text	Not applicable if 'Adequacy of specimen

		for diagnostic purposes, Adequate' is selected.
Histological appearance	Free text	May be selected from complete list in ICCR dataset.
Histological WHO grade	Single selection value list: • I • II • III • IV • N/A • Cannot be determined	
Integrated final diagnosis	Free text	May be selected from complete list in ICCR dataset.
Molecular parameters	Free text	May be selected from complete list in ICCR and COSD datasets.
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix I Reporting proforma for extra-axial tumours in list format

Element name	Values	Implementation notes
Site of lesion	Single selection value list: • Skull • Dura • Leptomeninges • Brain • Cerebral lobes • Deep grey matter • Ventricle • Pineal • Brainstem • Cerebellum • Sellar/supersellar/pituitary, anterior • Sellar/supersellar/pituitary, posterior • Spine/vertebral column • Spinal cord • Spinal nerve roots • Peripheral nerve • Other	
Site of lesion, Other, specify	Free text	Only applicable if 'Site of lesion, Other' is selected.
Details of location	Free text	
Laterality	Single selection value list: • Left • Right • Midline • Bilateral • Not specified • Other	
Laterality, Other, specify	Free text	Only applicable if 'Laterality, Other' is selected.
Focality	Single selection value list: • Unifocal • Multifocal • Indeterminate	
Number of lesions	Integer	Only applicable if 'Focality, Multifocal' is selected.
Relationship of tumour to adjacent tissue	Single selection value list: • Well demarcated	

	• Diffuse/infiltrative • Mixed • Indeterminate	
Peritumoural oedema	Single selection value list: • Absent • Present • Contrast enhancement	
Operative procedure	Single selection value list: • Biopsy • Resection • Other • Not provided	
Operative procedure, Other, specify	Free text	Only applicable if 'Operative procedure, Other' is selected.
Specimen dimensions	Size in mm x mm x mm	Either estimated tumour dimensions or tumour weight should be given.
Specimen weight	Weight in grams	Either estimated tumour dimensions or tumour weight should be given.
Specimen description	Free text	
Adequacy of specimen for histological assessment	Single selection value list: • Adequate • Adequate but limited by • Inadequate	
Adequacy of specimen for histological assessment, Adequate but limited by, specify	Free text	Not applicable if 'Adequacy of specimen for histological assessment, Adequate' is selected.
Adequacy of specimen for histological assessment, Inadequate, specify	Free text	Not applicable if 'Adequacy of specimen for histological assessment, Adequate' is selected.
Adequacy of specimen for diagnostic purposes	Single selection value list: • Adequate • Adequate but limited by • Inadequate	
Adequacy of specimen for diagnostic purposes, Adequate but limited by, specify	Free text	Not applicable if 'Adequacy of specimen for diagnostic purposes, Adequate' is selected.
Adequacy of specimen for diagnostic purposes, Inadequate, specify	Free text	Not applicable if 'Adequacy of specimen

		for diagnostic purposes, Adequate' is selected.
Microscopic invasion of adjacent CNS or other tissues	Single selection value list: • Present • Not identified	
Histological appearance	Free text	May be selected from complete list in ICCR dataset.
Histological WHO grade	Single selection value list: • I • II • III • IV • N/A • Cannot be determined	
Integrated final diagnosis	Free text	May be selected from complete list in ICCR dataset.
Molecular parameters	Free text	May be selected from complete list in ICCR and COSD datasets.
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix J Reporting proforma for neuroendocrine pituitary tumours in list format

