Data Sets for the Reporting of Tumors of the Central Nervous System

Recommendations From The International Collaboration on Cancer Reporting

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• *Context.*—Standards for pathology reporting of cancer are foundational to national and international benchmarking, epidemiology, and clinical trials, with international standards for pathology reporting of cancer being undertaken through the International Collaboration on Cancer Reporting (ICCR).

***Objective.*—To develop standardized templates for brain tumor diagnostic pathology reporting.**

***Design.*—As a response to the 2016 updated 4th edition of the *WHO* (World Health Organization) *Classification of Tumours of the Central Nervous System* (2016 CNS WHO), an expert ICCR committee developed data sets to facilitate reporting of brain tumors that are classified histologically and molecularly by the 2016 CNS WHO; as such, this represents the first combined histologic and molecular ICCR data set, and required a novel approach with 3 highly related data sets that should be used in an integrated manner.**

***Results.*—The current article and accompanying ICCR Web site describe reporting data sets for central nervous system tumors in the hope that they provide easy-to-use and highly reproducible means to issue diagnostic reports in consort with the 2016 CNS WHO.**

***Conclusions.*—The consistent use of these templates will undoubtedly prove useful for patient care, clinical trials, epidemiologic studies, and monitoring of neuro-oncologic care around the world.**

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The value of a structured or synoptic approach to cancer reporting, leading to improvement in the quality and completeness of pathology cancer reports, has been recognized through many studies[1–4] and the colleges of the United Kingdom, Australia, and the United States, and many other centers around the world have engaged in the development of national or local standards as a result. However, while each of these local standards often uses the same cohort of evidence as its basis, each is constructed differently and uses different terminology, and similar

elements may be based on different methodologies, and they are therefore not comparable.

The US (College of American Pathologists [CAP]), Australasian (Royal College of Pathologists of Australasia), and UK (Royal College of Pathologists) Colleges of Pathology and the Canadian Association of Pathologists-Association canadienne des pathologistes, in association with the Canadian Partnership Against Cancer, recognized the value of agreed international standards and in 2011 a formal collaboration commenced: the International Collaboration on Cancer Reporting (ICCR). This initial collaboration addressed the development of reporting standards for 4 cancers: lung, melanoma, prostate (radical prostatectomy), and endometrium.[5] Each was undertaken by an expert committee with representatives from each of the 4 countries. The results were extremely positive and encouraging, and in 2013 the collaboration expanded to include the European Society of Pathology and these 5 organizations became the founding members of the ICCR, which was incorporated as a not-for-profit organization in late 2014. The ICCR continues to expand its membership and affiliations with like-minded organizations from around the world.

The ICCR data sets are made freely available for use by organizations and individuals globally. It is anticipated that, in time, this will enable the alignment and normalization of pathology cancer data around the world as producers of data sets adopt and incorporate the ICCR data sets.

The identification and classification of tumor types is essential to the pathology reporting of cancer and is a feature of all ICCR data sets. The International Agency on Cancer Research (IARC) is responsible for the development and publication of the *World Health Organization Classification of Tumours* series ("WHO Blue Books"), which is a vital resource for worldwide pathology reporting of cancer. In 2013, the ICCR agreed to synchronize its schedule of data set development with the publication of the WHO Blue Book series. In 2016, the IARC released the updated 4th edition of the *WHO Classification of Tumours of the Central Nervous System*[6] (2016 CNS WHO), and as a result, the ICCR commenced development of a data set to align with this publication.

METHODS

The process followed the Guidelines for the Development of ICCR Datasets[7] (http://www.iccr-cancer.org/datasets/dataset-development; accessed March 1, 2019). This development framework dictates the process as well as the format and the content of the data sets.

