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MEETING REPORT

cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading

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Abstract

cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established to evaluate and make practical recommendations on recent advances in the field of CNS tumor classification, particularly in light of the rapid progress in molecular insights into these neoplasms. For Round 2 of its deliberations, cIMPACT-NOW Working Committee 3 was reconstituted and

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convened in Utrecht, The Netherlands, for a meeting designed to review putative new CNS tumor types in advance of any future World Health Organization meeting on CNS tumor classification. In preparatory activities for the meeting and at the actual meeting, a list of possible entities was assembled and each type and subtype debated. Working Committee 3 recommended that a substantial number of newly recognized types and subtypes should be considered for inclusion in future CNS tumor classifications. In addition, the group endorsed a number of principles—relating to classification categories, approaches to classification, nomenclature, and grading—that the group hopes will also inform the future classification of CNS neoplasms.

INTRODUCTION

Following the 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors, there have continued to be exciting developments in understanding how molecular changes impact the CNS tumor typing and grading. The need to evaluate and incorporate such developments into CNS tumor classification led about 3 years ago to the formation of cIMPACT-NOW, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy. To date, cIMPACT has published two explanatory introductions (44,45), four Round 1 updates (9,21,47,51), and a Round 1 summary (46). cIMPACT leadership, in setting the topics for the Round 2 of cIMPACT discussions, felt that a few of them would best be addressed at an in-person meeting (rather than in teleconference and email formats as the other cIMPACT deliberations had been). As a result, Working Committee 3 for cIMPACT Round 2 convened on September 16 and 17, 2019, in Utrecht, The Netherlands. The intended topics for the cIMPACT-Utrecht meeting were definitions of "new" entities and revised definitions of "old" entities, both pediatric and adult. The meeting brought together an alliance of individuals involved to date in the cIMPACT Steering Committee, Clinical Advisory Panel, and Round 2 Working Committee 3, as well as others who have not been prior cIMPACT participants. A total of 26 neuropathologists attended as well as three oncologists (an additional two oncologists had been invited but could not attend) and three representatives from the International Agency for Research on Cancer, which oversees the WHO tumor classification process.

To prepare for the meeting, the participants generated a list of 40 types as potential subjects of discussion. Eight groups of individuals then met via teleconferences and group emails to evaluate histopathologically related novel tumor types and to address the following issues for each: (i) to assemble the literature on each possible type and to evaluate whether the literature was strong enough to support endorsing the entity as distinct; (ii) to decide if it was a type or a subtype (see below); (iii) to generate a new definition or to change an existing definition; and (iv) to suggest where in the WHO CNS tumor classification it might fit best. Each group was led by two neuropathologists. Subsequently, these eight lists of putative tumor types/subtypes formed the basis of eight breakout sessions; in addition, a breakout session was added on methylome diagnostics, given the emerging importance of this methodology in neuropathology. The majority of the 2-day meeting, however, was spent in plenary sessions in which the suggestions of the breakout sessions were discussed and in which consensus principles were derived.

For each possible type/subtype, the groups decided whether the lesion, as described in the literature to date, was one (or more) of the following, as summarized in Table 1:

Newly recognized type, subtype, diagnostic criteria, or family of tumors.
Existing type with suggested name modification.
Existing type with no recommended name changes.
Lesion *sub judice* (ie, lacking sufficient published evidence to make a decision).

The following report summarizes the findings of the meeting in two parts. We first describe principles that were presented to and discussed by the committee and that might be helpful in future approaches to the CNS tumor classification. We next catalog those newly recognized or changed types/subtypes/criteria/families that were endorsed by cIMPACT Round 2 Working Committee 3 (the first two categories above and in Table 1).

For all of these findings, while it is hoped that they guide future efforts in brain tumor classification and grading, at the present time they represent recommendations only, and it is possible that the next WHO guidelines will not be identical if they incorporate newer published findings and additional nosological concepts.

PRINCIPLES

The cIMPACT-Utrecht meeting established the following principles in the hope that they will guide future efforts in CNS tumor classification and grading.

Types/subtypes vs. entities/variants

Prior CNS tumor classifications used the terms "entities" and "variants" (48). Current WHO recommendations use the parallel terms "types" and "subtypes", and the meeting participants encouraged future CNS tumor classifications to

Table 1. Summary of cIMPACT-Utrecht recommendations.