Element name	Values	Implementation notes
Summary of clinical and neuroimaging features	Free text	
Specimen dimensions	Size in mm x mm x mm	
Tumour architecture	Free text	
Cytological features	Multiple selection value list: • Nuclear atypia • Presence fibrous bodies • Crooke's hyaline changes • Cytoplasmic vacuoles	
Ganglion cells or neurones	Single selection value list: • Present • Absent	
Necrosis	Single selection value list: • Present • Absent	
Macrophages and/or lymphocytic infiltrates	Single selection value list: • Present • Absent	
Rathke's rests	Single selection value list: • Present • Absent	
Cavernous sinus, respiratory mucosa and/or bone	Single selection value list: • Present • Absent	
Normal anterior and/or posterior pituitary	Single selection value list: • Present • Absent	
Number of mitoses per mm^2 or per HPF	Integer	
ACTH	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
LH	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
FSH	Multiple selection value list: • Test performed	

	• Marker expressed • Not applicable	
Alpha-subunit	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
TSH	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Prolactin	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Growth hormone	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Ki67	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Pit-1	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
T-Pit	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
SF1	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Cytokeratin 7 or cytokeratin 8 (CAM5.2)	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
Chromogranin A and/or synaptophysin	Multiple selection value list: • Test performed • Marker expressed • Not applicable	
p53	Multiple selection value list: • Test performed	

	• Marker expressed • Not applicable	

Appendix K Diagnostic testing algorithm for gliomas in adults

Figure legend (figure overleaf)
The first layer is the histological assessment. The histological identification of a glial tumour is followed by the standard use of the antibodies to detect IDH1 (R132H) and ATRX expression.[48] This identifies a majority of IDH-mutant gliomas (columns A and B). IDH-mutant astrocytomas with ATRX loss may be further tested for *CDKN2A/B* homozygous deletion to discriminate high risk from lower risk astrocytomas[46] (column A). Lower risk IDH-mutant astrocytomas can also assessed for copy number variation, a suggested prognostic factor. This can, for example, be achieved by the readout of the copy number variation (CNV) component of the methylation arrays. IDH-mutant gliomas with retained ATRX expression (column B) are further tested for 1p/19q codeletion with a conventional copy number assay. This may be combined with *TERT* promoter mutation analysis to achieve additional diagnostic certainty when the 1p/19q test method returns ambiguous results. A further useful test that can serve as a preliminary surrogate for the 1p/19q codeletion is the loss of histone H3 K27me expression.[49] IDH-mutant tumours that have retained ATRX expression and no clear-cut result on targeted examination of 1p/19q status may benefit from unbiased methylation array analysis for classification. This helps to differentiate IDH-mutant oligodendrogliomas from IDH-mutant astrocytomas or glioblastomas with retained ATRX protein expression, in particular if the 1p/19q test with FISH or copy number assay suggested a false negative (no codeletion) result. Gliomas that are negative for IDH1 R132H are further tested for a panel of biomarkers (columns C–J): *IDH1*, *IDH2*, H3 K27 and G34, *BRAF*, *TERT* promoter, *EGFR* and *CDKN2A/B*. IDH-mutant gliomas are shown in columns C, D and E. The subsequent testing algorithm in column C is the same as in column A. Column E (representing IDH mutant tumours identified by sequencing) corresponds to column B with regard to the testing algorithm and outcome. The outcomes from histone mutation testing are in columns F and G. A significant proportion of IDH-wildtype, EGFR-amplified and *TERT* promoter-mutant glioblastomas are represented in column H. These molecular entities do not require further testing at present. Additionally, the detection of a *BRAF* V600E mutation usually does not require further methylation array analysis (column I). Glial tumours with unequivocal histology (e.g. DNET, RGNT, ganglioglioma, IDH-wildtype GBM) usually do not need further testing. Instead, tumours with non-characteristic/non-specific low-grade or high-grade histology and inconclusive molecular profile may be considered for methylation array analysis. This informs the methylation class, which may suggest candidate mutations that can be further tested for subsequent validation, such as rare mutations in histone variant encoding genes other than *H3F3A* (column J). Often the methylation analysis also serves as a risk stratifier.