Key to the success of the development of an international standard such as the ICCR data sets is the selection of a suitably qualified chair and Data Set Authoring Committee (DAC). Committee members were chosen primarily for their expertise in CNS tumors but also with the goal of achieving a committee with both geographic and practice diversity. In-depth familiarity with the updated *WHO Classification of Tumours of the Central Nervous System*[6] was essential. The DAC was composed of 14 pathologists/neuropathologists and 1 clinician (MW) and supported by an ICCR representative (BR) and project manager (MJJ); in this case, because CAP was updating its CNS reporting protocol, a representative of the CAP CNS group was also included (EMH).

ICCR data sets are composed of 2 types of elements: core and non-core. Core elements are defined as those that are unanimously agreed upon by the panel to be mandatory for diagnosis, clinical management, staging, or prognosis. Non-core elements are non-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.

Table 1. Data Items for the Histologic Assessment of Tumors of the Central Nervous System

Element Name
Clinical information – prior therapy
Clinical information – relevant patient/family history
Operative procedure
Tumor site(s)
Tumor laterality
Tumor focality
Tumor dimensions
Relationship of tumor to adjacent tissue
Contrast enhancement
Specimen description
Specimen dimension
Adequacy of specimen for histologic assessment
Adequacy of specimen for diagnostic purposes
Histologic appearance
Histologic grade
Invasion
Histologic evidence of prior therapy

Evidentiary support at level III-2 or above[8] is required to support core elements; however, where level III-2 evidence is not available (a common situation for CNS tumor classification), an element was categorized as core with unanimous agreement of the DAC. Commentary such as explanatory text, diagrams, or tables is added where necessary to clarify the elements: to define the way an item should be reported, to ensure clarity and conformity, to explain why an item is included (eg, how an item assists with clinical management or prognosis of the specific cancer), to cite published evidence in support of the element, and to state any exceptions or issues that may be encountered by the reporting pathologist. Detailed commentary is designed to provide contextual guidance to the reporting pathologist.

A working draft was initially developed by the chair and formatted into a voting document for distribution to the DAC. Feedback from the DAC was compiled and provided a basis for discussion for each of 3 Web/teleconferences. A further 3 detailed surveys were undertaken to garner opinion from the DAC on a variety of issues. Members of the DAC were appointed to provide further information on specific elements that then formed the basis of commentary. Once completed and endorsed by the DAC, the data set was formatted and posted to the ICCR Web site for a period of 2 months for public comment. Following this feedback, the data set was reviewed, and final changes were made by the DAC. After final review by the DAC, the data set was approved for publication and submitted to the ICCR Data Set Steering Committee for ratification.

RESULTS

The CNS data set has been developed for the pathology reporting of benign and malignant tumors of the CNS and its coverings, as well as tumors from those aspects of the peripheral nervous system immediately adjacent to the CNS. The data set applies to both biopsy and resection specimens. Tumors of the anterior pituitary gland and hematologic lesions that may originate in the CNS are included.

The DAC agreed that, per the recommendations in the 2014 ISN (International Society of Neuropathology)–Haarlem guidelines,[9] a pathology report format should consist of 4 layers: Layer 1: Integrated diagnosis (incorporating all tissue-based information); Layer 2: Histologic classification;

Table 2. World Health Organization Grades Based on Histologically Defined Diagnostic Category (Based on Histologic Appearance Only)

Tumor Group	Tumor Type	Grade I	Grade II	Grade III	Grade IV
Astrocytic tumors	Diffuse astrocytoma		X		
	Anaplastic astrocytoma			X	
	Glioblastoma (and variants)				X
	Pilocytic astrocytoma	X			
	Pilomyxoid astrocytoma (grade not assigned)				
	Subependymal giant cell astrocytoma	X			
	Pleomorphic xanthoastrocytoma		X		
	Anaplastic pleomorphic xanthoastrocytoma			X	
Oligodendrogliomas	Oligodendroglioma		X		
	Anaplastic oligodendroglioma			X	
Oligoastrocytomas	Oligoastrocytoma		X		
	Anaplastic oligoastrocytoma			X	
Ependymal tumors	Ependymoma (and variants)		X		
	Anaplastic ependymoma			X	
	Subependymoma	X			
	Myxopapillary ependymoma	X			
Choroid plexus tumors	Choroid plexus papilloma	X			
	Atypical choroid plexus papilloma		X		
	Choroid plexus carcinoma			X	
Other neuroepithelial tumors	Chordoid glioma of the third ventricle		X		
	Angiocentric glioma	X			
Neuronal-glial tumors	Gangliocytoma	X			
	Desmoplastic infantile ganglioglioma/astrocytoma	X			
	Dysembryoplastic neuroepithelial tumor	X			
	Ganglioglioma	X			
	Anaplastic ganglioglioma			X	
	Central neurocytoma		X		
	Extraventricular neurocytoma		X		
	Cerebellar liponeurocytoma		X		
	Papillary glioneuronal tumor	X			
	Rosette-forming glioneuronal tumor of the fourth ventricle	X			
	Paraganglioma of the spinal cord	X			
Pineal parenchymal tumors	Pineocytoma	X			
	Pineal parenchymal tumor of intermediate differentiation		X	X	
	Pineoblastoma				X
	Papillary tumor of the pineal region		X	X	
Embryonal tumors	Medulloblastoma (and variants)				X
	Central nervous system embryonal tumor, not otherwise specified				X
	Medulloepithelioma				X
	Central nervous system neuroblastoma				X
	Central nervous system ganglioneuroblastoma				X
	Ependymoblastoma				X
	Atypical teratoid/rhabdoid tumor				X
Cranial and peripheral nerve tumors	Schwannoma (and variants)	X			
	Neurofibroma (and variants)	X			
	Perineurioma	X			
	Malignant peripheral nerve sheath tumors		X	X	X
Meningeal tumors	Meningioma (and most variants)	X			
	Atypical meningioma		X		
	Clear cell meningioma		X		
	Chordoid meningioma		X		
	Anaplastic meningioma			X	
	Papillary meningioma			X	
	Rhabdoid meningioma			X	
Mesenchymal tumors[10,11]	(Named as soft tissue counterpart)	X	X	X	X
	Solitary fibrous tumor/hemangiopericytoma	X	X	X	
Tumors of uncertain histogenesis	Hemangioblastoma	X			

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Table 3. World Health Organization (WHO) Histologic Grading System for Diffuse Astrocytic Neoplasms

WHO Grade	WHO Designation	Histologic Criteria
II	Diffuse astrocytoma	Nuclear atypia
III	Anaplastic astrocytoma	Nuclear atypia and mitotic figures
IV	Glioblastoma	Nuclear atypia, mitotic figures, and microvascular proliferation and/or necrosis

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Layer 3: WHO grade (reflecting natural history); and Layer 4: Molecular information.

To accomplish this, the CNS ICCR data set has taken a different approach from prior ICCR data sets in that 3 interrelated data sets were generated. The 3 data sets are as follows: (1) Histological assessment of CNS specimens (including both layers 2 and 3, ie, histologic classification and grade); (2) Molecular information for CNS specimens; and (3) Final integrated report/diagnosis for CNS specimens.

Importantly, it is strongly recommended that these data sets be used together for tumors in which molecular information is captured in their diagnosis, resulting in an integrated report/diagnosis. A full diagnosis of CNS tumors should ideally conform to the 2016 CNS WHO, which requires integration of elements from histologic and ancillary analyses. However, because most 2016 CNS WHO entities can be diagnosed solely on the basis of histologic features, in many situations, only the histologic and final data sets need to be completed. Thus, the molecular assessment (whether nucleic acid or protein based) does not need to be completed for those tumors in which molecular information is not captured for diagnostic purposes. Nonetheless, diagnostic molecular data are being used to diagnose a growing subset of CNS tumors and it is anticipated that use of such data will further increase over time; for this reason, the importance of molecular data sets and integrated diagnoses is likely to increase as well over time. Lastly, taking into account that the ICCR data sets are intended for use throughout the world, this sectional approach to the data set allows the histologic assessment to be used standalone in the event that molecular testing is not available or failed.

For prior ICCR data sets, the accompanying journal article has essentially replicated the data set, including all of the detailed commentaries. For the CNS ICCR data sets, that approach would not be practical, given the multiple data sets and the length of the explanatory commentary. For this reason, we have chosen to highlight only selected aspects herein, and the reader is instead directed to the on-line data sets for the full details.

Notably, for the CNS data sets, the discussion 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 data sets therefore only included 2 core elements:

Table 4. World Health Organization (WHO) Grading of Meningiomas

WHO grade I
- Benign meningioma (and variants)
- None of the criteria below for WHO grades II or III

WHO grade II
- Atypical meningioma
  - Mitotic figures ≥4/10 HPFs
  - *or*
  - At least 3 of 5 parameters:
    - Sheeting architecture (loss of whorling and fascicles)
    - Small cell formation
    - Macronucleoli
    - Hypercellularity
    - Spontaneous necrosis
  - *or*
  - Brain invasion
- *or*
- Clear cell meningioma
- *or*
- Chordoid meningioma

WHO grade III
- Anaplastic (malignant) meningioma
  - Mitotic figures ≥20/10 HPFs
  - *or*
  - Frank anaplasia (sarcoma, carcinoma, or melanoma-like histology)
- *or*
- Papillary meningioma
- *or*
- Rhabdoid meningioma

Abbreviation: HPFs, high-power fields.

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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 of these elements may not always be present in pathology reports of CNS tumors. The distinction between core and non-core is therefore not of primary importance for the CNS data sets.

The elements of the histologic data set are listed in Table 1, with the corresponding detailed commentaries provided in the on-line data set. To guide histologic grading of the more common CNS tumors, Tables 2 through 4 are provided here, in particular for the common diffuse astrocytic gliomas and the meningioma, with commentary to be found on-line. These guidelines are current as of the workings of the DAC in mid-2018 but do not fully include more recent published suggestions that could affect grading in future WHO classifications.[10–12]

The elements of the molecular data set are shown on the left in Table 5, with the table guiding the pathologist in determining which molecular tests are required or recommended, either for classification and/or differential diagnosis. It is anticipated that such a table could change fairly quickly over time. The designations are divided into those markers that are components of the 2016 CNS WHO

Table 5. Overview of Selected Molecular Diagnostic Markers for Central Nervous System Tumors

Test	Gliomas							
	DA, AA	O, AO	Diffuse Midline Glioma	GBM	Pilocytic Astrocytoma	PXA, GG	Ependymoma – Supratentorial	Ependymoma – Posterior Fossa
ATRX mutation								
ATRX mutation	D			D				
ATRX loss of expression (immunohistochemistry)	D			D				
BRAF alterations								
BRAF mutation	(D)			(D)	D	D		
BRAF V600E expression (immunohistochemistry)	(D)			(D)	D	D		
BRAF rearrangement/duplication					D			
CDKN2A/B homozygous deletion	(D)					(D)		
Chromosome 19 microRNA cluster (C19MC) alteration								
Chromosomal arm 1p/19q codeletion		W						
Chromosome 7 gain combined with chromosome 10 loss (see below)				D				
Chromosome 10q23 (*PTEN* locus) deletion and *PTEN* mutation								
Chromosome 10q23 (*PTEN* locus) deletion or monosomy 10				D				
PTEN mutation				D				
EGFR amplification and EGFRvIII mutation								
EGFR amplification				D				
EGFRvIII mutation				D				
Histone H3 mutation and H3 K27 trimethylation (me3)								
Histone H3 K27M mutation (sequencing) and expression (immunohistochemistry)	(D)		W	D				
Histone H3 G34 mutation (sequencing) and expression (immunohistochemistry)	(D)			D				
Histone H3 K27me3 expression (immunohistochemistry)			D					D
IDH1/IDH2 mutation								
IDH1/IDH2 mutation	W	W	D*	W	D*	D*		
IDH1 R132H expression (immunohistochemistry)	W	W	D*	W	D*	D*		
Ki-67 immunohistochemistry		D						
L1CAM expression (immunohistochemistry)							D	
LIN28A expression (immunohistochemistry)								
Medulloblastoma immunohistochemistry								
β-Catenin nuclear expression (immunohistochemistry)								
GAB1 expression (immunohistochemistry)								
YAP1 expression (immunohistochemistry)								
MGMT promoter methylation				D				
Monosomy 6								
MYC gene family amplification								
MYC amplification								
MYCN amplification								
NAB2-STAT6 fusion								
NAB2-STAT6 fusion								
STAT6 nuclear expression (immunohistochemistry)								

Table 5. Extended

Embryonal Tumors			Other					
Medulloblastoma	AT/RT	ETMR	Extraventricular Neurocytoma	Meningioma	SFT/HPC	Craniopharyngioma	MPNST	Pituitary Tumors
						D		
						D		
		W						
							D	
			D*					
			D*					
				D				D
		D						
D						D		
D								
D								
D								
D								
D								
					D			
					D			

Table 5. Continued

Test	Gliomas							
	DA, AA	O, AO	Diffuse Midline Glioma	GBM	Pilocytic Astrocytoma	PXA, GG	Ependymoma – Supratentorial	Ependymoma – Posterior Fossa
Pituitary hormones and transcription factors (immunohistochemistry)								
RELA fusion							W	
SMARCA4/BRG1 alteration								
SMARCA4/BRG1 mutation								
BRG1 loss of expression (immunohistochemistry)								
SMARCB1/INI1/HNSF5 alteration								
SMARCB1/INI1/HNSF5 mutation								
INI1 (BAF47) loss of expression (immunohistochemistry)								
TERT promoter mutation		D		D				
TP53 mutation								
TP53 mutation	D							
p53 expression (immunohistochemistry)	D							
YAP1 fusion							D	

Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AT/RT, atypical teratoid/rhabdoid tumor; CNS, central nervous system; DA, diffuse astrocytoma; ETMR, embryonal tumor with multilayered rosettes; GBM, glioblastoma; GG, ganglioglioma; MPNST, malignant peripheral nerve sheath tumor; O, oligodendroglioma; PXA, pleomorphic xanthoastrocytoma; SFT/HPC, solitary fibrous tumor/hemangiopericytoma; WHO, World Health Organization.

Note: This is a summary and the reader is referred to the specific notes for details on use of each test.

W = Component of the 2016 CNS WHO diagnostic criteria and 2017 WHO diagnostic criteria for pituitary adenomas.

D = Commonly used to support or refine the diagnosis, or provide important ancillary information in the corresponding tumor type.

D* = Commonly used to rule out the diagnosis; see commentary for details.

(D) = Can be used to support or refine the diagnosis, or provide important ancillary information in specific tumor subtype(s); see commentary for details.

diagnostic criteria and 2017 WHO diagnostic criteria for pituitary adenomas (designated as "W"); those that are commonly used to support or refine the diagnosis, or provide important ancillary information in the corresponding tumor type (designated as "D"); those that are commonly used to rule out the diagnosis (designated as "D*"); those that can also be used to support or refine the diagnosis, or provide important ancillary information in specific tumor subtypes (designated as "(D)"); see commentary for details. As mentioned above, it is likely that molecular parameters will change fairly quickly over time and therefore there is a section for Other Findings that should be used for documenting results for other genetic alterations and/or for molecular results in other tumor types, such as metastases and hematologic lesions. Once again, extensive details concerning each of these molecular parameters are provided on-line, and an example of how molecular data can contribute to a diagnosis is given for medulloblastoma in Table 6.

Table 7 provides the current 2016 CNS WHO classification, which forms the basis for the Integrated Diagnosis data set. All reports should strive to render a diagnosis from the 2016 CNS WHO,[6] although it is recognized that this may not be possible in all instances (ie, that more descriptive diagnoses may be needed for tumors that do not meet criteria for 2016 CNS WHO entities).[6,13] In many situations, 2016 CNS WHO diagnoses "integrate" histologic and molecular information and have been referred to as "integrated" diagnoses; for these entities, both histologic and molecular information is needed. (In this context, "molecular information" refers to data from any type of molecule [eg, DNA, protein], so that an immunohistochemical test provides "molecular information.") In some scenarios, there may be differences between histologic appearance and 2016 CNS WHO diagnosis (eg, a diffuse glioma without overt oligodendroglial features but with IDH mutation and 1p/19q codeletion). Moreover, in other scenarios, necessary molecular information may not be available, leading to one of the "not otherwise specified" (NOS) 2016 CNS WHO diagnoses.

It is important to keep in mind that most 2016 CNS WHO entities can be diagnosed solely on the basis of histologic features. While for such entities the diagnosis may be identical to the histologic appearance (eg, choroid plexus tumors), for others there may be differences (eg, a diffuse glioma with an integrated diagnosis of "diffuse astrocytoma, IDH-mutant" that has a histologic appearance that is not fully or classically a diffuse astrocytoma yet has a characteristic astrocytic genotype—*IDH1*, *ATRX*, and *TP53* mutations as well as 1p/19q retention). In the latter type of case, layered reports (see above)[9] have most value in distinctly conveying such findings.

"Diagnosis not elsewhere classified": In the event that all diagnostic information is present but the tumor still does not meet criteria for an entity defined by the 2016 WHO classification (eg, a pediatric diffuse glioma that does not harbor IDH or H3 mutations), a "descriptive" or NEC (not elsewhere classified) diagnosis can be issued, which draws attention to the unusual nature of the lesion. Such designations are distinct from NOS diagnoses, which are

Table 5. Continued, Extended								
Embryonal Tumors			Other					
Medulloblastoma	AT/RT	ETMR	Extraventricular Neurocytoma	Meningioma	SFT/HPC	Craniopharyngioma	MPNST	Pituitary Tumors
								W
D	W							
D	W							
D	W							
D*	W							
W								
W								

included in the 2016 WHO classification and that are cases in which necessary diagnostic information is not available.[13]

DISCUSSION AND SUMMARY

The 2016 WHO Classification of CNS Tumors[6] differs from the prior, 2007 classification in that it not only incorporates some new entities and deletes old ones, but also formulates a number of common diagnoses in terms of both histologic and molecular parameters. Having diagnostic terms based on both histology and molecular analysis has, however, created a set of challenges for pathologists: How does a pathologist make 2016 CNS WHO diagnoses in a setting in which molecular assays are not available? How does a pathologist display the histologic and molecular findings in a way that is most accessible and understandable to clinicians, patients, and researchers seeking to use these diagnoses? How does a pathologist produce an initial diagnostic report in advance of molecular findings being ready, and then adjust that report once the molecular findings are generated—particularly in settings in which the molecular results may take weeks?

The 2016 CNS WHO Blue Book addressed the first of these challenges through the creation of NOS entities. Such diagnoses were intended to be used in those situations in which molecular assays were either not available or did not generate usable results. They have proved useful in allowing WHO diagnoses in resource-challenged settings. Most importantly, they in turn provide a "red flag" to an oncology center when a patient presents for treatment with such a diagnosis, hopefully encouraging molecular workup at that time. And, while NOS diagnoses have generated questions as to their best use, clarifications have already come out of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) effort.[13] Similarly, cIMPACT-NOW has generated other sets of recommendations that are reviewed in detail elsewhere and in the Notes accompanying the on-line ICCR data sets[11,14]

Table 6. Medulloblastoma Molecular Groups – Immunohistochemical Markers			
Antibodies to:	WNT	SHH	non-WNT/ non-SHH
β-Catenin	Cytoplasmic and nuclear	Cytoplasmic	Cytoplasmic
GAB1	Negative	Positive	Negative
YAP1	Positive	Positive	Negative

Abbreviations: GAB1, GRB2-associated binding protein 1; SHH, sonic hedgehog pathway activation; WNT, WNT pathway activation; YAP1, yes-associated protein 1.

The second and third of the abovementioned challenges—those relating to reporting formats—were not addressed in the 2016 CNS WHO Blue Book but are considered here as part of the ICCR. Notably, a key element of the ICCR approach is based on the guidelines issued from the ISN-Haarlem meeting held in 2014[9]: a layered report. A layered report provides the diagnosis in a stereotypically layered format (see above), which readily allows visualization of histologic and molecular findings, as well as the final or "integrated" diagnosis that corresponds to the 2016 CNS WHO classification. To do so, the ICCR committee has created and recommends the use of 3 separate data sets for histologic, molecular, and integrated components of the report. In addition, the layered report and separate data sets also more readily allow modification of the molecular and integrated sections once molecular results are available.

Addressing these challenges required a DAC that had, in addition to neuropathology expertise, input from clinical neuro-oncology and general pathology. It also required relaxing the criteria regarding so-called core elements versus non-core elements, and it may be that as other organ systems incorporate molecular markers into classifications, the distinction between core and non-core elements needs to be revisited.

These 3 data sets should be used together, with the histologic and molecular data sets contributing to the final integrated report/diagnosis. Nonetheless, because most 2016 CNS WHO entities can be diagnosed solely on the basis of histologic features, in many situations, only the

Table 7. 2016 World Health Organization Classification of Tumors of the Central Nervous System[a]

Entities	ICD-O Code
Diffuse astrocytic and oligodendroglial tumors	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH–wild type	9400/3
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH–wild type	9401/3
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH–wild type	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	9440/3
Glioblastoma, IDH-mutant	9445/3[b]
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3[b]
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	9451/3
Oligoastrocytoma, NOS	9382/3
Anaplastic oligoastrocytoma, NOS	9382/3
Other astrocytic tumors	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumors	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, RELA fusion–positive	9396/3[b]
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumors	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumors	
Dysembryoplastic neuroepithelial tumor	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumor	9509/1

Table 7. Continued

Entities	ICD-O Code
Rosette-forming glioneuronal tumor	9509/1
Diffuse leptomeningeal glioneuronal tumor	
Central neurocytoma	9506/1 ISN-Haarlem
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumors of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumor of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumor of the pineal region	9395/3
Embryonal tumors	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3[b]
Medulloblastoma, SHH-activated and TP53-mutant	9476/3[b]
Medulloblastoma, SHH-activated and TP53–wild type	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3[b]
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell/anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumor with multilayered rosettes, C19MC-altered	9478/3[b]
Embryonal tumor with multilayered rosettes, NOS	9478/3
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumor, NOS	9473/3
Atypical teratoid/rhabdoid tumor	9508/3
CNS embryonal tumor with rhabdoid features	9508/3
Tumors of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumors	
Malignant peripheral nerve sheath tumor	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0

Table 7. Continued	
Entities	**ICD-O Code**
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumors	
Solitary fibrous tumor/hemangiopericytoma[c]	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Hemangioblastoma	9161/1
Hemangioma	9120/0
Epithelioid hemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma/PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumor	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma/ malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumors	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3

Table 7. Continued	
Entities	**ICD-O Code**
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumors	
Langerhans cell histiocytosis	9751/3
Erdheim-Chester disease	9750/1
Rosai-Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumors	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumor	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumor	9085/3
Tumors of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumor of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumors	

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; EBV, Epstein-Barr virus; IARC, International Agency for Research on Cancer; ICD-O, International Classification of Diseases for Oncology; MALT, mucosa-associated lymphoid tissue; MPNST, malignant peripheral nerve sheath tumor; NK, natural killer; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor; SHH, sonic hedgehog; WHO, World Health Organization.

The morphology codes are from the ICD-O. Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors.

The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

[a] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. *WHO Classification of Tumours of the Central Nervous System, Revised*. 4th ed. Lyon, France: IARC; 2016. *World Health Organization Classification of Tumours*; vol 1. Copyright WHO/International Agency for Research on Cancer (IARC). Reproduced with permission.

[b] These new codes were approved by the IARC/WHO Committee for ICD-O.

[c] Grading similar to that of non-CNS solitary fibrous tumors as proposed in the 2013 *WHO Classification of Tumors of Soft Tissue and Bone*.[15]

histologic and final data sets will need to be completed. It is anticipated that fewer diagnoses will be amenable to histology-only classification, but complete transition to combined histologic-molecular classification may take a long time—or may never happen given the relative ease and low cost of histologic diagnosis. The current data sets are therefore flexible and can be used for either histologic-molecular or histology-only reporting of CNS tumors, whether molecular testing is not needed or not available.

In conclusion, the current article and accompanying ICCR Web site[16] present reporting data sets for CNS tumors in the hope that they provide easy-to-use and highly reproducible means to issue diagnostic reports in consort with the 2016 CNS WHO. The Notes that clarify the data sets in turn provide extensive practical guidance to pathologists in areas that range from clinical to histologic to molecular. The consistent use of these templates could prove extraordinarily useful for patient care, clinical trials, epidemiologic studies, and monitoring of neuro-oncologic care around the world.

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References

1. Cross SS, Feeley KM, Angel CA. The effect of four interventions on the informational content of histopathology reports of resected colorectal carcinomas. *J Clin Oncol*. 1998;51(6):481–482.

2. Mathers M, Shrimankar J, Scott D, Charlton F, Griffith C, Angus B. The use of a standard proforma in breast cancer reporting. *J Clin Pathol*. 2001;54(10):809–811.

3. Srigley JR, McGowan T, MacLean A, et al. Standardized synoptic cancer pathology reporting: a population-based approach. *J Surg Oncol*. 2009;99(8):517–524.

4. Gill AJ, Johns AL, Eckstein R, et al. Synoptic reporting improves histopathological assessment of pancreatic resection specimens. *Pathology*. 2009;41(2):161–167.

5. International Collaboration on Cancer Reporting (2013–2018). *Histopathology Reporting Guides for Cancer Specimens*. http://www.iccr-cancer.org/datasets. Accessed October 28, 2016.

6. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. *WHO Classification of Tumours of the Central Nervous System, Revised*. 4th ed. Lyon, France: IARC; 2016. *World Health Organization Classification of Tumours*; vol 1.

7. International Collaboration on Cancer Reporting (2017). *Guidelines for the Development of ICCR Datasets*. http://www.iccr-cancer.org/datasets/dataset-development. Accessed March 1, 2017.

8. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol*. 2009;9:34.

9. Louis DN, Perry A, Burger P, et al. International Society of Neuropathology—Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol*. 2014;24(5):429–435.

10. Stichel D, Ebrahimi A, Reuss D, et al. Distribution of EGFR amplification, combined chromosome 7 gain and chromosome 10 loss, and TERT promoter mutation in brain tumors and their potential for the reclassification of IDHwt astrocytoma to glioblastoma. *Acta Neuropathol*. 2018;136(5):793–803.

11. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". *Acta Neuropathol*. 2018;136(5):805–810.

12. Shirahata M, Ono T, Stichel D, et al. Novel, improved grading system(s) for IDH-mutant astrocytic gliomas. *Acta Neuropathol*. 2018;136(1):153–166.

13. Louis DN, Wesseling P, Paulus W, et al. cIMPACT-NOW update 1: Not Otherwise Specified (NOS) and Not Elsewhere Classified (NEC). *Acta Neuropathol*. 2018;135(3):481–484.

14. Louis DN, Giannini C, Capper D, et al. cIMPACT-NOW update 2: diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant. *Acta Neuropathol*. 2018;135(4):639–642.

15. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France: IARC Press; 2013. *World Health Organization Classification of Tumours*; vol 5.

16. Louis DN, Brandner S, Brat D, et al. *Tumours of the Central Nervous System (CNS) Reporting Guide*. 1st ed. Sydney, Australia: International Collaboration on Cancer Reporting; 2018. http://www.iccr-cancer.org/datasets/published-datasets/central-nervous-system. Accessed March 27, 2019.