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

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Authors: Professor Sebastian Brandner, University College London Hospitals NHS Foundation Trust (NHSFT)
Associate Professor Zane Jaunmuktane, University College London Hospitals NHSFT
Professor Federico Roncaroli, University of Manchester, Northern Care Alliance
Professor Maria Thom, University College London Hospitals NHSFT
Dr Ashirwad Merve, Great Ormond Street Hospital and University College London Hospitals NHSFT
Dr Simon Paine, Nottingham University Hospitals NHS Trust

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Produced by	Professor Sebastian Brandner (lead author), Professor Maria Thom and Associate Professor Zane Jaunmuktane are consultant neuropathologists at the National Hospital for Neurology and Neurosurgery, University College London Hospitals NHSFT. Professor Federico Roncaroli is a consultant neuropathologist at Salford Royal NHSFT. Associate Professor Simon Paine is a consultant neuropathologist at Nottingham University Hospitals NHS Trust. Dr Ashirwad Merve is a consultant neuropathologist at Great Ormond Street Hospitals

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	NHSFT and at the National Hospital for Neurology and Neurosurgery, University College London Hospitals NHSFT.
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The Royal College of Pathologists
6 Alie Street, London E1 8QT
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

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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 B, C and F) 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 were consulted on this document:

- British Neuropathological Society
- Society of British Neurological Surgeons
- British Neuro-Oncology Society

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

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched were (((brain tumour and (astrocytoma or oligodendroglioma or glioblastoma or ependymoma or meningioma or pituitary adenoma or pituitary tumour or K27M or BRAF or IDH or MGMT) and (methylation array or NGS or temozolamide)) OR (brain tumour and (astrocytoma or oligodendroglioma or glioblastoma

or ependymoma or meningioma or K27M or BRAF or IDH or MGMT) and (methylation array or NGS or temozolamide))) OR ((pituitary adenoma or pituitary tumour and "transcription factor" and diagnosis)) AND (("2014"[Date - Publication]: "3000"[Date - Publication]))). (Retrieved in January 2024) The dates searched were between January 2014 and January 2024.

Further evidence used in this dataset comprises: *The 2021 WHO Classification of Tumors of the Central Nervous System*,[1] NICE guidance *Brain tumours (primary) and brain metastases in adults*[2] and consensus and clinical practice guidelines on neuroendocrine and non-neuroendocrine tumours of the pituitary gland, including *The WHO Classification of Tumours of the Endocrine Organs*.[3–7]

Published evidence was evaluated using modified SIGN guidance (see Appendix H). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

A formal revision cycle for all cancer datasets takes place on a 3-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 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 2 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 Professional Guidelines team, Working Group on Cancer Services and the Lay Advisory Group and was placed on the College website for consultation with the membership from 8 July to 5 August 2024. 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.

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 Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

Central nervous system (CNS) tumours form a large and heterogenous group of neoplasms that affect the brain and spinal cord and their coverings.[1] Intra-axial tumours, such as gliomas, arise from within the CNS parenchyma; 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 on diencephalic structures and cranial nerves. Brain tumours also comprise metastases originating from tumours outside the CNS, whereas haematological neoplasms can be primary CNS or secondary.

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],*[8] and the RCPath neuropathology workforce survey.[9]

1.1 Target users and health benefits of this guideline

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 the National Cancer Registration and Analysis Service (NCRAS). Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help to ensure that clinicians have the relevant pathological information required for tumour grading, staging, management and prognostication. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

1.2 Purpose of these guidelines

The guidelines are intended to assist pathologists to:

- provide the core data that should be included in histopathology reports from biopsy and resection specimens of CNS and related tumours in adults
- 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 NCRAS (http://www.ncin.org.uk/home).

Separate guidelines deal with non-neoplastic CNS lesions.[10]

1.3 Who reports CNS tumours?

CNS tumours are commonly reported by neuropathologists working in specialist centres. 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.[8] Pathologists reporting CNS tumours should attend these meetings and participate in the relevant EQA scheme. The role and responsibilities of neuropathologists are also described in the 2023 RCPath neuropathology workforce survey.[9]

2 Epidemiology and prevalence

CNS tumours have an estimated incidence of around 20 per 100,000 per year,[11] with approximately 12,000 new brain tumours diagnosed every year in the UK. Brain tumours represent 3% of all cancer cases. 5-year relative survival for all malignant brain tumours combined has increased from 23% in 1975 to 1977 to 36% in 2009 to 2015, with larger gains among younger age groups. Less improvement among older age groups largely reflects a higher burden of glioblastoma, for which there have been few major advances in

early detection and treatment over the past 4 decades. Specifically, 5-year glioblastoma survival only increased from 4% to 7% during the same time period.[12]

CNS tumours cause morbidity and mortality that is disproportionate to the incidence. Patients' quality of life is severely compromised and only 11% survive 10 or more years.[11] Reported brain tumour incidence varies across different regions of the world, reflecting different methods of ascertainment and also access to healthcare, with 5.74 per 100,000 person-years in the USA and 6.95 in Europe.[12–14]

Brain metastases occur in 2.0% of all patients with cancer and in 12.1% of those patients with systemic metastatic disease. The estimated annual incidence of identified brain metastases in the US among patients with newly diagnosed cancer is approximately 23,000.[15] The highest 5-year survival rates were recorded for ependymomas (76% in Southeast Europe and 92% in the US) and the worst were recorded for glioblastomas and anaplastic astrocytomas (28% in Southeast Europe and 37% in the US). Advancing age, male sex and rural residency at diagnosis adversely affected outcomes in both regions.[14]

3 Clinical information required on the specimen request form

A core dataset of clinical information has been established by the ICCR.[16] This document, published in 2020, provides guidance on which data items are required for the histological assessment of CNS tumours. The elements of the histological dataset are up to date, while guidance to histological grading and molecular markers for the diagnosis of CNS tumours have been superseded by the 2021 CNS WHO classification.[1]

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 and must be part of the header of the pathology report, relevant clinical information should include location and focality of the tumour, neuroimaging findings and history, including previous relevant diagnoses, biopsies or therapies.

3.1 Clinical information: previous relevant diagnoses, biopsies or therapies

The clinical presentation with relevant patient history (duration and nature of symptoms, family history) is essential to formulate relevant differential diagnoses.

Prior therapies, such as radiotherapy, radiosurgery or some forms of chemotherapy or immunotherapy, may modify histological appearances. Knowledge of prior therapies is essential for correct interpretation of histological findings and assignment of WHO grade. Preoperative embolisation of meningiomas may induce necrosis and increased proliferation, which are 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; the long-term effects of radiotherapy include increased risk of cavernous haemangioma or meningioma development. Prior biopsy in the same or adjacent areas can cause additional reactive changes (haemorrhage, gliosis, ischaemia).

The knowledge of any prior histological and molecular results is essential for an accurate interpretation of a case and may also save time and efforts to reestablish a precision diagnosis. Comparative testing of current and prior biopsies can yield important information on molecular alterations occurring during tumour recurrence and progression. Endocrine dysfunction, signs of arginine vasopressin deficiency (formerly known as diabetes insipidus),[17] history of rapid growth and resistance to medical treatment, and cranial nerve deficits are essential to the interpretation of pituitary tumours.

[Level of evidence B – Previous diagnosis is relevant for grading.]

3.2 Location and focality of the tumour, neuroimaging

Neuroradiological features and neurosurgical intraoperative findings provide important information to the diagnostic interpretation of the case. Whenever the work-up of CNS neoplasm raises differential diagnostic considerations, access to neuroimaging results is helpful; information of tumour site, laterality, focality, dimension, relationship to adjacent tissue and contrast enhancement can signal potential discrepancy to the histological interpretation. These features are relevant to an integrated diagnostic work-up. For example, the close association of histone H3.3 K27M mutations with midline gliomas, risk stratification of ependymomas, differential diagnosis of a high-grade astrocytoma with piloid features (posterior fossa).

Certain imaging appearances in conjunction with the histological appearance of a low-grade, IDH-wildtype astrocytoma should prompt consideration and appropriate investigations to identify the infiltration margin or early forms (i.e. prior to development of classical high-grade features) of a glioblastoma, IDH-wildtype. During intraoperative assessment of tissue samples, access to a picture archiving and communication system can provide essential information, including location, growth pattern and evidence of contrast enhancement, and can enable the neuropathologist to provide useful guidance to the surgical team regarding biopsy target and nature of lesion.

[Level of evidence A – Location is relevant for diagnosis in many CNS tumours.]

4 Preparation of specimens before dissection and frozen archiving

4.1 Specimen reception and fixation

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, should not be used, as they hinder downstream molecular studies.[18]

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 and accelerated penetration of fixative. However, over-fixation impacts on subsequent molecular genetic tests and may also denature some antigens, in particular nuclear markers (e.g. transcription factors [TFs]), certain cell surface antigens (e.g. cluster of differentiation [CD] markers), or other proteins that are sensitive to denaturation (e.g. NeuN), which can result in difficulties in detecting these markers with diagnostic antibodies.

Recommendations on tissue retention and storage can be found in an RCPath document published in 2015.[19]

[Level of evidence C – Relevance of adequate fixation time and type of fixative.]

4.2 Importance of fresh frozen tissue samples

There are advantages to specimens being received fresh from the operating theatre (see points below in this section). Collection of fresh tissue requires good communication and

an established tissue pathway with robust standard operating procedures 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 12). Residual tissue from the intraoperative assessment should be fixed in formalin for subsequent conventional paraffin histology. The archiving of frozen samples should become part of a standard tissue pathway, for subsequent studies such as whole genome sequencing (WGS) (see below).

When possible, frozen material should be archived routinely (this is already standard practice for muscle biopsies). The availability of frozen tissue must be recorded, ideally in the laboratory information management system (LIMS), allowing for audits and evidence of record keeping for the Human Tissue Authority (HTA). Availability of frozen tissue will allow certain molecular genetic studies for diagnostic or research/clinical trials purposes, which currently cannot be carried out on formalin-fixed and paraffin-embedded (FFPE) tissue. While most routine tests (MGMT promoter methylation, Sanger sequencing, copy number assay, fluorescent in situ hybridisation [FISH] and advanced molecular tests, next generation sequencing [NGS] on DNA or RNA, or methylation arrays) can be readily performed on FFPE tissue, WGS, or long-read sequencing (Nanopore technology)[20–22] currently require fresh or frozen tumour tissue. There is an increasing drive from NHS England to offer WGS; the routine archiving of frozen tissue should become standard of care.[23]

Following the successful conclusion of the Genomics England 100,000 Genomes project, WGS has been commissioned for some CNS tumours, e.g. paediatric neoplasms. One of the missions of Genomics England 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.[24]

[Level of evidence – GPP.]

4.3 Frozen archiving of diagnostic tissue samples

Frozen archiving of diagnostic tissue samples is recommended in the recent *Criteria for the Definition of Pituitary Tumor Centres of Excellence* published by the Pituitary Society[25] and more generally in pathology practice.[23]

Availability of systematically archived and highly characterised (i.e. with corresponding histological and molecular data) frozen tumour samples also 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), or as a national resource, for example through BRAIN UK, a national virtual neuropathology brain bank.[26]

Importantly, the archiving of frozen diagnostic material does not require additional ethical approval. It does however require access to suitable infrastructure with availability of low-temperature freezers (−70 °C or −80 °C) or liquid nitrogen storage. The use of frozen tissue for research and clinical trials is subject to appropriate ethical, clinical and research governance frameworks and can be greatly facilitated through BRAIN UK.[26]

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

[Level of evidence – GPP.]

4.4 Other fixation and preparation methods

Rare cases may require ultrastructural examination. In such instances, 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, using FFPE, fresh or frozen material, can provide more informative results than ultrastructural examination.

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 before decalcification, in particular bearing in mind that the acid used for decalcification depurinates DNA and RNA, making it unsuitable for nucleic acid-based molecular tests. For optimal tissue decalcification procedures, please refer to the RCPath *Tissue pathways for bone and soft tissue pathology* guideline.[27]

[Level of evidence C – Relevance of adequate fixation time and type of fixative.]

5 Specimen handling and block selection

5.1 General comments

There are limited evidence-based recommendations for the macroscopic handling of specimens from CNS tumours, although there are some published recommendations.[28,29] The specimen should be measured in 3 dimensions and/or weighed. In many cases, CNS

tumour specimens will be submitted in the form of multiple small fragments; in these instances, an aggregate measurement should be taken. In particular, collections of surgical aspirates may be difficult to assess in 3 dimensions and weighing may give an additional useful, more consistent, quantitative value.

The specimen should be described fully, including the 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. This is integrated in the table-formatted dataset (Appendices C and F).

5.2 Biopsies

Stereotactic biopsies should be embedded in their entirety for processing into a paraffin block (see section 11 for further information). 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 (see section 4). Levels (step sections or serial sections through the paraffin block) may be considered if the initial section is non-informative. It is best practice to retain all unstained serial sections between the levels for molecular analysis and immunohistochemistry (IHC). In small biopsies, priority should be given to molecular work-up over the use of IHC beyond the absolute minimum, which can often be achieved with no more than 3–5 IHC sections.[30,31]

For larger (open) biopsies (other than burr-hole or stereotaxic biopsies), surgical ultrasonic aspirates (e.g. Cavitron ultrasonic surgical aspirator [CUSA]) may provide additional diagnostically important information[32] 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 can be frozen, if there is a presumed high tumour content. Even where cytology and architecture are less well preserved in aspirated material, it may be suitable for IHC; if the sample contains predominantly viable tumour, it is useful for molecular genetic tests.

[Level of evidence C – The importance of a strategical approach for optimal balance between histological and molecular diagnostics.]

5.3 Intra-axial tumour resections, including lobectomy specimens

Resection specimens may be received as anatomically intact lobectomy specimens or fragmented specimens removed piecemeal (see above, surgical aspirates). For diffuse

gliomas, complete resection is, with only rare exceptions, precluded because of their infiltrative nature. Most resections are, therefore, subtotal.