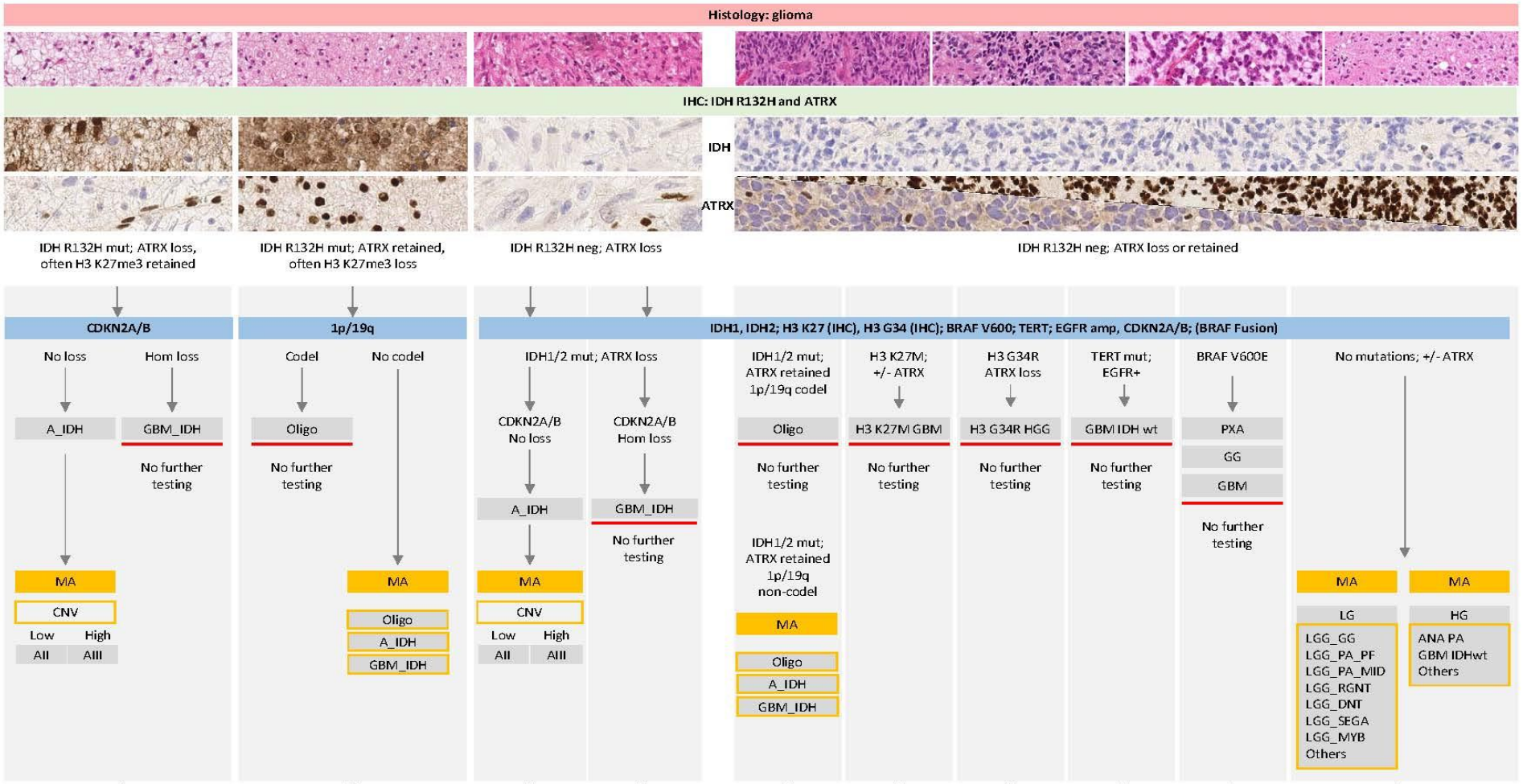
Methylation class acronyms: Oligo: Oligodendroglioma, IDH-mutant and 1p/19q codeleted; A_IDH: Astrocytoma, IDH-mutant; GBM_IDH: Glioblastoma, IDH-mutant; LGG_GG: Ganglioglioma; LGG_PA_PF: Pilocytic astrocytoma, posterior fossa subclass; LGG_PA_MID: Pilocytic astrocytoma, midline subclass; LGG_RGNT: Rosette-forming glioneuronal tumour; LGG_DNT: Dysembryoplastic neuroepithelial tumour; LGG_SEGA: Subependymal giant cell astrocytoma; LGG_MYB: Low-grade glioma with MYB or MYBL alteration, contains a high proportion of histological angiocentric glioma and to a lesser extent other low-grade gliomas or glioneuronal tumours such as DNETs and gangliogliomas; ANA_PA: Anaplastic astrocytoma with piloid features; GBM IDHwt: Glioblastoma, IDH-wildtype.