A	Newly recognized type, subtype, diagnostic criteria, or family of tumors
	Specific genetic features sufficient for diagnosis of "glioblastoma, IDH-wildtype"
	Astrocytomas, IDH-mutant, grades 2 through 4
	Pediatric-type glial/glioneuronal tumors (see Table 3)
	Diffuse glioma, H3.3 G34-mutant
	High-grade astrocytoma with piloid features
	Astroblastoma, *MN1*-altered
	Diffuse leptomeningeal glioneuronal tumor, subtypes
	Myxoid glioneuronal tumor
	Polymorphous low-grade neuroepithelial tumor of the young
	Multinodular and vacuolating neuronal tumor
	Supratentorial ependymoma, *YAP1-MAMLD1* fusion-positive
	Posterior fossa ependymoma, pediatric-type/PFA
	Posterior fossa ependymoma, adult-type/PFB
	Spinal ependymoma, *MYCN*-amplified
	CNS neuroblastoma, *FOXR2*-activated
	CNS tumor with *BCOR* internal tandem duplication
	CIC sarcoma (aligned with the WHO classification of tumors of soft tissue and bone)
2.	Existing types with suggested name modifications (see also Table 4)
	Chordoid glioma
	Supratentorial ependymoma, *RELA* fusion-positive
3.	Existing types discussed but with no name changes recommended[†]
	Diffuse leptomeningeal glioneuronal tumor (also see above)
	Extraventricular neurocytoma
	Papillary glioneuronal tumor
	Pilocytic astrocytoma
	Pleomorphic xanthoastrocytoma
	Pineal parenchymal tumor of intermediate differentiation
4.	Lesions *sub judice* (ie, lacking sufficient published evidence to make a decision)[‡]
	Diffuse glioma, FGFR-TACC fusion-positive
	ETMR-like infantile cerebellar embryonal tumors, *DICER1*-altered
	Glioneuronal tumor, *EWSR1-PATZ1* fusion-positive
	Hemispheric high-grade glioma, *SETD2*-mutant
	Infantile hemispheric glioma, NTRK fusion-positive
	Infantile hemispheric glioma, *ALK* or *ROS1* fusion-positive
	Infantile hemispheric glioma, *MET* fusion-positive
	Myxopapillary ependymoma with anaplastic features
	Neuroepithelial tumor, *BCOR*/*BCORL1* fusion-positive
	CNS high-grade neuroepithelial tumor with *MN1* alteration
	Pilocytic astrocytoma with anaplastic features[§]
	Pleomorphic xanthoastrocytoma with anaplastic features[§]

[†]These entities are not discussed further in the manuscript except for diffuse leptomeningeal glioneuronal tumor subtypes.

[‡]These entities are not discussed further in the manuscript; their names are primarily from literature; because lesions were not considered mature enough for recommendation, nomenclature was not discussed.

[§]For the last two tumors, information was not considered mature enough to change the description as given in the 2016 WHO classification.

use these terms so that they conform with terminology used across organ systems. As a result, this paper uses the terms "types" and "subtypes," which are defined as:

- Type: a neoplasm in which multiple parameters (eg, clinical, anatomic, histopathologic, and/or molecular) differ from other types (eg, myxoid glioneuronal tumor).
- Subtype: a variant of a type in which a single or couple of parameters (eg, clinical, anatomic, histopathologic, and/or molecular) suggest it differs from other subtypes and thus make it desirable to recognize the variant (eg, MC-1 and MC-2 subtypes of diffuse leptomeningeal glioneuronal tumor).

Approaches to tumor categories: pediatric-type glial/glioneuronal tumors and ependymomas

Classifications can group tumor types into categories of related entities in different ways. For example, tumor types can be grouped by a single feature (eg, an astrocytic phenotype or a particular genotype); such pronounced "lumping" can result in the grouping of quite different tumors (eg, *BRAF*-mutant pleomorphic xanthoastrocytomas and *BRAF*-mutant metastatic melanomas). Another approach is to divide types into as many subtypes as possible; such "splitting" is seen in current leukemia classifications, with subtypes of a morphologic type defined by the range of genotypic variation, even if some subtypes are rare. An alternative method is to "mix and match" in a matrix similar to the approach in the 2016 CNS WHO for classification of medulloblastomas: a histologically defined list of tumors and a genetically defined list of tumors, which can be combined into an integrated diagnosis (49). This approach affords great flexibility while at the same time conveying the key diagnostic information in a succinct format that can be layered (or tiered) (50). Importantly, some combinations are more common than others, so that the number of routinely used integrated diagnoses is manageable. This approach was presented at the first plenary session as a potential model, and those "pediatric-type" IDH-wildtype and H3-wildtype gliomas with a predominantly diffuse architecture (21) were used as one example (Table 2). As described below, the cIMPACT-Utrecht group strongly endorsed the clinical utility of this two-list approach for a range of glial/glioneuronal tumors, a category in which there are many histological appearances and many genotypes (Table 3).

Among ependymomas, overlapping histopathologic features can be associated with markedly different clinical behaviors. Such variability relates in part to the biologic heterogeneity shown by ependymomas across the three principal anatomic compartments of the CNS, with their distinct genetic and epigenetic signatures (61). The cIMPACT-Utrecht committee favored categorizing ependymomas by anatomic site and incorporating site into tumor nomenclature (see below). For example, a category of *Supratentorial ependymomas* would include *Supratentorial ependymoma, RELA fusion-positive* and *Supratentorial ependymoma, YAP1 fusion-positive* while a category of *Posterior fossa ependymomas* would include *Posterior fossa ependymoma, pediatric-type*/*PFA* and *Posterior fossa ependymoma, adult-type*/*PFB*. Respective proposals for these new types of ependymal tumors as well as spinal ependymomas

Table 2. Classification of "pediatric-type" IDH-wildtype and H3-wildtype diffuse gliomas illustrating the principle of a matrix approach for reaching an integrated, tiered diagnosis. One tumor type defined by histopathology and a second by genetic alteration are combined in the top layer of the integrated diagnosis, with other tiers of information provided.