When possible, a large resection 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.[33]

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.

Several studies, including the NICE guidelines,[2] showed that the extent of resection is a favourable prognostic factor.[34–36] Neuroradiological assessment from postoperative imaging/computer-assisted volumetric studies is a much better measure of the extent of surgical excision than pathological measurements. Nevertheless, pathological assessment of tumour volume removed provides some indication of the extent of excision and so an approximate measurement of tumour size in 3 dimensions should be given.

Photography may be helpful in selected cases to confirm the orientation of the specimen with the neurosurgeon.

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. 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 and, in most instances, cannot be achieved. 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.[29]

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.[32] Moreover, 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.[32]

In some cases, gliomas may involve multiple lobes or may be multifocal; this information from neuroimaging and the request form should be recorded. If 2 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.

[Level of evidence – GPP.]

5.4 Extra-axial tumours

Meningioma is the most common extra-axial tumour, followed by schwannoma, but a range of other tumours may occur in the CNS coverings. 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 1 block per centimetre diameter of tumour. This seems a reasonable, pragmatic approach to ensure that any higher-grade areas are not missed.

Blocks for histology should include the tumour and provide a clear representation of 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.[1,37] It is considered unnecessary to mark the surface of tumours with ink in most scenarios.

If bone and other samples from adjacent anatomical structures accompany the specimen, these should be separately described and sampled. Decalcification may be required; however, decalcification protocols involving acid can affect nucleic acid quality and, thus,

downstream molecular testing. It can be helpful to orientate and ink the margins of any infiltrated bone. In meningiomas, infiltration through the dura, into skull and into extra-cranial tissues can occur with tumours of all histological grades. Thus, even a CNS WHO grade 1 tumour may show an infiltrative behaviour. Invasion of bone and soft tissue is not considered to be a prognostic factor in the CNS WHO grading scheme; however, particularly in the skull base, infiltration may make surgical resection more difficult, affect recurrence and impact the delivery of postoperative radiotherapy. Therefore, invasion of extra-dural structures should be included in the report when this can be assessed.

[Level of evidence – GPP.]

Archiving of frozen tissue for molecular genetics should always be considered. 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 or nanopore sequencing) will require frozen material. Frozen material can be stored as part of the diagnostic tissue archive (also see sections 5.2 and 5.3).

[Level of evidence – GPP.]

Resection margins are often difficult to assess in extra-axial tumours. It is usually not advisable to comment on the completeness of surgical resection in the macroscopic or microscopic description. Extent of surgical resection is more accurately assessed with neuroimaging. Assessment of surgical margins are, therefore, not included as a core data item. Nevertheless, a comment on a specific margin may be requested by the surgeon. Sampling of margins should, therefore, be carried out where possible.

[Level of evidence – GPP.]

5.5 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 much less likely to be required for diagnosis and can be performed 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 on whenever possible, although it is recognised that the dura mater and other surrounding structures are not always submitted for histological examination.[38,39]

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.

[Level of evidence D – The basis in evidence for inclusion is expert opinion.]

5.6 Immunostainings to identify diagnostically relevant biomarkers

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,[40] histone H3.3 K27M[41] or BRAF V600E[42]), a loss of protein expression (e.g. SMARCB1/INI1[43], ATRX[44], histone K27me3[45]) or pathological translocation of a protein (nuclear expression of STAT6[46] or p65 RELA[47]). For neuroendocrine tumours of the pituitary gland, the immunopanel should cover anterior pituitary hormones (prolactin, growth hormone [GH], adrenocorticotropic hormone (ACTH), luteinising hormone [LH], follicle stimulating hormone [FSH], thyroid stimulating hormone [TSH]) and lineage-specific pituitary TFs TPIT, Pit1 and SF1.[6,48,49] GATA3 can also be helpful to further characterise gonadotroph, thyrotroph and rarely corticotroph tumours. Gonadotropinomas with weak, focal SF1 staining usually show intense GATA3 expression.[50,51] Pan-cytokeratin or cytokeratin CAM5.2 should be considered as a routine addition to the ‘pituitary panel’ to identify sparsely granulated somatotroph tumours and a subset of corticotroph tumours that display weak TPIT and ACTH labelling. The definition of Crooke cell corticotropinoma also requires cytokeratin staining.[48,49]

Additional makers commonly used in the assessment of gliomas or other tumour types, including ATRX, p53, BRAFV600E, p16 and mismatch repair proteins, can be considered as a screening tool for molecular studies in potentially aggressive corticotroph tumours. The use of the antibody clone VE1 to detect the BRAF V600E mutation can produce false positive results in adenohypophyseal tumours. Positive immunolabeling, which has been successfully validated for melanomas,[52] lung adenocarcinomas[53] and thyroid carcinomas,[54] could not be confirmed by sequencing in a proportion of neuroendocrine tumours of the pituitary gland.[55,56] It has been hypothesised that an as yet unknown homologous protein particularly associated with GH and ACTH-positive pituitary tumours

may be the cause of cross-reactivity.[56] For non-endocrine pituitary tumours, the immunopanel should include TTF1 and, depending on light microscopic features, additional epithelial, neuronal and glial markers.[48] If available, the assessment of vasopressin can resolve the differential diagnosis between normal neurohypophysis and pituicytoma. Immunostaining for Ki-67 allows the proliferation fraction to be estimated in both neuroendocrine and non-endocrine tumours.

For the use of level sections through a block, see section 10. It is, however, strongly recommended that a panel of immunostainings is applied to poorly differentiated tumours to confirm or exclude epithelial neoplasms, mesenchymal tumours, melanoma and haematological malignancy. We recommend that such tumours are referred to pathologists with relevant expertise in soft tissue and bone tumours, haematological malignancies and general histopathology.

[Level of evidence A – Molecular investigations including mutation-specific antibodies have an established role in the diagnosis and management of CNS tumours.]

6 Core data items

6.1 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[57] and 2020.[16] Proforma reporting will assist in future data collection strategies, but it is also important to retain free text comment. Recent progress in and availability of 'neural language models', i.e. algorithms to extract data from narrative reports to generate structured output, will allow data extraction from reports of multiple formats.[58–61]

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 latter was created to provide a comprehensive dataset for all histopathology subdisciplines, while the 2018 edition of the ICCR guidelines was tailored specifically to tumours of the CNS.

ICCR datasets are composed of 2 elements: core and non-core. Core elements are defined as those that are unanimously agreed by the panel to be mandatory for diagnosis, clinical management, staging or prognosis. Non-core elements are not mandatory and are

defined as clinically important and recommended as good practice; they should ideally be included in the report but may not yet be validated or regularly used in patient management.

Notably, for the CNS dataset, the discussion (during the development of the dataset) as to whether an element was core or non-core often became complex, with different opinions expressed that reflected the customs at multiple institutions around the world. The resulting datasets, therefore, only included 2 core elements: specimen dimension and histologic grade. In general, this decision did not reflect an underlying opinion that the non-core data elements were not important, but rather that reasons could typically be found why nearly all these elements may not always be present in pathology reports of CNS tumours. The distinction between core and non-core is, therefore, not of primary importance for the CNS datasets.[16,57]

6.2 Macroscopic core data items

Core items include the specimen dimensions (mm x mm x mm).

6.3 Microscopic core items

Core items include:

- WHO 2021 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.]

7 Histological classification and molecular approaches

Primary CNS tumours are classified and graded according to the WHO grading scheme – currently, the 5th edition of the WHO classification for CNS tumours (WHO CNS5), published in 2021.[1] This scheme is used in all neuropathology centres in the UK and its use is endorsed by the British Neuropathological Society and its national EQA scheme (NEQAS). The WHO scheme is also widely used internationally, allowing comparison of data from centres worldwide. This provides a uniform system of nomenclature, which is essential for comparative studies and multicentre trials.

WHO CNS5 has further advanced the classification and grading of tumours based on molecular profile. It builds on the 2016 update of the WHO classification and the recommendations of the consortium to inform molecular practical approaches to CNS tumour taxonomy (cIMPACT-NOW),[62–68] which initiated the integration of well-established molecular parameters into the classification of several brain tumour types. When the update of the 4th edition of WHO classification was released in 2016, concerns were raised that the inclusion of tumour types defined by the genotype (methylome-based classification was not yet established at that time) would have created challenges to neuropathologists with limited accessibility to molecular tests (e.g. mutation-specific antibodies, surrogate immunostainings, gene sequencing and copy number assays).

Over the last 5 years, genomic testing in the NHS has been rolled out and in England delivered through a national network of 7 genomic laboratory hubs (GLHs). Hubs are responsible for regional and supraregional coordination of services. A test directory specifies the test portfolio and the tumour types covered for genomic testing and is periodically updated to reflect changes in diagnostic practice and clinical requirements (NHS England: the National Genomic Test Directory, www.england.nhs.uk/genomics/the-national-genomic-test-directory).

Molecular analysis (DNA- or RNA-based) is now established practice in the diagnostic work-up of intra and extra-axial tumours. In Scotland, the NHS Scotland's National Services Division is responsible for commissioning and performance managing national specialist services, including laboratory genetics services, across the country. The genetic testing services are delivered through four collaborating regional centres.[69] In Wales, genomic services including cancer testing are delivered through the All Wales Medical Genomics Service.[70] In Northern Ireland, somatic cancer tests are delivered through the

Northern Ireland Centre for Genomics Medicine.[71] As of January 2024, the test directories in the devolved nations lack some of the tests that are currently available in the NHS England GLH. This is mitigated by referrals from these regions to the NHS England GLH through informal referral pathways.

The access to advanced molecular tests across GLHs has reduced the need for the testing algorithm that was available in the previous dataset. A comprehensive table (Appendix G) with detailed information of expected diagnostic mutations and recommended tests for glial, glioneuronal and neuronal tumours are available (modified from the European Association of Neuro-Oncology (EANO) recommendations published in 2023).[31]

[Level of evidence A – Molecular investigations have an established role in the diagnosis and management of CNS tumours.]

7.1 Adopting the concept of integrated diagnosis

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

For some tumour types (previously called ‘entities’), the relevance of this grading scheme has been gradually eroded by the discovery of prognostically relevant markers and by advancements in the understanding of tumour pathogenesis. For example, a diffusely infiltrative glioma appearing histologically low-grade can sometimes represent an incompletely sampled, or an early manifestation of, glioblastoma, IDH-wildtype CNS WHO grade 4 and, based on molecular findings, will be correctly diagnosed as such even in the absence of high-grade histological features.[1,68,72] Similarly, the grading of IDH-mutant astrocytoma incorporates the histological appearance and, in addition, the presence of loss of genetic material on the CDKN2A/B locus.[1,64,73,74] Molecular features – such as homozygous deletion of RB1,[74] amplification of the *CDK4* or *PDGFRA* genes,[75] MYCN amplification[74] or presence of chromosomal copy number changes (gains and losses over 350 megabases),[74] or chromosome 14 loss[76] – can provide a useful indication of a biological risk for recurrence, but these are currently not formally recognised as grading criteria in the 2021 WHO classification.

To aid the diagnostic process and to advise on how and when to test intrinsic brain tumours with molecular markers, see Appendix G for guidance.

[Level of evidence A – Molecular investigations have an established role in the diagnosis and management of CNS tumours.]

7.2 Molecular biomarkers

The genomic and epigenetic analysis of brain tumours has made considerable progress towards improved understanding of the pathogenesis of brain tumours and contributes to their evidence-based classification. Molecular markers of diagnostic or prognostic relevance continue to be discovered. It is not the purpose of these guidelines to provide a comprehensive review, but to summarise and provide guidance for the use and integration of clinical parameters (age, tumour 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 molecular tests, either with surrogate IHC or nucleic acid analysis, for accurate classification. Information about necessary further molecular work-up should be integrated in the preliminary report. Subsequently, all performed molecular results should be added in the final integrated diagnostic report, with diagnostically relevant molecular findings described in the integrated diagnosis. Such reports may require supplementary data, sometimes in several iterations. It is, therefore, essential that the planned diagnostic work-up is discussed in the preliminary reports and with the oncology MDT to manage expectations and guide treatment decisions.

The most common alterations of relevance for an integrated diagnosis of CNS tumours are (i) *single nucleotide variants* (SNV) (often colloquially referred to as point mutations), (ii) *small insertions/deletions* (InDels) and (iii) *gains or losses of chromosomes or chromosomal arms*. In diagnostic practice, these alterations are interrogated with single gene sequencing or with NGS panels.

Gene fusions are the result of chromosomal rearrangements, and one partner of such fusions often is a receptor tyrosine kinase. The fusion event often maintains kinase activity with constitutive activation and augmentation of a downstream signal. Tyrosine kinase fusions have been identified across various cancer types, including *ALK, ROS1, RET, NTRK1/3* and *FGFR1/2/3*.[77,78] Serine-threonine kinase fusions are those involving for example BRAF.[77,78] Many of these genes can bind to one of several partners, though some have a clearly preferred partner (e.g. *KIAA1549::BRAF* in pilocytic astrocytoma).[79]

An alternative mechanism of oncogenesis is conferred by aberrant transcription, by which a chimeric protein can transform cells through a fusion that includes a TF. For example,

the *EWSR1–FLI1* translocation results in a protein that can bind to DNA and alter transcription.[80]

Specific fusions can be identified at low frequencies across many cancer types, but they are typically enriched in certain CNS tumours such as BRAF fusions in pilocytic astrocytoma, *FGFR1* in DNET, *FGFR1* or *FGFR3* fusion in extraventricular neurocytoma, *FGFR2* in multinodular and vacuolated neuronal tumour. Other known alterations are tyrosine kinase duplication and internal tandem duplication.[81] Kinases are ideal targets for directed therapy; several inhibitors are routinely used in the treatment of cancers harbouring such fusions.[82]

While fusions can be technically detected by DNA sequencing, most fusion breakpoints are in regions not covered by NGS panels (introns); current bioinformatics tools are not yet sufficiently sensitive. Therefore, additional tests (RNA sequencing, FISH or reverse transcriptase (RT) PCR analysis) are needed when specific fusion partners are suspected. Overall, the method of choice is RNA sequencing, either targeted or whole transcriptome. Targeted RNA sequencing achieves higher sensitivity and requires less input material and simpler bioinformatics analysis tools, rendering it particularly attractive for diagnostics in clinical practice.