Yellow boxes: indication for methylation array (MA); grey boxes: diagnosis; grey boxes with yellow outline: final diagnosis achieved with methylation arrays; red lines: no further tests required.

See also www.molecularneuropathology.org/mnp/classifier/2, Capper *et al.*[76] and Capper *et al.*[44]

An A3 version of Figure 1 can be found as a separate document.

Figure 1: Diagnostic testing algorithm for gliomas in adults.



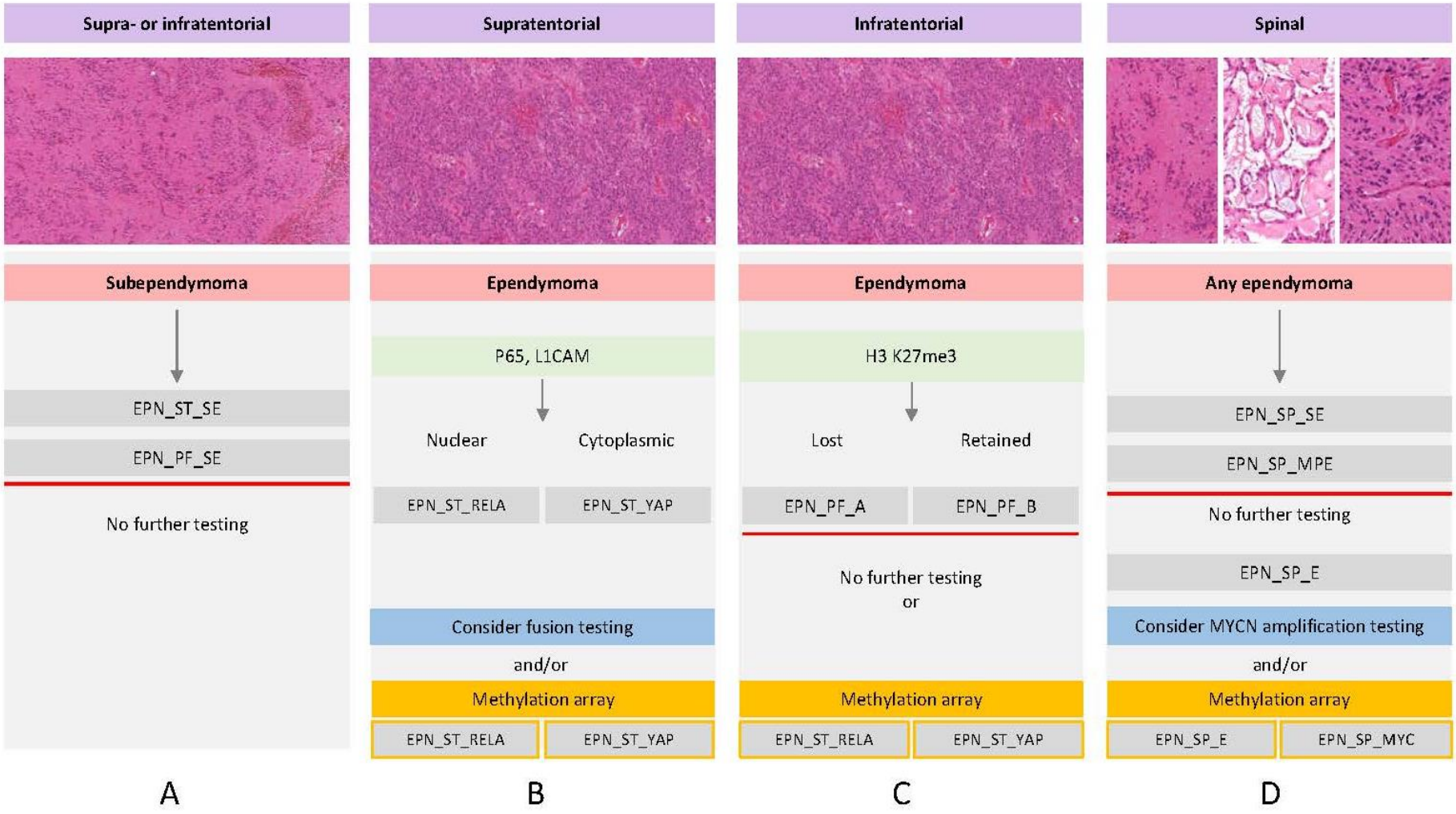
Appendix L Integrated diagnostic algorithm for ependymomas