Pediatric-type diffuse glioma, IDH-wildtype, and H3-wildtype	
Diffuse glioma, genetically defined	
Diffuse glioma, *MYB*-altered	
Diffuse glioma, *MYBL1*-altered	
Diffuse glioma, *FGFR1* TKD-duplicated	
Diffuse glioma, FGFR-altered	
Diffuse glioma, *BRAF* V600E-mutant	
Diffuse glioma, other MAPK pathway alteration	
Diffuse glioma, histologically defined	
Diffuse astrocytoma	
Oligodendroglioma	
(Etc., other related histologies)	
Integrated diagnosis	
Cerebrum	
Integrated diagnosis	Diffuse astrocytoma, *MYB*-altered
Histopathology	Diffuse astrocytoma
Histological grade	WHO grade II (or "2", see text)
Molecular information	H3-wildtype by sequencing
	MYB-PCDHGA fusion gene by sequencing
	MYB rearrangement by interphase FISH

with *MYCN* amplification are summarized below. *Subependymoma* would be an additional category, since these occur in all three compartments and have a similar clinical course. A more comprehensive proposal for ependymoma classification, however, is under consideration in the Round 2 deliberations of cIMPACT Working Committee 2 and these subsequent recommendations may differ somewhat, as may the next WHO classification. The ideas are presented here to give the reader insights into the current and changing thinking regarding ependymoma classification.

Tumor nomenclature

The group considered general principles regarding naming tumor types, cognizant of the fact that previous decisions had not been wholly consistent. For example, some tumor names have anatomic site modifiers (eg, chordoid glioma of the third ventricle), whereas others do not, despite occurring in specific locations (eg, medulloblastoma), and some included genetic modifiers (eg, glioblastoma, IDH-wildtype), whereas others did not despite having specific genotypes (eg, atypical teratoid/rhabdoid tumor). It was felt that names should be as simple as possible, and only location, age or genetic modifiers with clear clinical utility should be used (eg, extraventricular neurocytoma vs. central neurocytoma; also see discussion of ependymal tumors above). In this context, inclusion of specific features in tumor definitions and descriptions (eg, chordoid gliomas occur in the third ventricle) provides a mechanism to characterize the entity and is therefore not necessary in the name itself. Following these recommendations, suggestions were made for modifying the names of some tumor types (see Table 4).

Methylome profiling

Methylome profiling has been shown to provide powerful information for the classification and diagnosis of CNS tumors (11-12,37). The cIMPACT-Utrecht committee agreed that many CNS tumor types and subtypes can be reliably identified by their methylome profile, with the caveats that optimal methodologic approaches and regulatory issues have yet to be resolved and that it remains difficult to recommend methylome profiling as the only method to identify a particular tumor type or subtype (see sections on "High-grade astrocytoma with piloid features" and "Diffuse leptomeningeal glioneuronal tumor" below). Indeed, most tumor types and subtypes can also be reliably identified by other techniques (eg, from a combination of histology and defining genetic alteration).

Grading: Arabic vs. Roman numerals

Traditionally, CNS WHO tumor grades have been in Roman numerals, with a grade assigned to each entity. For example, if a tumor is classified as an anaplastic astrocytoma, it is automatically assigned a WHO grade of III and there is no option for an anaplastic astrocytoma to be grade I, II, or IV. However, many tumors in other organ systems are graded *within* tumor types, for example, a malignant peripheral nerve sheath tumor can be either grade 1, 2, or 3, and such grades are often given in Arabic numerals. In the 2016 CNS WHO classification, hemangiopericytoma/solitary fibrous tumor is graded in the latter manner, using a single name but with the option of three grades. The danger of using Roman numerals in a within-tumor grading system is that a "II" and a "III" or a "III" and a "IV" can be mistaken for one another and an uncaught typographical error could have clinical consequences. Moreover, the 5th edition of the WHO Blue Books is emphasizing more uniform approaches to tumor classification and grading, and has favored the use of Arabic numerals. Given these considerations, the cIMPACT-Utrecht group recommended (i) that IDH-mutant astrocytomas shift to a within-tumor grading system (see below) and (ii) that all WHO CNS tumor grades switch to Arabic numerals to decrease the possibility of such errors. [In this manuscript, given that the suggestion to move to Arabic numerals has not been endorsed yet for the next (5th edition) CNS WHO classification, we have kept the use of Roman numerals when referring to WHO entities and their designated grades. We anticipate that all CNS WHO grades will change to Arabic numerals in the 5th edition Blue Book.]

SPECIFIC TYPES, SUBTYPES, DEFINITIONS, AND GRADING CRITERIA

The participants at the cIMPACT-Utrecht meeting endorsed the following specific types, subtypes, definitions, and

grading criteria and recommended that these be considered for the next WHO classification (corresponding to Section A in Table 1). Following WHO guidelines for 5th edition Definition sections, we have tried to make the definitions as brief as possible, including only those features necessary for the diagnosis, leaving additional details for other sections in the description.

Diagnostic criteria for Glioblastoma, IDH-wildtype

cIMPACT Update 3 (9) suggested that, in the setting of an IDH-wildtype diffuse astrocytic tumor in adults, the presence of one of three genetic parameters [*TERT* promoter mutation, *EGFR* gene amplification, combination of gain of entire chromosome 7 and loss of entire chromosome 10 (+7/−10)] would be sufficient to assign a WHO grade IV. At the time, the somewhat cumbersome designation of "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV" was suggested. The specific criteria for this designation are discussed in more detail in cIMPACT Update 3 and the reader is referred there for additional details (9). Recent data confirm that survival of patients with these tumors is similar to patients with histologically classic glioblastoma, IDH-wildtype, WHO grade IV (80). The cIMPACT-Utrecht meeting recommended that the nomenclature could be simplified and entry into clinical trials could be facilitated using these three genetic parameters as criteria for a diagnosis of "Glioblastoma, IDH-wildtype." In other words, an IDH-wildtype diffuse astrocytic glioma could be diagnosed as "Glioblastoma, IDH-wildtype, WHO grade 4" if there is microvascular proliferation or necrosis or one (or more) of the three genetic alterations (*TERT* promoter mutation, *EGFR* gene amplification, +7/−10 chromosome copy number changes) (Table 5). Notably, while this would simplify nomenclature and trial entry, it creates a possible situation in which an IDH-wildtype diffuse astrocytic glioma lacks the histological hallmarks of glioblastoma (ie, microvascular proliferation and necrosis) but is still is classified as a "glioblastoma".

Table 3. Possible future classification for pediatric-type glial/glioneuronal tumors, which could be used in a matrix approach to an integrated diagnosis (see Table 2). TKD = tyrosine kinase domain. NOS = not otherwise specified.

Genetically defined
BRAF V600E-mutant
BRAF fusion-positive
FGFR1 TKD-duplicated
FGFR1-mutant
FGFR1 fusion-positive
FGFR2 fusion-positive
MYB-altered
MYBL1-altered
NTRK fusion-positive
Histologically defined
Astrocytoma
Oligodendroglioma
Angiocentric glioma
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Rosette-forming glioneuronal tumor
Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)
Glial/glioneuronal tumor, NOS

Nomenclature for Astrocytoma, IDH-mutant, grades 2 through 4

For Round 2 of cIMPACT updates, Working Committee 1 addressed the question of grading and nomenclature for IDH-mutant diffuse astrocytomas and their recommendations were presented and approved at the cIMPACT-Utrecht meeting, as captured in Table 6. Key features of this system are: the conversion to a single name ("Astrocytoma, IDH-mutant") with Arabic numeral grades assigned within the type; the discontinuation of the term "Glioblastoma, IDH-mutant"; the retention of histological features; and the introduction of a genetic parameter (*CDKN2A*/*B* homozygous deletion) that connotes a grade 4 designation. In this proposed system, IDH-mutant tumors that meet 2016 CNS WHO criteria for anaplastic astrocytoma (WHO grade III) should be tested for *CDKN2A*/*B* homozygous deletion; if *CDKN2A*/*B* homozygous deletion is present, the tumor should

Table 4. Suggested name changes to make nomenclature more uniform and simple.

	Location	Genotype	Other
Chordoid glioma†	Deleted	No	
Multinodular and vacuolating neuronal tumor‡	Deleted	No	
Myxoid glioneuronal tumor§	Deleted	No	
Extraventricular neurocytoma	Required	No	
Supratentorial ependymoma, *RELA* fusion-positive	Required		
Papillary glioneuronal tumor		No	
Pineal parenchymal tumor of intermediate differentiation		No	
CIC sarcoma			WHO

*These were discussed at the Utrecht meeting but are not a comprehensive list of all CNS tumors. Location required = information on location required for better discrimination from other types/subtypes; No genotype: no information regarding genotype included in name since this is not needed to signify the type/subtype; Other: name changed to conform to nomenclature in WHO 2019 Classification of Tumours of Soft Tissue and Bone.

†Location deleted ("of the third ventricle").

‡Location deleted ("of the cerebrum").

§Location deleted ("of the septum pellucidum and lateral ventricle").

Table 5. Suggested criteria for Glioblastoma, IDH-wildtype.

An IDH-wildtype diffuse astrocytic glioma with:

- Microvascular proliferation, or
- Necrosis, or
- One or more of the following molecular features of glioblastoma:
  - *TERT* promoter mutation, or
  - *EGFR* gene amplification, or
  - +7/−10 chromosome copy number changes

Table 6. Suggested definitions and grading of Astrocytomas, IDH-mutant.

Astrocytoma, IDH-mutant, WHO grade 2
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or low. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, WHO grade 3
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, WHO grade 4
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion or any combination of these features

then be designated grade 4. (The prognostic significance of functionally equivalent alterations to *CDKN2A*/*B* homozygous deletion that are also found in IDH-mutant astrocytomas, such as *RB1* mutation or *CDK4* amplification, remains less well-defined at this time, and these genetic parameters are not yet recommended for grading IDH-mutant astrocytomas.) Significant mitotic activity remains as the criterion to differentiate grade 2 from grade 3 tumors, although it is not yet clear if this (loosely defined) criterion will hold in the future. Microvascular proliferation and necrosis remain criteria for diagnosing a grade 4 tumor; although such tumors may behave less aggressively if they lack CDNK2A/B homozygous deletion, they are nonetheless highly aggressive tumors. Additional details are provided in cIMPACT Update 5 from cIMPACT Round 2 Working Committee 1 (8).

Diffuse glioma, H3.3 G34-mutant

Proposed definition: A diffuse IDH-wildtype glioma of the cerebral hemispheres with a missense mutation exchanging glycine for arginine or valine at position 34 of the mature histone H3.3 protein.

Characteristic features (24,41-42,89): Diffuse glioma, H3.3 G34-mutant most frequently presents in pediatric and young adult patients and is located in the cerebral hemispheres. Histopathology typically shows a diffusely infiltrating glioma with astrocytic differentiation and features of anaplasia, including mitotic activity, microvascular proliferation and/or necrosis. Some cases may histologically resemble CNS embryonal tumors; that is, they are composed of densely packed monomorphic small cells with high nuclear-to-cytoplasmic ratio and sometimes without obvious necrosis or microvascular proliferation. The type-defining diagnostic criterion is a missense mutation replacing glycine (G) with arginine (R) or valine (V) at position 34 of the mature form of the H3 histone family 3 (H3.3) protein ("H3.3 G34 mutation"). The H3.3 protein is encoded by two replication-independent genes, namely *H3F3A* at 1q42.12 and *H3F3B* at 17q25.1, with H3.3 G34 mutations in gliomas typically affecting *H3F3A*. Immunohistochemical detection of H3.3 G34-mutant proteins, that is, H3.3 G34R or H3.3 G34V, can serve as an alternative diagnostic method to DNA sequencing (31). Lack of OLIG2 expression is a common immunohistochemical feature (reported in up to 90% of cases) and loss of ATRX expression and p53 overexpression in tumor nuclei, associated with *ATRX* and *TP53* mutation, respectively, are found in nearly all cases. Despite their heterogeneous histological features, these tumors display a distinctive DNA methylation profile that may facilitate their diagnosis.

Comment: Diffuse glioma, H3.3 G34-mutant should be listed in future classifications with the diffuse glial tumors as a novel tumor type distinct from the established types of IDH-mutant and IDH-wildtype gliomas, as well as from the H3 K27M-mutant diffuse midline gliomas. Diffuse glioma, H3.3 G34-mutant corresponds to WHO grade IV. The overall survival of patients treated according to the current standard of care is slightly longer compared to patients with glioblastoma, IDH-wildtype, but considerably shorter compared to patients with WHO grade IV IDH-mutant astrocytomas (77). However, a recent study of pediatric high-grade gliomas reported a poor outcome similar to patients with H3 K27M-mutant diffuse midline gliomas (54). While certain histological or molecular features have been suggested as prognostically relevant factors within the group of H3.3 G34-mutant diffuse glioma patients, definitive diagnostic criteria for separating these tumors into WHO grade III and IV lesions have not been defined. Lastly, there remains debate as to the best numbering to be applied to the molecular defect mentioned in the name of these tumors, that is, whether to follow the amino acid numbering (G34) or the DNA codon numbering (G35) (20).

High-grade astrocytoma with piloid features

Proposed definition: An astrocytoma displaying histological features of anaplasia alongside a piloid cytology and frequent MAPK pathway gene alterations, combined with homozygous deletion of *CDKN2A*/*B* and loss of nuclear ATRX expression (indicative of mutation), as well as a distinct DNA methylation pattern.

Characteristic features (67): High-grade astrocytoma with piloid features may arise either *de novo* or from a lower-grade precursor. Similar to pilocytic astrocytoma, MAPK pathway gene mutations are frequent, most often affecting *NF1*, followed by *BRAF* and *FGFR1*. Homozygous deletion of *CDKN2A*/*B* and/or *ATRX* mutation or loss of expression are common additional features. The tumor occurs most frequently in the cerebellum and patients have an unfavorable clinical course when compared to those with pilocytic astrocytoma, while mean survival is longer when compared to IDH-wildtype glioblastoma patients.

Comment: There was extensive debate over this new type, in that the histological features vary considerably (with not all cases having a piloid cytology) and that the entity has only been defined in the published literature on the basis of a distinct methylome profile. Moreover, the type has only been characterized in a single publication (68), with one additional publication that came out after the Utrecht meeting (67). Nonetheless, the committee felt that, while

there was much to be learned about this entity, the tumor was distinct from both histologically defined anaplastic astrocytoma and pilocytic astrocytoma. The term "high-grade" was used instead of "anaplastic" in order to avoid confusion with terms such as "anaplastic astrocytoma" and with "pilocytic astrocytoma with anaplastic features / anaplastic pilocytic astrocytoma", which remains less well-defined and which has been used terminologically in different ways. Lastly, because survival data are limited to small, uncontrolled retrospective patient cohorts, additional studies are required to determine if all of these tumors follow a course similar to WHO grade III tumors.

Astroblastoma, *MN1*-altered

Proposed definition: A circumscribed glial neoplasm with *MN1* alteration (usually a fusion between *MN1* and *BEND2*), and usually with cuboidal or columnar cells with variable pseudopapillary or perivascular growth, perivascular anuclear zones, and vascular and pericellular hyalinization, and focal immunohistochemical expression of EMA and podoplanin.

Characteristic features (10,34,43,56,76,85): The tumors preferentially arise in the cerebral hemispheres of young patients. EMA and podoplanin are expressed in all tumors, and GFAP, OLIG2, and S100 protein are often immunopositive but show variability in their extent of reactivity. Deletions in 22q and X chromosome are frequently identified (10,34).

Comment: Astroblastoma, *MN1*-altered is a specific tumor type; subtypes of this entity have not been described and definitive grading criteria have not been established. While a high-proportion of tumors in the methylation class "CNS high-grade neuroepithelial tumor with *MN1* alteration" show a histological appearance compatible with astroblastoma, the morphology of some does not conform to astroblastoma. Whether the future definition of Astroblastoma, *MN1*-altered should include such disparate histologic patterns remains unresolved. For future classifications, the tumor fits best in the group of "Other gliomas." Tumors with classic astroblastoma morphology in which *MN1* alterations cannot be tested could be given an "Astroblastoma, NOS" (Not Otherwise Specified) (51) designation and histologically classic astroblastomas that have been tested but lack *MN1* alterations (and do not carry molecular alterations characteristic of other types of astrocytic or ependymal tumors such as *BRAF* V600E mutation or *RELA* fusion) could be designated as Not Elsewhere Classified, that is, "Astroblastoma, NEC" (51).

Diffuse leptomeningeal glioneuronal tumor (DLGNT)

Proposed definition: A glioneuronal neoplasm composed of oligodendrocyte-like cells; chromosome arm 1p deletion and a mitogen-activated protein kinase (MAPK) pathway gene alteration, KIAA1549-BRAF fusion being most frequent; without IDH mutation; and commonly with diffuse leptomeningeal tumor spread.

Characteristic features (70-71,73): Most DLGNTs occur in children and feature widespread leptomeningeal dissemination at presentation. Occasionally, a parenchymal primary is evident, most commonly in the spinal cord, and the tumor can also present without leptomeningeal dissemination (16). Rare examples show neurocytic rosettes, ganglion cells, and/or histological features of anaplasia (74). Immunohistochemistry shows frequent expression of OLIG2, MAP2 and S100 in the oligodendrocyte-like tumor cells, while GFAP positivity may be sparse or absent. Expression of synaptophysin is seen in oligodendrocyte-like cells, as well as rare neuronal elements.

Comment: The data now suggest that DLGNT is a distinct tumor type, rather than a provisional entity. In future classifications, the type should be placed among "Neuronal and mixed neuronal-glial tumors" on the basis of consistent immunoreactivity for synaptophysin in oligodendrocyte-like cells and the occasional occurrence of ganglion cells. The behavior of these lesions varies, and there is no clear consensus on grade assignment. Two subtypes have been recognized, DLGNT-methylation class (MC)-1 and DLGNT-MC-2, but currently these can only be defined by methylome profiling (19). DLGNT-MC-2 is enriched for superimposed 1q gain and is associated with shorter patient survival compared to patients with DLGNT-MC-1. In non-subtyped DLGNTs, 1q gain is similarly associated with poor prognosis (15). 1p/19q codeletion is more common in DLGNT-MC-1. All DLGNTs are IDH-wildtype.

Myxoid glioneuronal tumor

Proposed definition: A circumscribed glioneuronal tumor centered most often in the septal region (septal nuclei and sometimes the septum pellucidum), but occasionally in the periventricular white matter or corpus callosum, and histologically characterized by oligodendrocyte-like tumor cells embedded in a prominent myxoid/mucin-rich stroma, sometimes including "floating" neurons, neurocytic rosettes, and/or perivascular neuropil.

Characteristic features (5,13,17,25,28,32,52,65,72,75,86,87): Myxoid glioneuronal tumors are slow-growing neoplasms. Clinical outcome data from the limited number of patients reported to date would suggest a clinical course similar to WHO grade I entities; however, ventricular dissemination is not uncommon. These tumors are genetically characterized by a recurrent dinucleotide substitution that results in either a K385L or a K385I mutation in the *PDGFRA* gene. Their DNA methylation signature is closely related to that of the cerebral dysembryoplastic neuroepithelial tumor (DNT).

Comment: Myxoid glioneuronal tumor could be placed in the category of "Neuronal and mixed neuronal-glial tumors." Their differential diagnosis includes a variety of other entities that can occur in the same region. In this regard, the occurrence of multiple mucin-containing nodules typical of DNTs of the cerebral cortex is not a radiographic or microscopic feature of these neoplasms, and the Rosenthal fibers of pilocytic astrocytoma are not a common feature. In addition, myxoid glioneuronal tumor lacks the *FGFR1* mutations or rearrangements that characterize most DNTs of the cerebral

cortex, as well as the *FGFR1* mutations or rearrangements that characterize rosette-forming glioneuronal tumors. These tumors also lack the *BRAF*, *RAF1*, or *FGFR1* mutations or fusions present in most pilocytic astrocytomas.

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)

Proposed definition: A cerebral neoplasm characterized by a mostly diffuse growth pattern, frequent presence of oligodendroglioma-like components and calcification, extensive immunohistochemical expression of CD34 by tumor cells as well as ramified neural elements in the associated cerebral cortex, and MAPK pathway-activating genetic abnormalities, mostly involving *FGFR2*, *FGFR3* or *BRAF* genes.

Characteristic features (7,29,33,36,69,78): These tumors occur predominantly in children and young adults and have a strong association with epilepsy. Elements indistinguishable from diffuse glioma may be present, as well as pleomorphic astrocytic components and tumor cells arranged in perivascular pseudorosettes.

Comment: PLNTY constitutes a distinct tumor type that future classifications should consider placing either within the group of "Neuronal and mixed neuronal-glial tumors" or, more specifically, in the family of "Pediatric-type glial tumors and glioneuronal tumors" (see Tables 2 and 3). Tumors with similar histology and clinical behavior have been previously reported as non-specific forms of DNT, diffuse glioneuronal tumors, long-term epilepsy-associated tumors, massively calcified low-grade glioma, and pediatric-type oligodendrogliomas. The exact relation of PLNTY to the various entities reported under these differing designations is not clear—a particular issue being their relation to *FGFR*-altered pediatric-type IDH-wildtype oligodendrogliomas, which have not been systematically investigated for CD34 expression or for their DNA methylation profiles.

Multinodular and vacuolating neuronal tumor (MVNT)

Proposed definition: A neuroepithelial tumor composed of monomorphous neuronal elements in discrete and coalescent nodules, with vacuolar changes in tumor cells and their matrix.

Characteristic features (18,35,57-58,64,81): MVNTs are clinically benign. These tumors may be asymptomatic or associated with epilepsy, headaches or other, non-localizing complaints. They are cerebral in location and generally superficial, most commonly involving the temporal and frontal lobes in adults (mean age at presentation ~40 years). Tumor nodules frequently colonize the deeper cortical layers and subjacent white matter, though a more diffuse distribution of neuronal elements producing band-like/gyriform expansion of the cortex or hippocampus may be seen. Constituent neurons are most often of intermediate-to-large size and are randomly disposed or aligned along thin-walled blood vessels. Some MVNTs also contain small oligodendrocyte-like elements of unclear lineage. Conspicuous neuronal dysmorphism is exceptional and lesions typically lack the eosinophilic granular bodies and inflammatory infiltrates of classic ganglion cell tumors. Mitotic activity is essentially absent. By immunohistochemistry, neuronal components are GFAP-negative, consistently express both the HuC/HuD neuron-associated antigens and OLIG2, and often display cytoplasmic synaptophysin, though this tends to be weak and synaptophysin expression within the nodular matrix is greatly reduced relative to cortex. Furthermore, neuronal components can express non-phosphorylated 200 kDa neurofilament protein antigens, but are usually negative for NeuN, chromogranin and phosphorylated neurofilament proteins. The finding of specialized glial antigen expression (eg, GFAP-delta) by cells within some MVNTs has been taken as evidence that these harbor neoplastic glial populations. Often associated with MVNTs are CD34-labeling neuritic elements of ramified type, but the neuronal components themselves are typically CD34-negative. Ki-67 labeling indices do not exceed 1% in most cases, labeling usually being restricted to small intranodular cells and not the neuronal components. To date, MVNTs have been found negative for *BRAF* V600E mutations, *KIAA1549-BRAF* fusions and abnormalities involving *IDH1* or *IDH2*, *ATRX*, *TP53*, *TERT*, *CIC*, *FUBP1*, *PRKCA*, *CDKN2A,* and *FGFR1*, but MVNTs have been shown to harbor clonal MAPK pathway-activating genetic abnormalities (including *MAP2K1* exon 2 mutations, non-V600E *BRAF* mutations and *FGFR2* fusions) (64).

Comment: MVNT was included in the 2016 WHO classification but only as a histopathological pattern in the commentary on ganglion cell tumors. The cIMPACT-Utrecht meeting opined that this should now be considered a distinct tumor type and that it could be placed within the section covering "Neuronal and mixed neuronal-glial tumors" as a WHO grade I lesion. This opinion is supported by the observation that MVNTs harbor clonal genetic alterations (64), which favors a neoplastic rather than malformative origin.

Supratentorial ependymoma, *YAP1-MAMLD1* fusion-positive

Proposed definition: An ependymoma that arises in the supratentorial compartment and has a fusion between *YAP1* and *MAMLD1*.

Characteristic features (2,23,61,63): Supratentorial ependymoma, *YAP1-MAMLD1* fusion-positive mainly occurs in young children (<3 years), but occasionally arises in adults. There is a female predominance. The tumors are often large intra-/paraventricular lesions with prominent cyst formation and account for approximately 4% of supratentorial ependymomas. Immunoreactivity for L1CAM or p65 is typically absent. Patients with *YAP1-MAMLD1* fusion-positive ependymoma usually have a favorable prognosis that is better than that of patients with *RELA* fusion-positive ependymomas. The tumors have a characteristic methylation profile (61).

Comment: *YAP1* may fuse with additional partners in rare cases of supratentorial ependymoma, for example, *FAM118B*, but the biological and clinical features of tumors with alternative *YAP1* fusion partners remain to be

characterized, and such alternative fusions are at present not included in this type.

Posterior fossa ependymoma, pediatric-type/PFA

Proposed definition: A posterior fossa ependymoma that has a PFA DNA methylation profile and/or immunohistochemical loss of nuclear H3 K27me3 expression.

Characteristic features (1,4,27,38,55,59-62,66,82,84): Posterior fossa ependymoma, pediatric-type/PFA mainly occurs in infants and young children. The tumors can show characteristic histological features of ependymal differentiation and most have anaplastic features. Overall, the prognosis of patients with posterior fossa ependymoma, pediatric-type/PFA is worse than that of patients with posterior fossa ependymoma, adult-type/PFB.

Comment: The presence of chromosome 1q gain is recognized as an adverse prognostic factor across all posterior fossa ependymomas and among pediatric-type/PFA tumors alone (27,60). However, some subtypes of pediatric-type/PFA ependymoma without a high frequency of 1q gain also have a relatively poor outcome (60). Rare examples of posterior fossa ependymoma, pediatric-type/PFA (4%–5%) can harbor an H3 K27M mutation. This finding does not prompt a diagnosis of diffuse midline glioma (47), and the mutation is currently of unknown prognostic significance in this tumor type. The nomenclature of ependymomas is being further considered by cIMPACT Working Committee 2 and the subsequent WHO terminology may differ from what has been proposed here.

Posterior fossa ependymoma, adult-type/PFB

Proposed definition: A posterior fossa ependymoma that has a PFB DNA methylation profile and/or immunohistochemical retention of nuclear H3K27me3 expression.

Characteristic features (14,59,61,66,83,84): Posterior fossa ependymoma, adult-type/PFB typically occurs in adolescents and adults. Histologically, these tumors display characteristic features of ependymoma and can appear identical to a pediatric-type/PFA ependymoma. Most do not show anaplastic features. These tumors typically show ploidy changes across multiple whole chromosomes. The prognosis of patients with posterior fossa ependymoma, adult type/PFB is more favorable than that of patients with posterior fossa ependymoma, pediatric type/PFA. As mentioned above, the nomenclature of ependymomas is being further considered by cIMPACT Working Committee 2 and the subsequent WHO terminology may differ from what has been proposed here.

Spinal ependymoma, *MYCN*-amplified

Proposed definition: An ependymoma in the spinal cord with *MYCN* amplification.

Characteristic features (26,79): Most ependymomas with *MYCN* amplification are located in the thoracic or cervical spinal cord and have anaplastic histological features. These tumors have a distinct DNA methylation profile, different from other ependymoma types. Nuclear immunoreactivity for MYCN may help to identify these tumors but definitive classification requires demonstration of *MYCN* gene amplification. Dissemination is frequent and prognosis is poor compared to that of other spinal ependymomas.

Comment: Although only recently described (26,79), the combined clinical and pathological features argue that this is a distinct tumor type.

CNS neuroblastoma, *FOXR2*-activated

Proposed definition: An embryonal neoplasm with neuroblastic and/or neurocytic cells, variable occurrence of ganglion cells and neuropil-rich stroma, frequent chromosome 1q gain, and activation of the transcription factor FOXR2 by various structural rearrangements.

Characteristic features (11,76): CNS neuroblastoma, *FOXR2*-activated, usually presents in children as a demarcated cerebral mass. Most tumors show overexpression of *FOXR2* and *NKX2-1*. The tumors co-express OLIG2 and synaptophysin but lack immunoreactivity for GFAP or vimentin in most cells.

Comment: For future classifications, the tumor should be listed with other CNS embryonal tumors. *FOXR2* activation represents the most frequent genetic alteration in tumors classified histopathologically as CNS neuroblastoma. However, CNS neuroblastomas with alternative genetic events may occur (eg, *MYC*-amplified CNS neuroblastoma) and these could be designated as CNS neuroblastoma, NEC. The frequency of *FOXR2* alterations in CNS ganglioneuroblastoma has yet to be determined. For therapeutic purposes, it is important to distinguish CNS neuroblastoma, *FOXR2*-activated, from malignant gliomas, anaplastic ganglioglioma, and extraventricular neurocytoma.

CNS tumor with *BCOR* internal tandem duplication (CNS-BCOR ITD)

Proposed definition: A malignant tumor with *BCOR* exon 15 internal tandem duplication, monotonous round to oval nuclei, predominantly solid growth pattern, a dense capillary network, and in some instances perivascular pseudorosettes.

Characteristic features (3,6,22-23,30,39-40,53,76,88): The histological features of CNS-BCOR ITD can be variable. Palisading necrosis is common, but microvascular proliferation is generally absent. Glioma-like fibrillarity is often present, along with variable OLIG2 and NeuN expression. However, mesenchymal features can also be encountered.

Comment: The histogenesis of these CNS tumors and their relationship to extra-CNS mesenchymal tumors with *BCOR* ITDs (namely, clear cell sarcoma of kidney and primitive myxoid mesenchymal tumor of infancy) are not clear. As a result, although the group felt that CNS-BCOR ITD is a distinct tumor type, with its own DNA methylation profile, and that it might be listed in the category of "Other Gliomas", further knowledge could affect its classification.

CIC sarcoma

The cIMPACT-Utrecht committee discussed CNS tumors that have *CIC* alterations and did not feel that there is

sufficient evidence to distinguish such tumors from histologically and genetically similar entities in other organ systems of the body. The group therefore recommended that classification of *CIC*-altered sarcomatous neoplasms conforms to the WHO 2019 Classification of Tumours of Soft Tissue and Bone. Notably though, the majority of intracranial sarcomas with *CIC* rearrangements studied to date have had *NUTM1* as the fusion partner (76), whereas those in extracranial bone and soft tissue have generally had *DUX4* as the fusion partner. It remains uncertain whether the specific fusion partner of *CIC* impacts the biology and prognosis of these tumors.

SUMMARY

The organizers intended the cIMPACT-NOW meeting in Utrecht to debate specific newly recognized CNS tumor entities, but the participants also discussed some key principles that arose from evaluating the individual tumor types. It is recognized that some of the proposed changes presented above are of considerable magnitude, for example, those affecting the grading of common diffuse astrocytic gliomas, and that adoption of such changes might take some time. For example, we recognize that there would now be a situation in which a histological diagnosis is not "glioblastoma" but in which a final, integrated diagnosis is "glioblastoma" (eg, a grade III "anaplastic astrocytoma" that is IDH- and H3-wildtype and has either *TERT* promoter mutation, *EGFR* amplification or +7/−10 copy number changes) as well as a situation in which a histologically defined "glioblastoma" is not classified as a "glioblastoma" in the integrated diagnosis (eg, an IDH-mutant astrocytoma that is WHO grade IV by histological or molecular criteria but that is classified as "Astrocytoma, IDH-mutant, grade 4"). We also recognize that the introduction of new technologies will require extensive adaptation of current clinical practice and that such adaptation will occur at varying paces in different health care facilities around the world. In places that do not have access to such technologies early on, the generous use of NOS labels (51) and of subsequent diagnostic referrals may provide utility in the transition period. We remain encouraged by how well adoption of the 2016 CNS WHO classification changes has proceeded over the past few years and remain hopeful that the proposed introduction of these new principles and tumor types will be equally well adopted in the near future.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relating to the information presented in the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing are not applicable to this article as no new data were created or analyzed in this study.

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