[Level of evidence A – Molecular investigations have an established role in the diagnosis and management of CNS tumours.]

7.3 Molecular test methods: overview

This subsection gives an overview of the utility of selected molecular tests that form the backbone of most of the molecular work-up of CNS tumours. It describes the use cases and pitfalls of the respective techniques/technologies and provides guidance for their use in CNS tumour diagnostics.

7.3.1 Single target analysis: Sanger sequencing

Sanger sequencing is a widely used method for DNA sequencing, suitable for the analysis of relatively short DNA segments (100–1,000 bp).[83] The sensitivity of mutation detection by Sanger sequencing is lower than that of other sequencing methods. Clinical DNA sequencing is currently performed by capillary-based, semiautomated Sanger sequencing. DNA is usually prepared by PCR amplification of a region of interest (generating an amplicon). It is unlikely that substantial further increases in throughput or decreases in cost

will be possible with Sanger sequencing because of its dependence on lengthy procedures.

[Level of evidence A – The utility, strengths and limitations of Sanger sequencing are firmly established.]

7.3.2 Next generation sequencing

NGS overcomes the limitations of single target Sanger sequencing and allows for the sequencing of many gigabases more quickly and economically than with Sanger sequencing. NGS can detect minor alleles more accurately and the 'digital' nature of NGS means that the number of times any DNA segment is sequenced is proportional to the relative abundance of that segment compared to the other segments in the original sample. Thus, when a sample is sequenced to sufficiently high depth, the copy number of any segment can be inferred from the frequency with which that segment is found among the molecules sequenced.[84] NGS commonly used in clinical diagnostics covers a 'gene panel' within a single analysis; 'molecular barcoding' allows for multiplexing and, thus, processing of several samples in parallel.

Technically, regions of interest can either be amplified by primers (amplicon-based) or enriched by hybridisation to probes designed to bind these regions (hybrid-capture). Amplicon-based tests are used for smaller panels, typically in the range of 20–50 genes. Hybrid-capture panels can cover several mega-bases and are also used for whole exome sequencing (WES). Sensitivity to the detection of mutations is generally similar for both methods. The amplicon-based approach is better suited for mutations occurring at very low abundance. However, the PCR amplification steps may obscure subtle copy number differences. For both approaches, sensitivity depends on tumour cell content and DNA quality and also on the read depth of subsequent sequencing, i.e. the unique sequence coverage.

NGS can inform of copy number variations (CNVs), by inferring large variations from the 'average' baseline or by assessing the variant allele frequency of SNVs.

WES or WGS are increasingly considered, but the costs at the time of this dataset are still prohibitive for a rollout into routine clinical practice. A further limitation of WGS in clinical pathology practice is the requirement of fresh/frozen material and necessity of relatively intensive bioinformatics support. The detection of many SNVs and InDels results in considerable workload for variant interpretation. In adults, sequencing of non-neoplastic reference tissue (containing germline DNA, most commonly blood leucocytes) is

considered non-mandatory for the identification of the most relevant somatic changes, since subtraction of general population SNVs/InDels is often sufficient, at least in target sizes <1 Mb; however, NHS England currently requires matched blood-derived DNA for WGS.

Interpretation of the relevance of identified variants should follow guidelines. The Clinical Genome Resource (ClinGen), the Cancer Genomics Consortium (CGC) and the Variant Interpretation for Cancer Consortium (VICC) have recently published a guideline on the classification of somatic variants in cancer.[85]

[Level of evidence A – The utility, strengths and limitations of DNA NGS are firmly established.]

7.3.3 Next generation RNA sequencing

RNA sequencing has become a valuable tool for the detection of gene fusions.[82] Targeted and whole transcriptome RNA sequencing are the main methods to detect gene fusions.[86] For clinical diagnostic applications, targeted RNA sequencing is often the technique of choice. It can achieve a higher sensitivity than whole transcriptome sequencing, even at lower sequencing depth. It requires less input material and benefits from simpler bioinformatic analyses. Whole transcriptome sequencing can identify fusion partners of predefined and novel fusion genes and is, therefore, an advantage in research settings as it also requires computational skills to interpret data.

Bioinformatics tools can detect gene fusions but there can be technical difficulties (e.g. fusion transcripts cannot be mapped to a standard transcriptome, and/or sequencing artefacts), which reduce detection sensitivity. Analysis tools are continuously improving. Their efficacy can vary depending on the specific analytical workflow, making it difficult to define a single most effective pipeline.[87,88] Several studies have discussed the efficacy of RNA sequencing to detect gene fusions in CNS tumours.[89,90] RNA sequencing can also identify intergenic rearrangements and deletions (such as EGFRvIII). SNVs and InDels may also be detected by RNA sequencing when present at sufficiently high levels, but DNA NGS is the method of choice for these. A technical limitation of all RNA-based technologies is the sensitivity to RNA degradation in FFPE tissue samples or frozen samples with delayed snap-freezing time.[91]

[Level of evidence A – The utility, strengths and limitations of RNA-NGS are firmly established.]

7.3.4 DNA methylation arrays

The introduction of genome-wide DNA methylation profiles has greatly contributed to a more precise CNS tumour classification,[92] often in combination with the DNA copy number profile derived from the same array.[93]

Methylation profiling can:

- establish a methylation class (often a surrogate for a diagnosis) for histologically ambiguous tumours in adult[30,94,95] and paediatric patients[96,97]
- subclassify or risk stratify established tumour types, such as ependymoma,[98–100] medulloblastoma[101–105] or meningioma[106,107]
- be useful as a diagnostic tool for very small biopsies.[30]

CNS tumours stratified by methylation profiles are generally more homogenous than those of tumours classified by histology alone.[94,108]

The use of methylome-based diagnosis requires the neuropathologists to have the knowledge to integrate data (methylation classification and copy number profile) and to interpret the results for their clinical relevance (e.g. risk prognostication of meningiomas).

The technology used for methylome-based tumour classification is currently based on hybridisation of bead chip arrays from a single supplier (Illumina). The processing of the methylation data requires a classification tool. Currently, the DKFZ/Heidelberg classifier for CNS tumours is the gold standard (www.molecularneuropathology.org),[92] although alternatives based on the same principle have been established to address accreditation issues[109] or to refine classifications.[95]

The DKFZ/Heidelberg classifier uses calibrated classifier scores to indicate likelihood of the assignment of a tumour to a distinct methylation class,[92] with classifier scores >0.9 indicating a significant match. Lower calibrated classifier scores need to be interpreted with caution and may not be reliable indicators of a certain diagnosis but can still provide useful guidance when integrated with results from orthogonal tests.[93,95]

This technology enables more accurate, reliable and reproducible diagnosis. It has, therefore, been recommended in WHO CNS5 for the diagnosis of selected tumour types,[1] such as high-grade astrocytoma with piloid features or the posterior fossa ependymoma, type B.

However, the use of the DNA methylome classifier requires caution and awareness of potential pitfalls.[95]

Methylation profiling often is a surrogate test for certain mutations, such as IDH mutations, or histone mutations, but the test method does not directly identify them. Confirmation of the specific mutation still requires DNA sequencing (see above), for example when different mutations (comprised within the same methylation class) are associated with distinct outcomes, e.g. H3.3, H3.1 or H3.2 K27-altered diffuse midline gliomas.[41] Likewise, the identification of the methylation class of an IDH-mutant astrocytoma does not specify the precise IDH1 or IDH2 mutation, i.e. it would require an orthogonal test method (such as DNA sequencing, e.g. single gene Sanger sequencing or NGS) to confirm the specific gene mutation.

Technical and operational risks include (i) sample mix-up, (ii) low DNA amount, (iii) poor quality DNA, (iv) high content of native CNS tissue or presence of inflammatory cells. It is recommended to process reasonably distinct tumour entities on each chip (currently 8 samples per chip). Results that cannot be reconciled with patient sex, histology, location or clinical presentation will require repeat investigation.

Interpretational pitfalls arise from incorrect classification results due to low tumour content, e.g. admixture of CNS tissue, inflammatory cells, tumour recurrences/post-radiotherapy, and tumours arising in genetic tumour syndromes. Generally, low-grade glial and glioneuronal tumours can be difficult to classify with the current algorithms.[110] CNVs are returned as part of the readout from the methylation array (or from long-read WGS),[111] and can complement the diagnosis, provide additional confidence in establishing a diagnosis when the methylation profile is returned with a low calibrated score,[93] or form part of a prognostication algorithm, such as in meningiomas.[112] Therefore, CNVs, including specific gene deletions or amplifications, should also be included in the report, if diagnostically relevant. Gene duplication and/or gene fusions can sometimes also be inferred from the plot,[113] but may need confirmation by other methods. Low amplitudes of CNVs may indicate low tumour cell content or clonal heterogeneity in the investigated tissue sample.

No formal recommendations currently exist to report methylome data. It has been suggested that pathology reports should contain the following information, but centres may individually decide on whether some of these items are necessary, as not all of them can be quantified:

- estimated tumour cell content of the extracted DNA (difficult to quantify, therefore optional)
- amount of DNA input (optional)
- estimated tumour cell fraction (difficult to quantify, depends on macro dissection and visual estimate)
- quality of bisulphite conversion (data returned with chip readout and can be reported quantitatively, may be relevant only for low calibrated scores or scattered copy number plot)
- CNS tumour classifier version(s) used (mandatory)
- highest scoring methylation category with the respective calibrated score(s) (mandatory)
- sub-classification with score(s) if applicable (mandatory).

In addition to the DNA copy number profile[111] and assignment to distinct methylation families, classes and subclasses, the DKFZ/Heidelberg classifier provides the *MGMT* promoter methylation status based on a specific algorithm.[114] Generally, there is good concordance with other methods of targeted assessment of *MGMT* promotor methylation;[115,116] however, there is currently no consensus on which testing method best predicts response to alkylating agent chemotherapy.[117]

For samples with low tumour content and a high proportion of admixed non-neoplastic cells such as inflammatory cells or normal tissue, methylation arrays are not the best first line diagnostic approach. NGS has a higher sensitivity and may also return diagnostically useful information from samples with low tumour cell content. In particular, NGS may be prioritised over methylation profiling for very small samples with low tumour content.

[Level of evidence A – The utility, strengths and limitations of methylation arrays in the diagnosis of CNS tumours are firmly established.]

7.4 Application of molecular markers in adult diffuse gliomas

7.4.1 IDH-mutant gliomas

The 2016 updated 4th edition of the WHO classification paved the way to a biomarker-based classification of oligodendrogliomas and astrocytomas. These tumours share mutations in the isocitrate dehydrogenase gene 1 or 2. Further molecular features have been identified to help grading (and thus prognosticating) IDH-mutant astrocytomas.

7.4.2 IDH-mutant astrocytomas

Astrocytomas are defined by an *IDH* mutation that is usually associated with a loss of expression of the nuclear protein ATRX, caused by a mutation in the open reading frame of the *ATRX* gene. However, a small proportion of IDH-mutant astrocytomas have silent *ATRX* mutations with retained ATRX protein expression.[118] 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,[73] may help to further clarify the molecular profile. This can be useful if 1p/19q testing fails. Test failure is a recurring problem with FISH or quantitative PCR methods. DNA methylation profiling is a robust method for IDH-mutant astrocytomas as it returns a copy number profile that confirms or excludes 1p/19q codeletion along with the methylation class output.

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,[73,74] IDH-mutant astrocytomas with histological low-grade features and no CNVs including absence of *CDKN2A/B* homozygous deletion have the best prognosis. Tumours with absence of *CDKN2A/B* deletion but high copy number variation load (CNVL) and/or presence of necrosis (irrespective of other histological features of malignancy) have an intermediate prognosis and have been described as CNS WHO grade 3. The split ('watershed') between lower risk and higher risk for recurrence was determined at approximately 350 mega-bases; this value (as some of gains and losses across the chromosomal profile) can be determined from the copy number profile derived from the methylation array.[74] IDH-mutant astrocytomas with a *CDKN2A/B* homozygous deletion have the highest risk of recurrence; this deletion mandates CNS WHO grade 4, as stipulated in the cIMPACT-NOW recommendations[64] and formalised in the WHO CNS5 grading scheme.[1]

In addition, there are several other genetic alterations which have been associated with higher malignancy and shorter recurrence. These are (i) homozygous deletion of RB1,[74] (ii) amplification of the *CDK4* or *PDGFRA* genes,[75] (iii) *MYCN* amplification,[74] (iv) *MET* amplification[119] and (v) the above-mentioned chromosomal copy number changes, with a 350 mega-base 'watershed' of combined gains and losses[74] and (vi) chromosome 14 loss.[76] These alterations all can provide a useful indication of a biological risk for recurrence, but there is currently insufficient clinical and epidemiological evidence to include them as criteria for CNS WHO grade 4 IDH-mutant astrocytomas.

The addition of molecular features as grading criteria now requires more extensive work, but at the same time provides neuropathologists with greater confidence in grading astrocytomas by complementing morphological features with molecular evidence.

DNA methylation array analysis is a useful method for comprehensive work-up of IDH-mutant astrocytoma, which not only returns the corresponding methylation class, but also a copy number profile that can be visually inspected and informs of chromosomal CNVs, including incipient *CDKN2A/B* loss, which can be taken as an indication of loss of genetic material in this locus in a subpopulation of tumour cells. It can provide helpful guidance to oncology teams to support decision-making in adjuvant treatment and to put incipient contrast enhancement into better clinical context.