Figure legend (figure overleaf)
Nine molecular classes of ependymoma exist, three of each in the supratentorial compartment, in the posterior fossa and spine. Tumours are grouped by location and histological appearance. Column A: supratentorial and posterior fossa subependymomas are histologically straightforward, and these tumours undergo no further testing. Column B: supratentorial ependymomas can be first tested by immunostaining for p65.[39] Nuclear p65 labelling suggests presence of a *RELA* fusion. This should be subsequently confirmed by detection of the *RELA* fusion gene, and correspondingly a p65 negative nuclear labelling by detection of the *YAP* gene fusion. Alternatively, methylation arrays can be used as surrogate tests.[56, 57, 76] For small samples one may consider prioritising methylation, as this test requires as little as 200 ng DNA, which can be extracted from as little as five serial 10 μm thick sections with three to four stereotactic tissue cores.[52] Column C: two molecular ependymoma subtypes (A and B) exist in the posterior fossa (EPN_PF_A and EPN_PF_B). They can be distinguished by immunostaining for H3 K27me3 (trimethylated K27), whereby type A shows loss of expression and type B retains expression.[36] Alternatively, these subtypes can be distinguished with methylations arrays. This may result in a reclassification of a small proportion of supratentorial ependymomas with 'classical' histology into subependymoma and may therefore have clinical implications. Column D: spinal tumours are in most instances clinically low risk, and their outcome is mainly determined by the extent of surgical removal. However, rarely spinal ependymomas can be MYCN amplified, which confers a poor clinical prognosis.[77]

Abbreviations: EPN_ST_SE: Supratentorial subependymoma; EPN_PF_SE: Posterior fossa subependymoma; EPN_ST_RELA: Supratentorial ependymoma with *RELA* fusion; EPN_ST_YAP: Supratentorial ependymoma with *YAP* fusion; EPN_PF_A: Posterior fossa ependymoma group A; EPN_PF_B: Posterior fossa ependymoma group B; EPN_SP_SE: Spinal subependymoma; EPN_SP_E: Spinal ependymoma; EPN_SP_MPE: Spinal myxopapillary ependymoma.

An A3 version of Figure 2 can be found as a separate document.

Figure 2: Integrated diagnostic algorithm for ependymomas.



Appendix M Diagnostic algorithm for pituitary tumours

Figure legend (figure overleaf)
Overview of the principles of the new classification of pituitary neuroendocrine tumours. The top category is the location, followed by the identification of the tumour type (neuroendocrine tumour). H&E is normally used, but reticulin silver stain is also an option. The basic assessment of these lesions is done by a panel of (anterior) pituitary hormones (TSH: thyroid stimulating hormone; GH: growth hormone; PRL: prolactin; FSH: follicle-stimulating hormone; LH: luteinising hormone; ACTH: adrenocorticotroph hormone; the proliferation marker Ki67; CK: pan-Cytokeratin).

The next step in the diagnostic process is the identification of an entity according to the hormone expression. (Abbreviations: THYR: thyrotroph; SOM: somatotroph; SOM-D and SOM-S: densely or sparsely granulated adenoma; MA-SOM: mammosomatotroph adenoma; Mix-ST/LT: mixed somatotroph-lactotroph adenoma; LAC: lactotroph, and the subtypes densely granulated [LAC-D], sparsely granulated [LAC-S] and acidophil stem cell [ACID-SC]; GON: gonadotroph; CORT: corticotroph with subtypes for densely granulated [CORT-D], sparsely granulated [CORT-S] and Crooke's cell adenomas [CORT-C], and plurihormonal [PLURI-H]). In somatotrophs, cytokeratin immunostaining can readily discriminate densely and sparsely granulated forms, which can give guidance of tumour behaviour and responsiveness to treatment.

The light blue bar below these categories indicates the adenohypophyseal cell lineage, acidophilic (ACID), gonadotroph (GON) and corticotroph (CORT), and below are corresponding lineage markers (transcription factors, acronyms see below).

Tumours that test positive with one or more of the antibodies against TSH, GH, PRL, FSH, LH and ACTH can be diagnosed as somatotroph, lactotroph, thyrotroph, corticotroph, gonadotroph or plurihormonal. Tumours that test negative will undergo a second test to establish their lineage (Pit-1: pituitary-specific POU-class homeodomain transcription factor; SF1: steroidogenic factor 1; T-PIT: T-box family member TBX19; ERα: oestrogen receptor α). Only tumours that are negative for these lineage markers should be classified as null cell adenoma (NUL). Tumours that contain more than 50% of oncocytic cells should be defined by their cell lineage with the addition of 'with oncocytic changes'.

Chromogranin (CR), synaptophysin (SYN) and CK are helpful if pituitary hormones and transcription factors are negative to demonstrate the neuroendocrine differentiation of the tumour. They can also be useful to identify other entities, such as sellar neurocytomas, sellar low-grade neuroblastomas or paragangliomas, and discriminate them from null cell adenomas. Other neuroendocrine tumours that have been described as mimicking null cell adenoma were low-grade gastropancreatic and lung neuroendocrine tumours. Further details about the diagnostic process and underlying pathobiology can be found in a summary by Lopes.[72]

Tumours in the posterior pituitary should be tested for TTF1 to confirm their origin in the posterior pituitary. Further work-up with GFAP, EMA and S100 should be considered. TTF1-positive tumours originating from the posterior pituitary include pituicytomas, granular cell tumours, spindle cell oncocytomas and sellar ependymomas. EMA immunolabelling discriminates spindle cell oncocytoma (membranous) from ependymoma (dot-like). For poorly differentiated tumours, INI1 and brachyury are recommended.