Notably, in rare instances, the current version of the Heidelberg DNA methylation classifier can incorrectly return the methylation class of astrocytoma, IDH mutant, in cases with 1p/19q codeletion, which must be reported according to the copy number profile.

NGS technologies can also return a copy number profile and can be used to report chromosomal gains and losses. NGS, however, does not return a methylation class and copy number changes (in particular their quantification) and is not always validated in the reporting laboratories. The advantage of NGS for the diagnosis of IDH-mutant astrocytomas is the simultaneous detection of the IDH mutation, in particular if the tumour carries a mutation not detected by IHC, and to identify *p53* gene mutations and losses and *ATRX* mutations when ATRX nuclear expression is retained.

[Level of evidence A, B – Diagnostic criteria for IDH-mutant astrocytoma are firmly established (IDH, ATRX, p53, CDKN2A/B) but some molecular data (CDK5, MYCN, etc) require further validation in larger prospective studies.]

7.4.3 IDH-mutant and 1p/19q-codeleted 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, particulary in gliomas with astrocytic and oligodendroglial features on H&E-stained sections. All IDH-mutant and 1p/19q codeleted oligodendrogliomas retain nuclear *ATRX* expression (but see the astrocytoma section 7.4.2 above for the caveat that not all ATRX mutations lead to a loss of protein expression). *TERT* promoter mutation, which is nearly always mutually exclusive with ATRX loss, is an additional useful marker that can help diagnose oligodendroglioma in

cases where the 1p/19q test is ambiguous. As for astrocytomas, also in oligodendrogliomas the grading is based on the morphological assessment, but there are less well-defined molecular biomarkers that could aid grading and prognostication.

The loss of the histone H3 trimethylation at position K27 cannot be used as a surrogate marker, as its expression can be highly variable, even within individual tumours.[120,121] Mutations in the CIC gene (located on chromosome 19q13.2) have been identified in approximately 70% of oligodendrogliomas[122] and mutations in the FUBP1 gene in around 20–30% (chromosome 1p31.1, i.e. within the chromosomal region that is consistently lost). 1 study has shown that the combined loss of *CIC* and *FUBP1* is associated with earlier progression;[123] several molecular alterations are associated with CNS WHO grade 3, such as loss of *CDKN2A/B*,[124] *PIK3CA* mutation,[125] *TCF12* mutation,[126] or increased MYC signalling, including *MYC* amplification.[127]

With the now relatively widespread access to and availability of methylation array technology and NGS in the UK, such as in England through the GLHs, there is an increasing use of these techniques in the diagnostic approach of diffuse gliomas, which also includes oligodendrogliomas. Methylation profiling is a relatively comprehensive and usually technically robust method that conveniently combines the tumour classification (methylome) and copy number assay (1p/19q codeletion). In addition, the copy number profile also reveals many other alterations, including the above-mentioned *CDKN2A/B* deletion and generally copy number profiles, although the CNVL (see the astrocytoma section 7.4.2) has not yet been defined to stratify for survival. DNA NGS can complement the diagnostic work-up for oligodendrogliomas but, given the often less well-validated copy number readout, this may not be the first choice for the initial work-up, but can provide additional information of SNV such as *CIC* and *FUBP1*.

[Level of evidence A, B, C – Diagnostic criteria for oligodendroglioma are firmly established (IDH, 1p/19q co-del) but some molecular data (CDKN2A/B, H3 K27me3, etc) require further validation in mechanistic and larger prospective studies.]

7.4.4 IDH-wildtype glioblastomas

It is important that neuropathologists convey information about IDH-wildtype gliomas clearly and consistently to clinical teams. IDH-wildtype glioma encompasses all gliomas without an IDH mutation. In clinical communications, this may at times be incorrectly referred to as IDH-wildtype glioblastoma. It is increasingly recognised that early, i.e. non-enhancing diffuse gliomas that correspond molecularly to glioblastomas, have

characteristic imaging properties.[128,129] These tumours have previously been diagnosed as IDH-wildtype astrocytomas (previously WHO grade II or III).[130,131] The correct nomenclature, IDH-wildtype glioblastoma despite the lack of histological high-grade features, has been proposed[68] and is now established in the 2021 CNS WHO classification.[1]

A study with a large sample cohort demonstrated that IDH-wildtype astrocytomas often represent as either incompletely sampled or early stages of glioblastoma.[72,132] A common molecular feature of IDH-wildtype glioblastoma and its precursor forms, i.e. non-enhancing tumours with morphological appearance of diffuse lower grade glioma, is gain in chromosome 7 and loss of chromosome 10.[133] Up to 50% of IDH-wildtype glioblastoma have *EGFR* amplifications, which are exceedingly rare in IDH-mutant astrocytomas or other brain tumours.[30,133] Therefore, *EGFR* amplification is a useful diagnostic marker, particularly in small, non-representative biopsies or early manifestations of *IDH*-wildtype glioblastoma. Likewise, *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 glioblastoma). For small, diagnostically ambiguous biopsies, methylation profiling is the method of choice to demonstrate the corresponding methylation class (glioblastoma, IDH-wildtype) and to additionally demonstrate chromosome 7 gain, chromosome 10 loss and sometimes EGFR amplification. Owing to the multiple readouts from methylation arrays, this method may be superior to NGS,[92] which may identify a TERT promoter mutation as the only pathological alteration or, if additional mutations are identified, indicate that these are not specific characteristics for IDH-wildtype glioblastoma but may also be found in many other glial tumours.[134]

[Level of evidence A – Diagnostic criteria for IDH-wildtype glioblastoma are firmly established.]

7.4.5 Midline gliomas

A significant milestone in the understanding of the biology of midline tumours was the identification of histone H3 K27M mutations.[135] This led to the adoption of H3 K27M-mutant diffuse midline glioma as a molecularly defined entity in the 2016 update of the WHO classification[130] and in the CNS WHO 2021 classification (now referred to as diffuse midline glioma, H3 K27-altered).[1]

The development of a mutation-specific antibody led to the discovery of (extremely rare) other tumour types that can also carry an H3 K27M mutation, such as posterior fossa ependymoma[136] pilocytic astrocytoma, or ganglioglioma.[137–139] Despite being H3 K27M-mutant, these tumours are not considered diffuse midline glioma; the cIMPACT-NOW recommendations specify that the diagnosis of diffuse midline glioma, H3K27M mutant, requires a midline location of the tumour and diffuse glioma morphology, in addition to presence of H3K27M mutation. Tumours that do not meet all 4 of these features should not be diagnosed as such, even if they have an H3K27M mutation.[66]

The use of antibodies against H3 K27M (positive nuclear labelling in the tumour cells) and H3 K27me3 (loss of expression in tumour cell nuclei) is a highly sensitive and specific approach to diagnose diffuse midline gliomas.[140,141] Antibodies against H3 K27me3 are of diagnostic utility for midline gliomas with the K27I or EZHIP overexpression, showing loss of nuclear H3 K27me3 immunostaining and should be further evaluated by molecular analyses (Appendix G).[45]

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; NGS is the most convenient and sensitive method. Varied frequency of ATRX loss of expression has been reported for H3 K27M tumours. It has been suggested that the rate of ATRX loss in these tumours increases with age.[140] Several paediatric series reported ATRX loss in 10–25% of H3.3 mutant tumours,[41,140] while ATRX loss was reported in more than 40% of H3 K27M mutant gliomas in an adult series. [30]

[Level of evidence A – Diagnostic criteria for H3 K27M-altered midline gliomas are firmly established.]

7.4.6 Gliomas with BRAF mutations and other MAP kinase pathway activation

The family of brain tumours with mitogen-activated protein (MAP) kinase activation is diverse, encompassing low-grade and high-grade CNS tumours. Many of the tumours with MAP kinase activation have 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).[142] Other genes in the MAP kinase pathway are *FGFR*, *NTRK*,

MAP2K and *NF1*.[79,81,143] Other tumour types with MAP kinase pathway alterations include diffuse low-grade glioma, MAP kinase pathway altered. Subtypes include diffuse low-grade glioma, *FGFR1* TKD–duplicated or FGFR1-mutant,[144] and diffuse low-grade glioma, BRAF p.V600E–mutant,[65] DNET, rosette-forming glioneuronal tumour,[145] high-grade astrocytoma with piloid features,[146] desmoplastic infantile ganglioglioma[147] and extraventricular neurocytoma.[148] The assessment of gene mutations in the MAP kinase pathway, in particular the *BRAF* V600E mutation, is important for diagnosis and for identifying potential therapeutic targets.[149]

BRAF mutations are detectable with a mutation-specific antibody,[42,150] but the much wider coverage of multiple mutations with NGS may reduce the diagnostic utility of this antibody, particularly as the staining in brain tumours is not always sufficiently strong.

[Level of evidence B – Diagnostic criteria for BRAF/MAPK are a molecular determinant of a range of tumours, some requiring larger studies to establish role for prognostication and therapy.]

7.4.7 Ependymal tumours

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.[100] Independently conducted genomic profiling efforts have identified clinically and molecularly distinct subgroups of ependymoma arising from the spinal, posterior fossa and supratentorial CNS compartments.[98,100] It has been recommended that molecular subgrouping of ependymomas should be part of all clinical trials. Distinct genetic alterations in supratentorial ependymomas include either *ZFTA* or *YAP* fusions.[151] p65 immunostaining is a useful surrogate marker for identifying *ZFTA*-fused ependymomas and universal cytoplasmic expression of L1CAM, although the latter has been found to have a slightly lower specificity for this molecularly defined ependymoma.[152]

Infratentorial ependymomas of molecular subtypes A and B can be discriminated with immunostaining for trimethylated histone H3 K27me3.[45] Spinal ependymomas need molecular work-up to identify an aggressive subset, characterised by *MYC-N* amplification.[99] While the majority of spinal ependymomas show favourable outcomes, several epidemiological studies have reported a subset of patients with highly aggressive disease and poor survival.[153,154] These cases were often diagnosed as anaplastic ependymoma WHO Grade 3 (Grade III at the time) and it is likely that these represented spinal ependymoma, *MYCN*-amplified.[99] The clinically favourable subependymomas occur

in all 3 anatomical compartments. Methylation profiling, however, is particularly recommended for posterior fossa subependymomas, as these can have distinct molecular alterations, with a *TERT* promoter mutation and chromosome 6 loss, and represent a high-risk subtype of ependymoma evolving from posterior fossa subependymoma.[155]

[Level of evidence A, B – Molecular diagnostic criteria for ependymal tumours are firmly established. Criteria for prognostication of subtypes requires additional clinical trials to reach evidence level A.]

7.4.8 Other intrinsic tumours with low-grade histological features

In addition to the low-grade glial and glioneuronal tumours described above (MAP kinase pathway activation), there is a wide range of glial and glioneuronal tumours with activations and pathways other than MAP kinase signalling. Many of these have varied histological presentation. It has been recognised that these tumours form more homogeneous molecular groups or groups based on a gene alteration alone.[156] Owing to the wide differential diagnostic spectrum, these tumours particularly benefit from methylation array technology supplemented by further genetic testing.[65] The detailed descriptions of all these tumour types is beyond the scope of this dataset; we recommend referring to the CNS WHO classification or primary literature.

[Level of evidence A, B – Molecular diagnostic criteria for some low-grade tumours are firmly established. Criteria for diagnosis of some subtypes requires additional studies to reach evidence level A.]

7.4.9 Other intrinsic tumours with high-grade histology

A proportion of high-grade intrinsic tumours can present with poorly differentiated histological features. Although the majority 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 wider spectrum of intrinsic high-grade neoplasms, most of which are now based on studies involving methylome profiling and NGS, molecularly defined.[105,157] Medulloblastomas occur predominantly in children and tail off in the adult population; adequate profiling can help classify them into molecular subgroups.[158] The benefit of methylation profiling, often in combination with NGS, is also evident in adult high-grade tumours. In such challenging cases, priority should be given to molecular techniques instead of attempting a tissue-consuming work-up with more than the essential immunostains.

[Level of evidence B – Molecular characteristics for recently characterised high-grade gliomas require additional studies to reach evidence level A.]

7.4.10 Application of molecular markers in adult extrinsic tumours

Meningiomas account for approximately a third of all intracranial and spinal neoplasms; 80% of meningioma patients can be cured by surgery alone. The limitation of the WHO criteria for morphological grading is that they are subject to some degree of inter and intra-observer bias and the established grading criteria have limited predictive value.[107,159] Mutations in the *TERT* promoter,[160] CDKN2A/B deletion[161,162] and loss of histone H3 K27me3[163] have been identified as risk factors for accelerated tumour progression and increased risk of recurrence. A classification tool based on methylation array data identified 6 molecular subclasses in meningiomas (3 benign, 2 intermediate and 1 malignant subclass).[164,165] These were subsequently combined with prognostically informative chromosomal losses, resulting in integrated risk scores incorporating CNS WHO grade, methylation class and copy number profile in a non-linear scale.[107,112,166] Together with the *CDKN2A/B* status derived from the methylation arrays, this integrated risk score provides additional information of recurrence risk.

[Level of evidence B – Molecular characteristics for the prognostication are well established, but consensus of a unified prognostication scheme is required to reach evidence level A.]

Solitary fibrous tumours (SFT), previously referred to as haemangiopericytomas, were notoriously difficult to diagnose. The lack of robust and discriminatory biomarkers contributed to inter- and intra-observer variability. The discovery of the *STAT6-NAB1* fusion gene product in SFT[167] has now practically eliminated these challenges and firmly established the utility of immunostaining for STAT6 protein (specifically its translocation from cytoplasm to nucleus in SFT) in identifying SFT.[46] Histological grading of SFT remains according to criteria set out in the CNS WHO classification.

[Level of evidence A – Molecular characteristics for the diagnosis of SFT are now well established.]

7.4.11 Diagnostic aspects of neuroendocrine and non-neuroendocrine pituitary tumours

Nomenclature

In the 5th edition of the *WHO Classification of Tumours of the Endocrine Organs* (ENDO5), the International Agency for Research in Cancer recommends the adoption of

the combined definition of PitNET/adenoma preceded by the type or subtype of the tumour (e.g. sparsely granulated somatotroph PitNET/adenoma). This terminology is intended to align adenohypophyseal tumours with the other neoplasms of the neuroendocrine system and to reflect their unpredictable clinical and biological behaviour.[6,168,169] Adenoma, in fact, defines a non-invasive, benign lesion of an epithelial origin that does not cause any or only little morbidity and does not impact on life expectancy.

WHO CNS5 included a chapter on anterior pituitary tumours, with the rationale that they are operated on by neurosurgeons and diagnosed by neuropathologists but still use the term ‘adenoma’, rather than PitNET.

A unified definition for tumours of the neurohypophysis as variants of pituicytoma based on the common expression of TTF-1 and ultrastructural similarities with normal pituicytes does not fully account for the spectrum of their clinical, neuroimaging, immunoprofile and molecular features. A diagnosis of ‘TTF-1 expressing tumour of the neurohypophysis with features of…’ followed by the defining morphological features therefore appears more appropriate.

The nomenclature of the other tumours affecting the sellar region has not changed since the previous RCPath dataset.

Structured diagnostic report

A formatted or a combined formatted and synoptic report is encouraged to improve diagnostic standardisation and data collection, rather than a narrative report. Structured reports offering pre-set options might limit the description of pathological features, given the heterogeneity encountered in PitNET and non-neuroendocrine pituitary tumours. An effort towards standardisation of neuroimaging, surgical, clinical and pathological reports has been advocated to improve a multidisciplinary approach to patients with pituitary tumours and their risk of tumour recurrence stratification, in view of the development of pituitary centres of excellence.[25,170–172]

It is advisable to add the essential clinical history and the description of neuroimaging to the neuropathology report. The speed of growth and extent of involvement of parasellar structures have considerable prognostic implications and can help the interpretation of pathological features in cases of suspected aggressive tumour.

The distinction between staging and grading is often a source of confusion in pituitary pathology. Neuropathologists are not in the position to stage a pituitary tumour and no reproducible, validated grading system based on pathological features is available. The

stratification proposed by Trouillas and colleagues[173] is best regarded as a scoring, rather than a grading, system.[174]

The report template suggested by the European Pituitary Pathology Group can be applied for the diagnosis of PitNETs.[49] Other formatted reports have been proposed.[175–179]

Notably, none of the sellar tumours are included in the ICCR list of synoptic reports.

Diagnostic approach

PitNETs should be assessed with the full panel of pituitary hormones, lineage-restricted pituitary TFs TPIT, PIT1 and SF1, MIB-1 (Ki-67). The utility of GATA3[51] is described below. Although the antibodies directed against TFs have been extensively validated, they cannot replace the use of pituitary hormones owing to the variability of their expression.

Some PitNET are defined as triple negative based on absent TF expression but can still express pituitary hormones and GATA3. The very rare ‘null cell’ tumours also lack expression of hormones but still retain GATA3.[51] In these rare cases, the possibility of another primary sellar tumour, such as paraganglioma, neurocytoma or a metastatic tumour, should be considered. A broader repertoire of immunomarkers, including synaptophysin and chromogranin, S100, TTF-1 and cytokeratin, is recommended to prove the neuroendocrine phenotype of the lesion and its origin from adenohypophyseal cells.

SF1 may be weak or negative in gonadotroph tumours with oncocytic change. Some clinically non-functioning corticotroph tumours show weak and focal TPIT expression. It is worth mentioning that TPIT appears to be sensitive to delayed fixation or hypoperfusion secondary to surgical deafferentation of vessels feeding the tumour.

Cytokeratin has a role in the diagnosis of the spectrum of somatotroph tumours and PIT1 plurihormonal and corticotroph tumours, particularly those corticotropinomas with weak expression of ACTH and TPIT.

Rare PitNETs show intermediate differentiation. Silent, clinically non-functioning corticotroph tumours can show TPIT and GATA3 co-expression. Somatotroph tumours, mainly GNAS wildtype, co-express PIT1 and SF1 but lack LH and FSH beta subunits.

The definition of plurihormonal PitNET remains vague as a cut-off for each hormone-expressing population has not been defined. A minimum expression of 10% seems reasonable.[6,48] Those tumours showing 2 TFs without expression of the corresponding hormones are best described as multi-lineage.

The clinical term non-functioning should be avoided in neuropathology reports but a comment suggesting the possibility of a clinically silent tumour may corroborate the diagnosis.

A quantitative approach to mitotic activity and Ki-67 labelling index is recommended, with the specification of methodology for quantification and the count in mm^2 or high-power fields. The measurement of all neoplastic cells stained for Ki-67 in two hotspots regardless of staining intensity for a total of 500 to 1,000 cells per hotspot reflects the quantification of Ki-67 for neuroendocrine tumours of other sites.[6,48]

Ancillary immunostains include somatostatin receptor 2a and 5, when requested by clinicians in treatment refractory tumours. SDH A and B and menin, when available, may help identify syndromic tumours. Given the financial pressure on departments and the strict validation expected by the accreditation bodies, outsourcing of these immunostains is probably more cost effective.

Genome-wide DNA methylation arrays can resolve the diagnosis of cases with weak or focal, equivocal or even lack of expression of TFs and/or pituitary hormones.[180] For instance, triple negative, hormone negative, ‘null cell’ tumours almost always cluster with gonadotropinomas and less commonly with corticotropinomas.

Multi-omics studies identified 3 subtypes of corticotroph tumours based on USP8 and USP48 status; 2 subtypes of somatotroph tumours exist when combining transcriptome and GNAS status. A subset of sparsely granulated somatotroph tumours is clustered in the same transcriptomic group of thyrotroph and plurihormonal PIT1-lineage tumours.[181] A subtype of TRIM65-altered corticotroph tumours show very low to absent ACTH and weak TPIT and are, therefore, difficult to recognise and distinguish from other clinically silent corticotropinomas.[182]

Despite the above advances in the molecular characterisation of PitNETs, reports integrating morphological features and molecular profile have not yet entered diagnostic practice in pituitary pathology.

[Level of evidence A – Molecular characteristics of PitNET are firmly established and form part of the WHO classification.]

The definition of aggressiveness of PitNET

According to the guidelines of the European Society of Endocrinology, the definition of aggressive PitNET requires the integration of clinical, neuroimaging and pathological features.[183,184]

The term ‘aggressive’ should not be used in neuropathology reports. Similarly, terms such as ‘refractory’ or ‘resistant tumour’ should be avoided as they define lesions unresponsive to treatment,[185] rather than defining a set of microscopic features.

Importantly, the evidence that tumour type and subtype such as immature PIT1-lineage tumours, silent corticotroph and Crooke’s cell tumours have prognostic and predictive value is not fully validated. Neuropathologists should neither comment on potential aggressive behaviour of tumour solely based on pathological features nor make any recommendations on treatment. Inappropriate comments in pathological reports often lead to overtreating lesions with very low risk of recurrence. Although Ki-67 is helpful, its relevance as a single prognostic maker is controversial. A cut-off of 10% is regarded as more informative on prognosis than the previously suggested 3% or 4%.[186]

The USP8 and USP48 status seems to be associated with a lower rate of tumour progression. Sequencing of these 2 genes is currently not routinely available at the GLHs that deliver molecular tests in the context of Genomic Medicine Service (GMS) in the NHS (England). Mutations in p53, BRAF and ATRX occur in USP8 and USP48 wildtype tumours and correlate with a worse outcome of corticotropinomas.[187–189] False positive immunolabelling of pituitary neuroendocrine tumours for BRAF V600E (Clone VE1) is discussed in section 5.6. Mutations in mismatch repair proteins have been associated with poor prognosis in patients with corticotroph tumours in Lynch syndrome.[190] SF3B1 altered prolactinomas can be unresponsive to medical treatment and behave more aggressively. No robust molecular markers have been identified for the other types and subtypes.[187,188]

If metastatic dissemination occurs, the tumour should be reported as ‘metastatic PitNET’, further specified by the tumour type and subtype rather than pituitary carcinoma.

The 5-tiered prognostic classification proposed in 2013 and validated by several independent studies can be used in neuropathology reports. This classification is based on presence or absence of invasion (1 or 2) and proliferative activity (a or b) (Ki-67 ≥3%, mitotic count >2/10HPF and p53 expression). As mentioned above, a cut-off of 10% for Ki-67 seems more robust,[186] while expression of p53 is not as relevant as previously suggested.[48] If accurately defined, 2b tumours represent about 8% of all surgical series

and show a 4- to 8-fold increased risk of recurrence and progression, irrespective of tumour type and subtype.

[Level of evidence D – Prognostic importance of Ki-67 index.]

Unsupervised transcriptome classification suggested that aggressive tumours are not characterised by distinct molecular signature and, therefore, do not constitute a separate group.[191] Therefore, the use of genome-wide DNA methylation arrays is not recommended for prognostic and predictive purposes.

Assessment of MGMT gene promoter methylation as routinely performed in neuro-oncology may not be as informative of the response to temozolomide as it is in patients with glioma.[192,193] However, *MGMT* promoter methylation status may be requested by clinical teams to guide salvage treatment in refractory, rapidly recurring PitNETs.

[Level of evidence D – MGMT promoter methylation based on clinical request.]

Assessment of TTF-1 expressing tumours of the neurohypophysis

Pituicytoma, spindle cell oncocytoma and granular cell tumour and, the most recent entity, primary papillary epithelial tumour of the sellar, share widespread, intense TTF-1 nuclear expression and similar epigenetic profiles. However, their immunoprofiles are different. Pituicytoma stains for GFAP and protein S100 but not for epithelial membrane antigen (EMA) and cytokeratin; spindle cell oncocytoma shows EMA and protein S100 expression; granular cell tumour strongly stains for protein S100; the rare primary papillary epithelial tumour of the sellar diffusely expresses cytokeratin but none of the other markers. Vasopressin is a useful marker to differentiate between infundibulum and pituicytoma in small biopsies.

No prognostic criteria have been identified but spindle cell oncocytoma has been reported to recur more frequently than the other neurohypophyseal tumours and even progress to an aggressive lesion. In this respect, the distinction of these tumours is of clinical relevance.

A recent multi-omics study identified a subset of pituicytomas and spindle cell oncocytomas that were enriched for pathogenic mutations in genes of the MAPK/PI3K pathways. Spindle cell oncocytomas demonstrate a higher rate of chromosome CNV than pituicytoma and granular cell tumour.[194]

Pituicytomas and granular cell tumours but not spindle cell oncocytomas can cause acromegaly and Cushing’s disease without expressing pituitary hormones or TFs.[194]

8 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.

9 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 of SNOMED CT. SNOMED ceased to be licenced by the International Health Terminology Standards Development Organisation from 26 April 2017. Histological grading of all tumours from the CNS and its coverings is as per criteria set out in the 2021 CNS 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.

9.1 International Classification for Disease-Oncology 4

With the new 5th edition of the Blue Books, the IARC WHO Classification of Tumours Group has started to create new codes. Owing to the lack of available codes for new morphological diagnoses in the current 4-digit morphology structure, it is proposed for the next International Classification for Disease-Oncology (ICD-O) edition (ICD-O-4) that a fifth digit will be added.

This approach, with the addition of a ‘0’ where there is no need for a more specific code, or other values if needed, was chosen for the ease of conversion and consistency with ICD-O-3 (like a MOTNAC to ICD-O-1 conversion). Adding an additional digit to the existing 4 retains the required consistency, including the possibility to collapse to previous versions, but will likely require minor changes in registry software, notification forms, etc.

As the previous IACR ICD-O Working Group has now concluded its work with ICD-O-3.2, IARC will establish a new working group with global representation, with terms of reference that focuses on the required planning for the implementation of ICD-O-4 in cancer registries worldwide.

10 Reporting of small biopsy specimens

The diagnostic approach needs to be carefully planned for any samples and, more specifically, for small, targeted biopsies from critical regions, such as eloquent areas in the cerebral hemispheres, intramedullary spinal cord, brainstem, thalamus and optic nerve. 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 and ancillary tinctorial stains (see also section 6.2),[195] to not exhaust the material and to preserve it for relevant molecular studies. Advanced molecular testing of small samples with methylation arrays,[92,93] if possible, also in combination with NGS, should be considered early during the diagnostic process, sometimes even as early as the stage of morphological evaluation (based on H&E impression). The use of ancillary markers, such as MAP2, vimentin, neuron-specific enolase and often also GFAP, synaptophsin or chromogranin can be counter-productive, as valuable tissue is being exhausted at the expense of material available for methylation array and NGS.

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 them for molecular tests. While DNA in tissue sections mounted on slides is reasonably stable, RNA degrades within weeks at room temperature.

11 Reporting of intraoperative biopsies

Either smear preparations and/or frozen sections may be used intraoperatively.[196] 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 on FFPE tissue and, where applicable, on

an integrated molecular diagnosis. 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.

12 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 2021 CNS WHO classification[1] (see Appendix B).

13 Criteria for audit

The following are recommended by the RCPath as key assurance indicators:[197]

- 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 are required to implement the structured recording of core pathology data in the COSD
- standard: 95% of reports must contain structured data.

Turnaround times and targets: The increasingly complex and multifaceted workup of neoplastic lesions of the CNS requires a tailored assessment of clinically useful and technically feasible turnaround times. Turnaround times should be defined on a specialty-specific basis and need to be aligned with sample type and clinical urgency.

For these guidelines, consider the following parameters when recommending turnaround times:

- **Sample type**: Different biopsy types (e.g. needle biopsy, excisional, larger resections) require varying fixation and processing times. Consider the complexity and handling requirements.
- **Clinical relevance**: Urgency varies based on clinical context. For suspected malignancies, faster reporting is essential. The clinical urgency is influenced by the clinical presentation, symptom progression, necessity of subsequent treatments with a

critical window between diagnosis and commencement of treatment, frequency of MDT.

- **Co-dependency on other factors**: Many cancer biopsies nowadays require subsequent molecular testing. Therefore, the time from biopsy to a final molecular diagnosis is important, but it is worth considering separating the pathway elements (transfer time from theatre to pathology laboratory, reporting a histological diagnosis, and establishing an integrated histomolecular diagnosis). Usually, the transfer times from theatres are reasonably within local control, and the reporting times are within control of pathology departments. Instead, the GLH should be in control of the molecular test turnaround times and these targets are mandated by the NHS England GMS.

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.

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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 ceased to be 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.

For comparison, the table also contains the ICD-O topographical coding of CNS tumours where an equivalent structure exists. A full list is published in Fritz A *et al*. *International Classification of Diseases for Oncology (ICD-O)*. Geneva, Switzerland: World Health Organization, 2013.

Topography codes

Tumour	SNOMED RT	SNOMED CT Concept ID	ICD-O Topographical coding of CNS tumours	Fully specified name
Brain	T-A0100	12738006	71.0	Brain structure (body structure)
Cerebellum	T-A6000	113305005	71.6	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	72.5	Cranial nerve structure (body structure)
Meninges not otherwise specified (NOS)	T-A1110	1231004	70.9	Meninges structure (body structure)
Pineal gland	T-B2000	45793000	75.3	Pineal structure (body structure)

Tumour	SNOMED RT	SNOMED CT Concept ID	ICD-O Topographical coding of CNS tumours	Fully specified name
Pituitary gland	T-B1000	56329008	75.1	Pituitary structure (body structure)
Skull	T-11100	89546000	-.-	Bone structure of cranium (body structure)
Spinal cord NOS	T-A7010	2748008	72.0	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 ICD-O codes of CNS tumours

Grade: 1, 2, 3, 4; Grades in [ ] are described in the WHO classification as ‘equivalent to’.

LG = low grade, HG = high grade, NS = not specified, NA = not applicable.

Tumour types in italics have undergone a change in terminology from a previous code.

Site	Category	Type	Grade	ICD-O-3.2
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Astrocytoma, IDH-mutant, grade 2	2	9400/3
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Astrocytoma, IDH-mutant, grade 3	3	9401/3
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Astrocytoma, IDH-mutant, grade 4	4	9445/3
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2	2	9450/3
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3	3	9451/3
Gliomas, glioneuronal tumours and neuronal tumours	Adult-type diffuse gliomas	Glioblastoma, IDH-wildtype	4	9440/3
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse low-grade gliomas	*Diffuse astrocytoma, MYB- or MYBL1-altered*	1	9421/1
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse low-grade gliomas	Angiocentric glioma	1	9431/1
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse low-grade gliomas	*Polymorphous low-grade neuroepithelial tumour of the young*	1	9413/0

Site	Category	Type	Grade	ICD-O-3.2
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse low-grade gliomas	*Diffuse low-grade glioma, MAPK pathway–altered*	NS	9421/1
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse high-grade gliomas	*Diffuse midline glioma, H3 K27–altered*	4	9385/3
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse high-grade gliomas	*Diffuse hemispheric glioma, H3 G34–mutant*	4	9385/3
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse high-grade gliomas	*Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*	4	9385/3
Gliomas, glioneuronal tumours and neuronal tumours	Paediatric-type diffuse high-grade gliomas	*Infant-type hemispheric glioma*	[4] [ns]	9385/3
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	Pilocytic astrocytoma	1	9421/1
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	High-grade astrocytoma with piloid features	[3]	9421/3*
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	Pleomorphic xanthoastrocytoma	2, 3	9424/3
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	Subependymal giant cell astrocytoma	1	9384/1
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	Chordoid glioma	2	9444/1
Gliomas, glioneuronal tumours and neuronal tumours	Circumscribed astrocytic gliomas	*Astroblastoma, MN1-altered*	NS	9430/3

Site	Category	Type	Grade	ICD-O-3.2
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Ganglioglioma	1	9505/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Gangliocytoma	1	9492/0
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Desmoplastic infantile ganglioglioma	1	9412/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Desmoplastic infantile astrocytoma	1	9412/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Dysembryoplastic neuroepithelial tumour	1	9413/0
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (provisional entity)	NS	n/a
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Papillary glioneuronal tumour	1	9509/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Rosette-forming glioneuronal tumour	1	9509/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	*Myxoid glioneuronal tumour*	1	9509/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Diffuse leptomeningeal glioneuronal tumour	2, 3	9509/3*
Gliomas, glioneuronal	Glioneuronal and neuronal tumours	Multinodular and vacuolating neuronal tumour	1	9509/0*

Site	Category	Type	Grade	ICD-O-3.2
tumours and neuronal tumours				
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	1	9493/0
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Central neurocytoma	2	9506/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Extraventricular neurocytoma	2	9506/1
Gliomas, glioneuronal tumours and neuronal tumours	Glioneuronal and neuronal tumours	Cerebellar liponeurocytoma	2	9506/1
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Supratentorial ependymoma, NOS*	2, 3	9391/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Supratentorial ependymoma, ZFTA fusion–positive*	2, 3	9396/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Supratentorial ependymoma, YAP1 fusion–positive*	NS	9396/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Posterior fossa ependymoma, NOS*	2, 3	9391/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Posterior fossa group A (PFA) ependymoma*	2, 3	9396/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Posterior fossa group B (PFB) ependymoma*	2, 3	9396/3
Gliomas, glioneuronal	Ependymal tumours	*Spinal ependymoma, NOS*	2, 3	9391/3

Site	Category	Type	Grade	ICD-O-3.2
tumours and neuronal tumours				
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	*Spinal ependymoma, MYCN-amplified*	NS	9396/3
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	Myxopapillary ependymoma	2	9394/1
Gliomas, glioneuronal tumours and neuronal tumours	Ependymal tumours	Subependymoma	1	9383/1
Choroid plexus tumours		Choroid plexus papilloma	1	9390/0
Choroid plexus tumours		Atypical choroid plexus papilloma	2	9390/1
Choroid plexus tumours		Choroid plexus carcinoma	3	9390/3
Embryonal tumours	Medulloblastomas, molecularly defined	Medulloblastoma, WNT-activated	4	9475/3
Embryonal tumours	Medulloblastomas, molecularly defined	Medulloblastoma, SHH-activated and TP53-wildtype	4	9471/3
Embryonal tumours	Medulloblastomas, molecularly defined	Medulloblastoma, SHH-activated and TP53-mutant	4	9476/3
Embryonal tumours	Medulloblastomas, molecularly defined	Medulloblastoma, non-WNT/non-SHH	4	9477/3
Embryonal tumours	Medulloblastomas, histologically defined		4	9470/3
Embryonal tumours	Medulloblastomas, histologically defined	Desmoplastic nodular medulloblastoma	4	9471/3
Embryonal tumours	Medulloblastomas, histologically defined	Medulloblastoma with extensive nodularity	4	9471/3

Site	Category	Type	Grade	ICD-O-3.2
Embryonal tumours	Medulloblastomas, histologically defined	Large cell medulloblastoma	4	9474/3
Embryonal tumours	Medulloblastomas, histologically defined	Anaplastic medulloblastoma	4	9474/3
Embryonal tumours	Other CNS embryonal tumours	Atypical teratoid/rhabdoid tumour	4	9508/3
Embryonal tumours	Other CNS embryonal tumours	Cribriform neuroepithelial tumour (provisional entity)	NS	n/a
Embryonal tumours	Other CNS embryonal tumours	Embryonal tumour with multilayered rosettes	4	9478/3
Embryonal tumours	Other CNS embryonal tumours	*CNS neuroblastoma, FOXR2-activated*	4	9500/3
Embryonal tumours	Other CNS embryonal tumours	*CNS tumour with BCOR internal tandem duplication*	NS	9500/3
Embryonal tumours	Other CNS embryonal tumours	CNS embryonal tumour, NEC/NOS	3 or 4	9473/3
Pineal tumours		Pineocytoma	1	9361/1
Pineal tumours		Pineal parenchymal tumour of intermediate differentiation	2, 3	9362/3
Pineal tumours		Pineoblastoma	4	9362/3
Pineal tumours		Papillary tumour of the pineal region	2, 3	9395/3
Pineal tumours		Desmoplastic myxoid tumour of the pineal region, SMARCB1-mutant (provisional entity)	NS	n/a
Cranial and paraspinal nerve tumours		Schwannoma	1	9560/0
Cranial and paraspinal nerve tumours		Neurofibroma	1	9540/0

Site	Category	Type	Grade	ICD-O-3.2
Cranial and paraspinal nerve tumours		Plexiform neurofibroma		9550/0
Cranial and paraspinal nerve tumours		Perineurioma	1	9571/0
Cranial and paraspinal nerve tumours		Hybrid nerve sheath tumour	NS	9563/0
Cranial and paraspinal nerve tumours		Malignant melanotic nerve sheath tumour	NS	9540/3
Cranial and paraspinal nerve tumours		Malignant peripheral nerve sheath tumour	LG or HG	9540/3
Cranial and paraspinal nerve tumours		Cauda equina neuroendocrine tumour (previously paraganglioma)	1	8693/3
Meningioma		Meningioma	1, 2, 3	9530/0
Mesenchymal, non-meningothelial tumours involving the CNS	Fibroblastic and myofibroblastic tumours	Solitary fibrous tumour	1, 2, 3	8815/1
Mesenchymal, non-meningothelial tumours involving the CNS	Vascular tumours	Cavernous haemangioma	NA	9121/0
Mesenchymal, non-meningothelial tumours involving the CNS	Vascular tumours	Capillary haemangioma	NA	9131/0
Mesenchymal, non-meningothelial tumours involving the CNS	Vascular tumours	Arteriovenous malformation	NA	9123/0
Mesenchymal, non-meningothelial	Vascular tumours	Haemangioblastoma	1	9161/1

Site	Category	Type	Grade	ICD-O-3.2
tumours involving the CNS				
Mesenchymal, non-meningothelial tumours involving the CNS	Skeletal muscle tumours	Embryonal rhabdomyosarcoma	NS	8910/3
Mesenchymal, non-meningothelial tumours involving the CNS	Skeletal muscle tumours	Alveolar rhabdomyosarcoma	NS	8920/3
Mesenchymal, non-meningothelial tumours involving the CNS	Skeletal muscle tumours	Rhabdomyosarcoma, pleomorphic-type	NS	8901/3
Mesenchymal, non-meningothelial tumours involving the CNS	Skeletal muscle tumours	Spindle cell rhabdomyosarcoma	NS	8912/3
Mesenchymal, non-meningothelial tumours involving the CNS	Tumours of uncertain differentiation	Intracranial mesenchymal tumour, FET::CREB fusion–positive (provisional entity)	NS	n/a
Mesenchymal, non-meningothelial tumours involving the CNS	Tumours of uncertain differentiation	CIC-rearranged sarcoma	4	9367/3
Mesenchymal, non-meningothelial tumours involving the CNS	Tumours of uncertain differentiation	*Primary intracranial sarcoma, DICER1-mutant*	NS	9480/3
Mesenchymal, non-meningothelial tumours involving the CNS	Tumours of uncertain differentiation	Ewing sarcoma	4	9364/3
Mesenchymal, non-meningothelial	Chondrogenic tumours	Mesenchymal chondrosarcoma	NS	9240/3

Site	Category	Type	Grade	ICD-O-3.2
tumours involving the CNS				
Mesenchymal, non-meningothelial tumours involving the CNS	Chondrogenic tumours	Chondrosarcoma	1, 2, 3	9220/3
Mesenchymal, non-meningothelial tumours involving the CNS	Chondrogenic tumours	Dedifferentiated chondrosarcoma	NS	9243/3
Mesenchymal, non-meningothelial tumours involving the CNS	Notochordal tumours	Chordoma	NS	9370/3
Mesenchymal, non-meningothelial tumours involving the CNS	Diffuse meningeal melanocytic neoplasms	Meningeal melanocytosis	NS	8728/0
Mesenchymal, non-meningothelial tumours involving the CNS	Diffuse meningeal melanocytic neoplasms	Meningeal melanomatosis	NS	8728/3
Mesenchymal, non-meningothelial tumours involving the CNS	Circumscribed meningeal melanocytic neoplasms	Meningeal melanocytoma	LG, IG	8728/1
Mesenchymal, non-meningothelial tumours involving the CNS	Circumscribed meningeal melanocytic neoplasms	Meningeal melanoma	NS	8720/3
Haematolymphoid tumours involving the CNS	CNS lymphomas	Primary diffuse large B-cell lymphoma of the CNS	NS	9680/3
Haematolymphoid tumours involving the CNS	CNS lymphomas	Lymphomatoid granulomatosis, grade 1	1	9766/1

Site	Category	Type	Grade	ICD-O-3.2
Haematolymphoid tumours involving the CNS	CNS lymphomas	Lymphomatoid granulomatosis, grade 2	2	9766/1
Haematolymphoid tumours involving the CNS	CNS lymphomas	Lymphomatoid granulomatosis, grade 3	3	9766/3
Haematolymphoid tumours involving the CNS	CNS lymphomas	Intravascular large B-cell lymphoma	NS	9712/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	MALT lymphoma of the dura	LG	9699/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	Lymphoplasmacytic lymphoma	LG	9671/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	Follicular lymphoma	LG	9690/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	Anaplastic large cell lymphoma (ALK+/ALK−)	NS	9714/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	T-cell lymphoma	LG, HG	9702/3
Haematolymphoid tumours involving the CNS	Miscellaneous rare lymphomas in the CNS	NK/T-cell lymphoma	LG, HG	9719/3
Haematolymphoid tumours involving the CNS	Histiocytic tumours	Erdheim–Chester disease	NS	9749/3
Haematolymphoid tumours involving the CNS	Histiocytic tumours	*Rosai–Dorfman disease*	NS	9749/3
Haematolymphoid tumours involving the CNS	Histiocytic tumours	*Juvenile xanthogranuloma*	NS	9749/1
Haematolymphoid tumours involving the CNS	Histiocytic tumours	Langerhans cell histiocytosis	NS	9751/1
Haematolymphoid tumours involving the CNS	Histiocytic tumours	Histiocytic sarcoma	NS	9755/3

Site	Category	Type	Grade	ICD-O-3.2
Germ cell tumours		Mature teratoma	NS	9080/0
Germ cell tumours		Immature teratoma	NS	9080/3
Germ cell tumours		Teratoma with somatic-type malignancy	NS	9084/3
Germ cell tumours		Germinoma	NS	9064/3
Germ cell tumours		Embryonal carcinoma	NS	9070/3
Germ cell tumours		Yolk sac tumour	NS	9071/3
Germ cell tumours		Choriocarcinoma	NS	9100/3
Germ cell tumours		Mixed germ cell tumour	NS	9085/3
Tumours of the sellar region		Adamantinomatous craniopharyngioma	1	9351/1
Tumours of the sellar region		Papillary craniopharyngioma	1	9352/1
Tumours of the sellar region		Pituicytoma	LG	9432/1
Tumours of the sellar region		Granular cell tumour of the sellar region	LG	9582/0
Tumours of the sellar region		Spindle cell oncocytoma	LG	8290/0
Tumours of the sellar region		*Pituitary adenoma/pituitary neuroendocrine tumour (PitNET)*	NS	8272/3
Tumours of the sellar region		Pituitary blastoma	NS	8273/3

Appendix C Reporting proforma for CNS tumours

Item class	Item subclass	Item detail	
Demographic information		Surname	
		Forenames	
		Date of birth	
		Sex	
		Hospital	
		Hospital no.	
		NHS number	
Clinical information		Date of surgery	
		Surgeon	
		Date of receipt in pathology	
		Date of report authorisation	
		Pathologist	
Topographic and imaging details of lesion	Type of lesion	Intra-axial	
		Extra-axial	
	Site of lesion	Skull	
		Dura	
		Leptomeninges	
		Cerebral lobes	
		Deep grey matter	
		Ventricle (specify)	
		Pineal	
		Brainstem	
		Cerebellum	
		Sellar/suprasellar/pituitary (specify anterior/posterior)	
		Spine/vertebral column	
		Spinal cord	
		Spinal nerve roots	
		Cranial nerve	
		Peripheral nerve	
		Other (specify)	

Item class	Item subclass	Item detail	
	Laterality of lesion	Left	
		Right	
		Midline	
		Bilateral	
		Not specified	
		Other (specify)	
	Focality of lesion	Unifocal	
		Multifocal (specify or estimate number of lesions)	
		Indeterminate	
	Relationship of lesion to adjacent tissue	Well demarcated	
		Diffuse/infiltrative	
		Mixed	
		Indeterminate	
		Peritumoural oedema	Absent
			Present
	Imaging characteristics	Contrast enhancement	Enhancing
			Non-enhancing
	Operative procedure	Stereotactic biopsy	
		Open biopsy	
		Resection	
		Lobectomy	
		Not provided	
		Other, specify (total macroscopic, extent uncertain	
Macroscopic items	Specimen dimensions	mm x mm x mm and or weight (g)	
	Specimen description		
Microscopic items	Adequacy of specimen for histological assessment	Adequate	
		Adequate but limited by (specify)	
		Inadequate (specify)	
		Adequate	

Item class	Item subclass	Item detail	
	Adequacy of specimen for diagnostic purposes	Adequate but limited by (specify)	
		Inadequate (specify)	
	Histological appearance	See non-core dataset	
	Histological grade	1, 2, 3, 4 See 2021 CNS WHO classification	
		Cannot be specified	
		Not applicable	
	Integrated final diagnosis (see core dataset)	See ICCR dataset for guidance	
	Molecular parameters	See non-core dataset	

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]

ET = extrinsic tumours, IT = intrinsic tumours, NA = not applicable, PitNET = pituitary neuroendocrine tumours

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
1	**Patient identity details**						
1.1		NHS number		Core	N/A	Yes	Yes
1.2		Local patient identifier (Hospital number)		Core	Core	Yes	Yes
1.3		NHS number status		Core	N/A	No	Yes
1.4		Birth date		Core	Core	Yes	Yes
1.5		Provider code		Core	N/A	No	Yes
2	**Demographics**						
2.1		Surname (family name)		Core	Core	Yes	Yes
2.2		Given name (forename)		Core	Core	Yes	Yes
2.2		Patient address		Core	N/A	No	Yes
2.3		Postcode		Core	N/A	No	Yes
2.4		Stated sex		Core	N/A	Yes	Yes
3	**Pathology details**						

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
3.1		Date and time of surgery/request		Core	Core	Yes	Yes
3.2		Date and time of receipt in pathology		Core	N/A	Yes	Yes
3.3		Date and time of report authorisation		Core	N/A	Yes	Yes
3.4		Report reference number		Core	Core	Yes	Yes
3.5		Pathologist		Core	N/A	Yes	Yes
3.6		Clinician		Core	N/A	No	Yes
4	**Clinical information[a]**						
4.1		Prior therapy – not administered[a]		Core	Non-core		Yes
4.2		Prior treatment not known[a]		Core	Non-core	Yes	Yes
4.3		Prior therapy administered (specify)[a]		Core	Non-core	Yes	Yes
4.4		Relevant patient family history: not provided		Core	Non-core	Yes	Yes
4.5		Relevant patient family history: previous history of cancer (specify)		Core	Non-core	Yes	Yes
4.6		Relevant patient family history: specify		Core	Non-core	Yes	Yes
4.7		Duration of symptoms		Core	Non-core	Yes	Yes
5	**Site of lesion[b] (radiological information)**						

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
5.1		Skull	Specify precise location, if known			Yes	NA
5.2		Dura	Specify precise location, if known	Core	Non-core	Yes	NA
5.3		Leptomeninges	Specify precise location, if known	Core	Non-core	Yes	NA
5.4		Brain	Specify precise location, if known	Core	Non-core	Yes	NA
5.5		Cerebral lobes	Specify precise location, if known	Core	Non-core	Yes	NA
5.6		Deep grey matter	Specify location	Core	Non-core	Yes	NA
5.7		Ventricle	Specify precise location, if known	Core	Non-core	Yes	NA
5.8		Pineal	Specify if applicable	Core	Non-core	Yes	NA
5.9		Sellar/suprasellar/pituitary	Specify anterior or posterior pituitary	Core	Non-core	Yes	Yes
5.10		Brainstem	Specify precise location, if known	Core	Non-core	Yes	NA
5.11		Cerebellum	Specify site, if known	Core	Non-core	Yes	NA
5.12		Spine/vertebral column	Specify precise location, if known	Core	Non-core	Yes	NA
5.13		Spinal cord	Specify precise location, if known	Core	Non-core	Yes	NA

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
5.14		Spinal nerve roots	Specify precise location, if known	Core	Non-core	Yes	NA
5.15		Peripheral nerve	Specify site, if known	Core	Non-core	Yes	NA
5.16		Other, specify		Core	Non-core	Yes	
6	**Laterality of lesion**						
6.1		Right		Core	Non-core	Yes	NA
6.2		Left		Core	Non-core	Yes	NA
6.3		Midline		Core	Non-core	Yes	NA
6.4		Bilateral		Core	Non-core	Yes	NA
6.5		Other (specify)		Core	Non-core	Yes	NA
6.6		Not applicable/Not specified		Core	Non-core	Yes	NA
7	**Focality of lesion**						
7.1		Unifocal		Core	Non-core	Yes	NA
7.2		Multifocal (specify or estimate number of lesions)		Core	Non-core	Yes	NA
7.3		Indeterminate		Core	Non-core	Yes	NA
8	**Relationship of tumour to adjacent tissue[c]**						
8.1		Well demarcated		N/A	Non-core	Yes	NA
8.2		Diffuse/infiltrative		N/A	Non-core	Yes	NA

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
8.3		Mixed (both well demarcated and diffuse in different areas)		N/A	Non-core	Yes	NA
8.4		Indeterminate		N/A	Non-core	Yes	NA
9	**Radiological characteristics**						
9.1		Peritumoural oedema	Absent	N/A	Non-core	Yes	NA
9.2			Present	N/A	Non-core	Yes	NA
9.3		**Contrast enhancement**					
9.3.1			Non-enhancing	N/A	Non-core	Yes	Yes
9.3.2			Enhancing	N/A	Non-core	Yes	Yes
9.3.3			Diffuse/solid	N/A	Non-core	Yes	Yes
9.3.4			Patchy/heterogeneous	N/A	Non-core	Yes	Yes
9.3.5			Ring/rim	N/A	Non-core	Yes	Yes
9.3.6			Information not available	N/A	Non-core	Yes	Yes
9.4		**Operative procedure[d]**					
9.4.1			Stereotactic biopsy	N/A	N/A	Yes	NA
9.4.2			Open biopsy	Core	Non-core	Yes	NA
9.4.3			Resection	Core	Non-core	Yes	NA
9.4.4			Lobectomy	N/A	N/A	Yes	NA
9.4.5			Not provided	Core	Non-core	Yes	NA

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
9.4.6			Other, specify (total macroscopic, extent uncertain)	Core	Non-core	Yes	NA
10	**Macroscopic items**						
10.1		**Specimen description**	Macroscopic description (including other characteristics: e.g. cystic, nodular, necrotic, haemorrhagic)[e]	Core	Non-core	Yes	Yes
10.2			Dimensions (mm x mm x mm)	Core	Non-core	Yes	Yes
10.3			Weight	Core	Non-core	Yes	Yes
10.4		**Adequacy of specimen for histological assessment[f]**	Specimen is adequate for analysis	N/A	Non-core	Yes	Yes
10.5			Specimen is adequate but limited by, specify	N/A	Non-core	Yes	Yes
10.6			Specimen is inadequate for analysis (crush, autolysis, cautery, necrosis, other [specify])	N/A	Non-core	Yes	Yes
10.7		**Adequacy of specimen for diagnostic purposes[g]**	Specimen is adequate for diagnostic purposes	N/A	Non-core	Yes	Yes

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
10.8			Specimen is adequate but limited by, specify	N/A	Non-core	Yes	Yes
10.9			Specimen is inadequate for diagnostic purposes (e.g. not representative of likely clinical and radiological diagnosis), specify	N/A	Non-core	Yes	Yes
11	**Microscopic items**						
11.1		**Histological appearance/pathology report text**					
11.1.1			Describe the appearance from the WHO 2021 entities and variants based on histological appearance only	Core	Non-core[h]	Yes	See Appendix F
11.1.2			Other, specify	Core	Non-core[h]	Yes	
11.2.3			Cannot be determined			Yes	
11.3		**Invasion**					
11.3.1			Not identified (i.e. tumour is well demarcated from	Core	Non-core	Yes	See Appendix F

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
			surrounding brain or other tissues)				
11.3.2			Cannot be assessed (e.g. only tumour is present)	Core	Non-core	Yes	
11.3.3			Present, specify type	Core	Non-core	Yes	
11.4		**Histological evidence of prior therapy**					
11.4.1			No evidence of prior therapy	Core	Non-core	Yes	Yes
11.4.2			Positive response, specify type of response (vascular changes, radiation type necrosis). Granulation and/or scar tissue, ischemic type of necrosis, foreign material (e.g. embolization / procoagulant material), reactive glial changes, inflammatory changes, other (specify).	Core	Non-core	Yes	Yes

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
11.5		**Grade of differentiation (COSD); histological grade (ICCR)**					
11.5.1			CNS WHO Grade 1	Core[i]	Core	Yes	
11.5.2			CNS WHO Grade 2	Core[i]	Core	Yes	
11.5.3			CNS WHO Grade 3	Core[i]	Core	Yes	
11.5.4			CNS WHO Grade 4	Core[i]	Core	Yes	
11.5.5			Cannot be specified	Core[i]	Core	Yes	
11.5.6			Not applicable	Core[i]	Core	Yes	
11.6		**Diagnosis**					
11.6.1			Integrated final diagnosis (see core dataset)	Core	Core	Yes	
11.6.2			Integrated final diagnosis (see Appendix C)	Core	Core	Yes	
11.6.3			Integrated diagnosis based on histology; integrated diagnosis based on molecular information[j]	Core	Core	Yes	
11.6.4			Diagnosis not elsewhere classified[k] (NEC)	Core	Core	Yes	
11.7		**SNOMED code**					

Item	Element name	Element descriptor		COSD v8	ICCR 2020 edition	Reporting proforma (IT & ET)	PitNET
11.7.1			T code	Core	Core	Yes	Yes
11.7.2			M code	Core	Core	Yes	Yes

[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 is, 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.

[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 tumour types and subtypes listed in the 2021 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 are, 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 tumour type defined by the 2021 WHO classification, a ‘descriptive’ or not elsewhere classified (NEC) 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 2021 WHO classification and cases in which necessary diagnostic information is not available.[6]

Appendix E Molecular testing and integrated reporting

Please see the 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 (NCRAS).

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.

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): CNS 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)

COSD code	Chromosomal or genetic markers associated with the brain tumour
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*
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

COSD code	Chromosomal or genetic markers associated with the brain tumour
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)
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

COSD code	Chromosomal or genetic markers associated with the brain tumour
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 neuroendocrine pituitary tumours

See Appendices C and D for elements that the reporting proforma for neuroendocrine pituitary tumours has in common with other reporting proformas.

Specific elements of the reporting proforma for neuroendocrine pituitary tumours.

Microscopic description

Descriptor	Feature/item	Result
Tumour architecture	Lobulated, diffuse	
Cytological features (select all that apply):	Nuclear atypia (particularly when severe)	
	Presence fibrous bodies	Present/absent
	Crooke's hyaline changes	Present/absent
	Cytoplasmic vacuoles	Present/absent
	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
	Mitotic figures	Number per mm^2 or per high-power field (x40)
Immunohistochemistry: Hormone (multiple values may be recorded)	ACTH	Tested: Expressed/not expressed Not tested
	LH	Tested: Expressed/not expressed Not tested

Descriptor	Feature/item	Result
	FSH	Tested: Expressed/not expressed Not tested
	Alpha-subunit	Tested: Expressed/not expressed Not tested
	TSH	Tested: Expressed/not expressed Not tested
	Prolactin	Tested: Expressed/not expressed Not tested
	Growth hormone	Tested: Expressed/not expressed Not tested
	Ki-67	Tested: Expressed/not expressed Not tested
Immunohistochemistry: Transcription factor To refine the diagnosis when immunostainings for pituitary hormones are equivocal or negative. Transcription factors can also help distinguish different cell populations in the diagnosis of plurihormonal PitNET/adenoma and double adenomas	Pit-1	Tested: Expressed/not expressed Not tested
	TPIT	Tested: Expressed/not expressed Not tested
	SF1	Tested: Expressed/not expressed Not tested

Descriptor	Feature/item	Result
Proliferation	Proliferation index (Ki-67)	Tested: Expressed/not expressed Not tested
Cytokeratins Relevant to subtype somatotroph adenoma and help diagnose corticotroph adenoma, particularly silent corticotroph adenoma	Cytokeratin 7 or cytokeratin 8 (CAM5.2)	Tested: Expressed/not expressed Not tested
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 and 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	Tested: Expressed/not expressed Not tested
Others Can be added to the panel in cases of aggressive-looking tumours	P53	Tested: Expressed/not expressed Not tested

Appendix G Relevant diagnostic and prognostic molecular alterations in gliomas, glioneuronal and neuronal tumours according to the 2021 CNS WHO classification

This list was adapted from the EANO recommendations of molecular diagnostic tools for the diagnosis of gliomas, glioneuronal and neuronal tumours.[31]

The list summarises key diagnostic molecular alterations and recommendations for testing. It is structured as follows:

- Left, tumour types as listed in the 2021 CNS WHO classification, with headings corresponding to the headings in the CNS WHO classification (gliomas, glioneuronal tumours, neuronal tumours etc) and subheadings to indicate the tumour diagnosis ('tumour type').

All subsequent columns are numbered for reference.

The markers are grouped by type of molecular alterations (SNV = single nucleotide variants ['point mutations']), copy number gains or losses.

- Columns **1–3:** recommendations of test methods. Essential and desirable criteria for methylation profiling (column 1) are adapted from the EANO recommendation,[31] where essential is considered as diagnostic criterion for 'unresolved lesions', otherwise designated as desirable test. Please note that the criteria indicated in blue deviate from the EANO recommendations and follow the NHS England recommendation for testing of neurological tumours.
- Column **2, 3**: suggestions for when to use NGS-DNA or NGS-RNA. These recommendations are not included in the EANO guidance. Importantly, columns 2 and 3 provide guidance for the utility of NGS for a molecular confirmation of a diagnosis but can be substituted by alternative techniques (such as small panels or surrogate IHC testing, as appropriate and available). Likewise, NGS-RNA (column 3) indicates use cases where this technique is available but can also be substituted by alternative methods as appropriate (for example, FISH or RT-PCR for single target testing of fusions).

- Columns 4–24: SNV. Colour coding according to the legend.
- Columns 25–37: gains and losses; comprising loss (32, 35–37), homozygous loss (25, 26, 31), combined whole arm deletion (33).
- Columns 38–52: gene fusions.
- Column 53: tyrosine kinase duplication/internal tandem duplication.
- Column 54**–56:** overexpression, loss of expression and unaltered expression.

Of note, this list of alterations is not exhaustive and not all possible mutations that can occur in these tumours are listed.

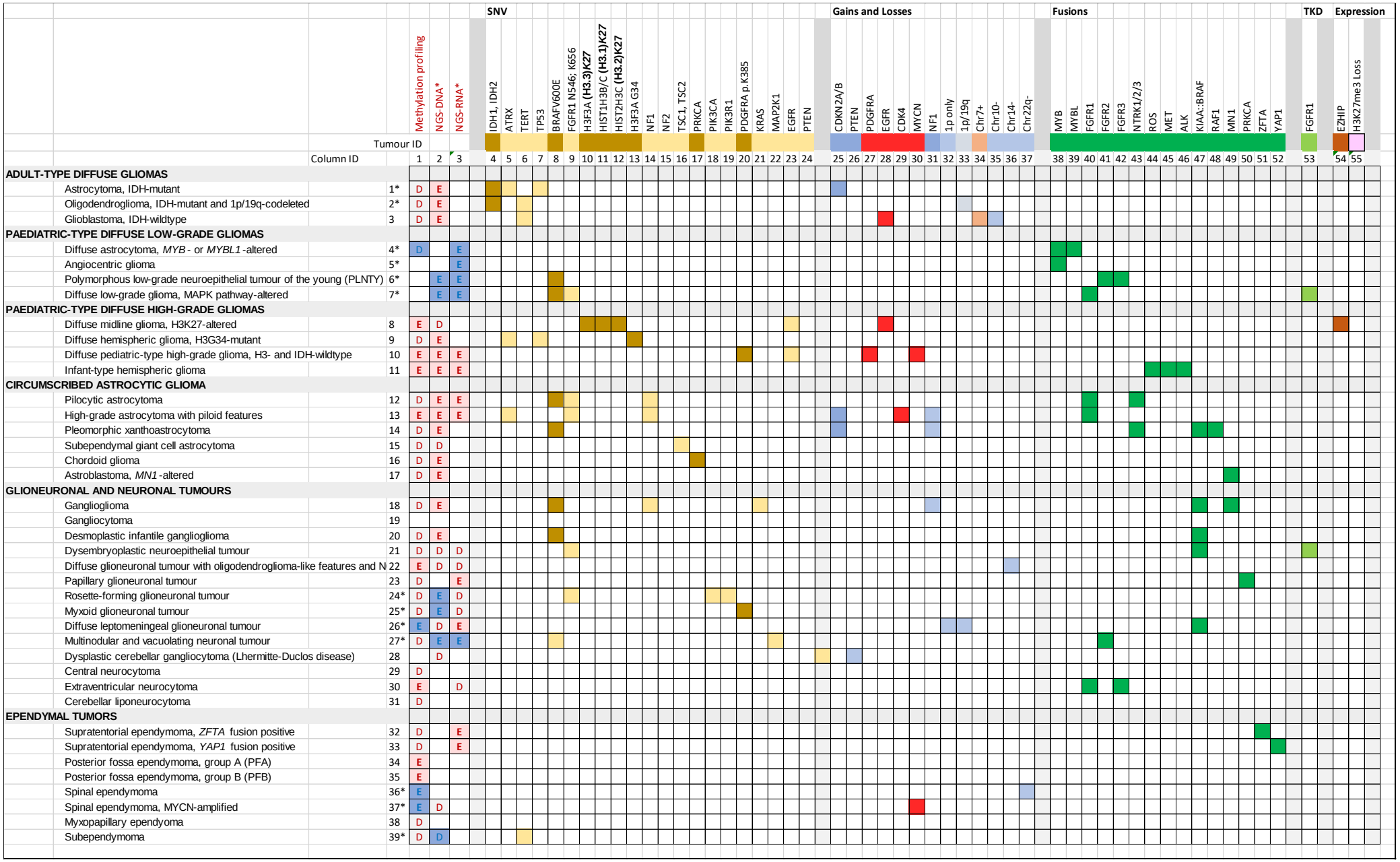
Specific comments to individual tumours (* next to the tumour ID), including justifications for a deviation from the EANO guideline:

- 1, 2: While not strictly necessary for a complete diagnosis of IDH-mutant astrocytomas and oligodendroglioma, we recommend methylation array for these tumour types, as it can conveniently determine the 1p/19q codeletion, CDKN2A/B deletion and, for astrocytomas, also an estimate of the global copy number changes to inform of prognosis and aid grading.[74]
- 4: These gliomas require testing for the MYB or MYBL fusion and, therefore, RNA NGS is considered an essential test. Methylation profiling is recommended for initial diagnosis.
- 5: Angiocentric glioma is characterised by MYB fusion and, therefore, at least requires RNA NGS.
- 6: PLNTY is, in our opinion, not always histologically distinct and it is recommended to test for the relevant variants (BRAF, FGFR1, FGFR2). Methylation array is currently not useful as the methylation class is not yet defined.
- 7: Diffuse low-grade glioma, MAPK pathway altered is, in our opinion, not sufficiently histologically distinct and should be confirmed with testing for relevant point mutations and fusions, therefore deviatin from the EANO guidance.
- 24: RGNT can have non-specific histological features and a robust diagnosis can be established by detection of the known mutations. As these mutations are, however, not specific for RGNT, a combination with methylation array is desirable.
- 25: Myxoid glioneuronal tumour requires detection of the PDGFRA mutation, as the histological features may not be entirely specific (and often overlap with DNET).

Ideally, molecular diagnostics also includes methylation array, as the PDGFRA mutation is not specific for this tumour.

- 26: Detection of chromosomal copy number changes and gene fusions should be complemented with a methylation array (or methylation array can fully substitute NGS). Methylation array also discriminates the 2 subtypes with different prognosis. Therefore, deviation from the EANO guideline and recommendation of methylation array as an essential test.
- 27: For the detection of possible mutations in the tumour type, we consider NGS (DNA, RNA) as essential. Methylation profiling is recommended.
- 36, 37 (spinal ependymoma): To exclude MYCN amplification, it is necessary to perform a test to detect MYCN amplification. Therefore, we recommend methylation array is an essential, catch-all test for all spinal ependymomas.
- 39: A small subset of subependymomas can have chromosome 6 loss and TERT promoter mutation, indicating a poorer prognosis; thus, we recommend methylation array profiling,[155] optionally complemented with promoter mutation testing. This should be applied to individual cases only and is not a mandate to test for *TERT* promoter mutation in all subependymomas.

	Genetic alteration	**Colour code**
1	Hotspot mutation	
2	Mutation	
3	Loss	
4	HomLoss	
5	Comb whole arm deletion	
6	amplification	
7	combined whole arm gain	
8	Gene fusion	
9	TKD	
10	Overexpression	
E	Test is essential according to the EANO guidelines	**E**
D	Test is desirable according to the EANO guidelines	D
E	Deviation from EANO guidelines, following NHS-E guidance for genomic testing in Neuro-oncology	**E**
D	Deviation from EANO guidelines, following NHS-E guidance for genomic testing in Neuro-oncology	D


SNV
Gains and Losses
Fusions
TKD
Expression
Methylation profiling
NGS-DNA*
NGS-RNA*
IDH1, IDH2
ATRX
TERT
TP53
BRAFV600E
FGFR1 N546; K656
H3F3A (H3.3)K27
HIST1H3B/C (H3.1)K27
HIST2H3C (H3.2)K27
H3F3A G34
NF1
NF2
TSC1, TSC2
PRKCA
PIK3CA
PIK3R1
PDGFRA p.K385
KRAS
MAP2K1
EGFR
PTEN
CDKN2A/B
PTEN
PDGFRA
EGFR
CDK4
MYCN
NF1
1p only
1p/19q
Chr7+
Chr10-
Chr14-
Chr22q-
MYB
MYBL
FGFR1
FGFR2
FGFR3
NTRK1/2/3
ROS
MET
ALK
KIAA::BRAF
RAF1
MN1
PRKCA
ZFTA
YAP1
FGFR1
EZHIP
H3K27me3 Loss
Tumour ID
Column ID
ADULT-TYPE DIFFUSE GLIOMAS
Astrocytoma, IDH-mutant 1*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted 2*
Glioblastoma, IDH-wildtype 3
PAEDIATRIC-TYPE DIFFUSE LOW-GRADE GLIOMAS
Diffuse astrocytoma, MYB- or MYBL1-altered 4*
Angiocentric glioma 5*
Polymorphous low-grade neuroepithelial tumour of the young (PLNTY) 6*
Diffuse low-grade glioma, MAPK pathway-altered 7*
PAEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMAS
Diffuse midline glioma, H3K27-altered 8
Diffuse hemispheric glioma, H3G34-mutant 9
Diffuse pediatric-type high-grade glioma, H3- and IDH-wildtype 10
Infant-type hemispheric glioma 11
CIRCUMSCRIBED ASTROCYTIC GLIOMA
Pilocytic astrocytoma 12
High-grade astrocytoma with piloid features 13
Pleomorphic xanthoastrocytoma 14
Subependymal giant cell astrocytoma 15
Chordoid glioma 16
Astroblastoma, MN1-altered 17
GLIONEURONAL AND NEURONAL TUMOURS
Ganglioglioma 18
Gangliocytoma 19
Desmoplastic infantile ganglioglioma 20
Dysembryoplastic neuroepithelial tumour 21
Diffuse glioneuronal tumour with oligodendroglioma-like features and N 22
Papillary glioneuronal tumour 23
Rosette-forming glioneuronal tumour 24*
Myxoid glioneuronal tumour 25*
Diffuse leptomeningeal glioneuronal tumour 26*
Multinodular and vacuolating neuronal tumour 27*
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) 28
Central neurocytoma 29
Extraventricular neurocytoma 30
Cerebellar liponeurocytoma 31
EPENDYMAL TUMORS
Supratentorial ependymoma, ZFTA fusion positive 32
Supratentorial ependymoma, YAP1 fusion positive 33
Posterior fossa ependymoma, group A (PFA) 34
Posterior fossa ependymoma, group B (PFB) 35
Spinal ependymoma 36*
Spinal ependymoma, MYCN-amplified 37*
Myxopapillary ependyoma 38
Subependymoma 39*

Appendix H 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 I 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	Foreword and 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 and all sections
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	All sections
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	All sections
16	The different options for management of the condition or health issue are clearly presented	All sections

17 Key recommendations are easily identifiable	All sections
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
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	13
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