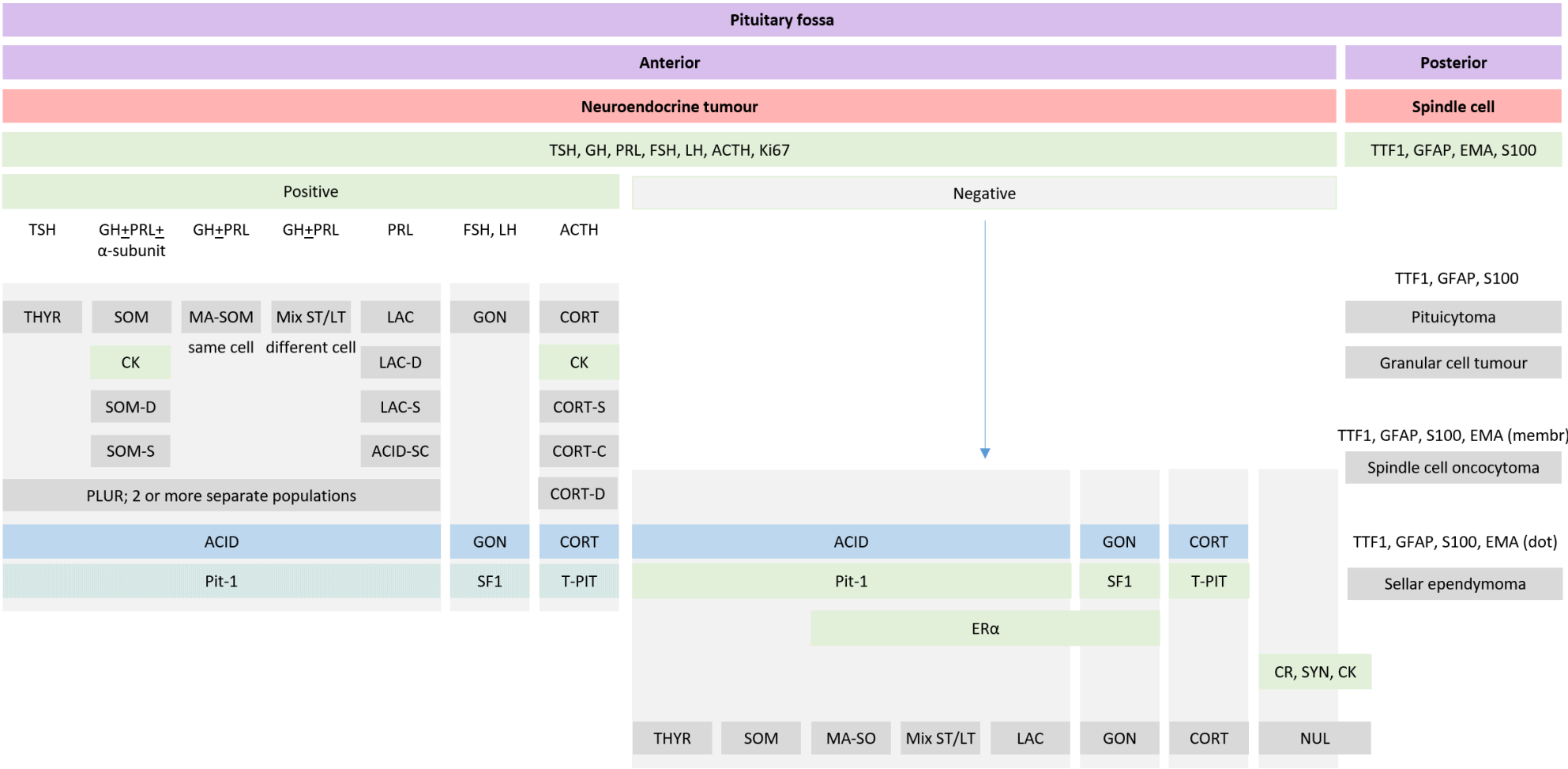
Diagnosis
The current WHO classification comprises well-differentiated neoplasms classified as (pituitary) adenomas, high-risk pituitary adenomas or well-differentiated (pituitary) carcinomas based on the presence of distant metastasis. They are subclassified depending on hormone production.

The proposed term of pituitary neuroendocrine tumour (PitNET) in place of adenoma can be adopted in line with the recommendations of the IARC and WHO consensus panel.[9,10]

Comments
A comment should be made for tumours showing aggressive microscopic features (high mitotic count >2 x 10 high power fields; Ki67 labelling index >3%). The current WHO classification suggests the term of 'high risk' adenoma for these tumours.

An A3 version of Figure 3 can be found as a separate document.

Figure 3: Diagnostic algorithm for pituitary tumours.



Appendix N Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least 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.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix O AGREE II monitoring sheet

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

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–11
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–11
16 The different options for management of the condition or health issue are clearly presented	2–11
17 Key recommendations are easily identifiable	2–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–M
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword