



# The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: the 10 basic principles

Takashi Komori<sup>1</sup>

© The Author(s) under exclusive licence to The Japan Society of Brain Tumor Pathology 2022

## Introduction

The 2021 WHO classification of tumors of the central nervous system (CNS), 5th edition (WHO CNS 5) [24] is built on the previous, revised 4th edition, published in 2016 (WHO2016CNS) [14], which incorporated molecular information into the diagnosis of brain tumors for the first time, breaking with the century-old histogenetic classification [1, 15]. The basic concept underlying WHO2016CNS was rooted in the Haarlem Consensus Guidelines [11] that aimed to establish instructions for incorporating molecular findings into the diagnosis of brain tumors and define diagnostic entities as narrowly as possible using molecular information. WHO CNS 5 also adopted a series of recommendations of “the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT)” [2, 3, 5, 6, 16, 18–20] that facilitates a consensus review of novel diagnostically relevant data and determines how such information can be fit into future CNS tumor classifications. Based on the above volumes and articles, the 5th edition moved molecular diagnosis forward [24]. However, the combination of histology and molecular information used to diagnose and grade CNS tumors remains at the center of tumor taxonomy [22].

This editorial focuses on the basic principles behind the 5th edition rather than covering all revisions because the editorial board of the 5th edition has comprehensively summarized the essential points of WHO CNS 5 in another review article [22].

## Histogenetic vs. molecular classification

Brain tumor research over two decades has clearly shown that a molecular assessment is more effective than a traditional histogenetic assessment using immunohistochemistry and electron microscopy in characterizing a tumor entity and evaluating the biological behavior of brain tumors, especially neuroepithelial tumors [4, 12, 13]. Such knowledge has made the histogenetic terminology and nomenclature of brain tumors irrational, and thus WHO CNS 5 has finally eliminated a cell of origin definition from the “Essential diagnostic criteria” for diffuse gliomas. For example, the term “astrocytic glioma” or “diffuse glioma” replaced the traditional, generic term “astrocytoma.” “Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted” needs not to possess oligodendroglial differentiation, and any diffusely infiltrating glioma with IDH mutation with the codeletion is diagnosed as such. This principle drastically reduced the provisional entities from the previous edition [14] and enabled restructuring of the tumor categories, particularly diffuse gliomas (Table 1).

## Integrated diagnosis

The layered reporting format, which is one of the critical principles introduced in the Haarlem consensus guidelines [13], presents a full range of diagnostic information, including histopathological features, CNS WHO grade, and molecular alterations (Table 2). Integrated assessment of all available information leads to the final diagnosis, prioritizing molecular information over histopathological features. This layered format became a part of the International Collaboration on Cancer Reporting (ICCR) dataset [21] and was recommended for pathological examinations in the clinical setting.

✉ Takashi Komori  
komori-tk@igakuken.or.jp

<sup>1</sup> Department of Laboratory Medicine and Pathology (Neuropathology), Tokyo Metropolitan Neurological Hospital, 2-6-1 Musashidai, Fuchu, Tokyo 183-0042, Japan

**Table 1** Diffuse gliomas in WHO CNS 5

	CNS WHO grade
Adult-type diffuse gliomas	
Astrocytoma, IDH-mutant	2/3/4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2/3
Glioblastoma, IDH-wildtype	4
Pediatric-type diffuse low-grade gliomas	
Diffuse astrocytoma, <i>MYB</i> -or <i>MYBL1</i> -altered	1
Angiocentric glioma	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffuse low-grade glioma, MAPK pathway-altered	NA
Pediatric-type diffuse high-grade gliomas	
Diffuse midline glioma, H3 K27-altered	4
Diffuse hemispheric glioma, H3 G34-mutant	4
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4
Infant-type hemispheric glioma	NA

NA not assigned

## Essential and desirable diagnostic criteria

In addition to the definitions of tumor types, each chapter gave a box describing the “[Essential and desirable diagnostic criteria](#)” for each tumor type. The essential diagnostic criteria are the minimum requirements to establish a diagnosis, whereas the desirable diagnostic criteria are the ones that support a diagnosis, but are not essentially needed for the diagnosis.

## NOS and NEC diagnoses

In addition to the not otherwise specified (NOS) diagnosis, the not elsewhere classified (NEC) diagnosis has been adopted in WHO CNS 5 [19, 22]. An NEC suffix indicates that the necessary diagnostic testing has been successfully performed but that the results do not allow for a complete WHO diagnosis because of a mismatch between the clinical, histological, immunohistochemical, and/or genetic features. For example, the diagnosis of histologically malignant glioma in the cerebral hemisphere harboring H3.3p.K28M (K27M)-mutation would be “pediatric-type diffuse high-grade glioma, H3.3 K27-mutant, NEC”. Nonetheless, since the diagnosis of NEC corresponds to what pathologists have called a “descriptive diagnosis,” [22] the usage of NEC may differ according to the pathologist.

## Grading across vs. grading within types

Traditionally, the CNS tumor grades have been applied across different entities in the WHO classification [7, 8, 10, 17]. However, WHO CNS 5 employed within-tumor-type grading rather than across-different-tumor-type grading to conform with WHO grading in non-CNS tumor types [22]. Nonetheless, WHO CNS 5 endorses the term “CNS WHO grade” because CNS tumor grading still differs from other tumor grading systems. In addition, to clearly differentiate it from the previous grading system, WHO CNS 5 adopted Arabic numerals (1, 2, 3, 4) rather than Roman numerals (I, II, III, IV).

**Table 2** An example of layered report structure

Cerebrum	
Integrated diagnosis	Diffuse high-grade glioma, IDH-wildtype, H3-wildtype, NEC
Histopathological diagnosis	Anaplastic oligoastrocytoma with microvascular proliferation
CNS WHO grade	Not assigned
Molecular information	IDH-wildtype, H3-wildtype, <i>TERT</i> promoter-wildtype, and <i>BRAF</i> -wildtype (Sanger sequencing), <i>BRAF</i> fusion-negative (Break apart FISH study), 1p/19q non-deleted (FISH study), <i>CDKN2A/B</i> non-deleted, <i>EGFR</i> not-amplified, and 7/10 chromosome copy number alterations-negative (MLPA)

Cf. This is an example of a right frontal mass with contrast enhancement on MRI in a 43-year-old male. Of note, the usage of NEC may differ according to the pathologist

CNS central nervous system, *FISH* fluorescence in situ hybridization, *NEC* not elsewhere classified

## Combined histological and molecular grading

Since some molecular markers can provide robust prognostic information, some molecular parameters were added as biomarkers for grading in WHO CNS 5. Examples include (i) *CDKN2A/B* homozygous deletion in the grading of “astrocytoma, IDH-mutant,” [3] and (ii) *TERT* promoter mutation, *EGFR* amplification, and +7/10- copy number changes for a diagnosis of glioblastoma, IDH wildtype, regardless of the presence or absence of high-grade histological features [2]. Because neither historical nor prospective data on the prognosis are available for the newly recognized tumors, the CNS WHO grade is not given to them [22].

## Pediatric-type vs. adult-type diffuse gliomas

WHO CNS 5 restructured diffuse gliomas into adult-type and pediatric-type diffuse gliomas [5, 9, 20], and the latter were subdivided into low-grade gliomas and high-grade gliomas (Table 1). Although the pediatric-type diffuse gliomas share overlying histology with their adult counterpart, the biology and genetics are distinctively different; they are generally indolent despite “anaplastic” histological features and lack IDH mutation and 1p/19q codeletion, the genetic hallmark of adult-type gliomas, but harbor characteristic genetic profiling such as MAPK-pathway alteration [23]. This distinction is essential to separating these two prognostically and biologically different sets of tumors, enabling improved care for both children and adults with CNS tumors. The definitions of pediatric-type and adult-type do not depend on the patient’s age. Instead, they are defined based on representative molecular alterations, implicating that pediatric-type gliomas may occur in adults and vice versa [9].

## Use of type/subtype instead of entity/variant

In WHO CNS 5, type is used instead of entity and subtype is used instead of variant to harmonize the terminology with other organ systems. Only types are listed in the main classification, whereas subtypes are listed under individual sections. For example, meningioma is a single type in the classification, and all the subtypes and grades are documented individually within the meningioma chapter.

## Gene and protein nomenclature

WHO CNS5 uses the Hugo Gene Nomenclature Committee system for gene symbols and names, and the Human Genome Variation Society (<https://www.hgvs.org/>) recommendations

for sequence variants. For histone sequence alterations, WHO CNS 5 uses the legacy protein numbering system in parentheses after the protein level variant description to avoid any confusion by clinicians (“prefix c.” for sequence alteration and “prefix p.” for protein sequence). For example, *H3-3A:c.83A > T p.Lys28Met* (K27M).

## DNA methylation profiling and newly recognized tumor types

Using a DNA methylation array, genome-wide profiling of DNA methylation patterns has become a powerful tool for the diagnosis and classification of CNS tumors, particularly those with atypical histology or discordant genetic features [4]. In WHO CNS 5, some new types, like “high-grade astrocytoma with piloid features,” are defined only by DNA methylation profiling. However, the WHO did not recommend methylome profiling as a primary or routine diagnostic method because of general inaccessibility of the test; it remains a desirable diagnostic criterion.

In the current classification, a strict definition of tumor types eliminated ambiguous types from the previous classification, reducing the number of tumor types to 110, with 22 newly recognized tumor types identified by DNA methylation profiling.

## Conclusions

WHO CNS 5 moved molecular diagnostics forward, beyond the legendary histogenetic classification, adopting as much possible knowledge about the recent progress in neuro-oncological studies. However, it is still incomplete for characterizing each tumor’s phenotype and identifying its biological behavior. Brain tumor classification remains an ongoing process as we move toward future precision medicine, and try to provide more precise and beneficial assessments for patients suffering from brain tumors.

## References

1. Bailey P, Cushing H (1926) Tumors of the glioma group. J. B Lippincott, Philadelphia
2. Brat DJ, Aldape K, Colman H et al (2018) cIMPACT-NOW update 3: recommended diagnostic criteria for “Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV.” Acta Neuropathol 136:805–810
3. Brat DJ, Aldape K, Colman H et al (2020) cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol 139:603–608
4. Capper D, Jones DTW, Sill M et al (2018) DNA methylation-based classification of central nervous system tumours. Nature 555:469–474

5. Ellison DW, Hawkins C, Jones DTW et al (2019) cIMPACT-NOW update 4: diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or BRAF(V600E) mutation. *Acta Neuropathol* 137:683–687
6. Ellison DW, Aldape KD, Capper D et al (2020) cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. *Brain Pathol* 30:863–866
7. Komori T (2019) The anticipated revision of the grading criteria for adult isocitrate dehydrogenase-mutant diffuse glioma within the neuro-oncology community. *Neuro Oncol* 21:1485–1486
8. Komori T (2020) Updating the grading criteria for adult diffuse gliomas: beyond the WHO2016CNS classification. *Brain Tumor Pathol* 37:1–4
9. Komori T (2021) The molecular framework of pediatric-type diffuse gliomas: shifting toward the revision of the WHO classification of tumors of the central nervous system. *Brain Tumor Pathol* 38:1–3
10. Komori T (2022) Grading of adult diffuse gliomas according to the 2021 WHO classification of tumors of the central nervous system. *Lab Invest* 102:126–133
11. Louis DN, Ohgaki H, Wiestler OD et al (2007) The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114:97–109
12. Louis DN (2012) The next step in brain tumor classification: “let us now praise famous men”... or molecules? *Acta Neuropathol* 124:761–762
13. Louis DN, Perry A, Burger P et al (2014) International Society of Neuropathology-Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol* 24:429–435
14. Louis DN, Ohgaki H, Wiestler OD et al (2016) WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon
15. Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 131:803–820
16. Louis DN, Aldape K, Brat DJ et al (2017) cIMPACT-NOW (the consortium to inform molecular and practical approaches to CNS tumor taxonomy): a new initiative in advancing nervous system tumor classification. *Brain Pathol* 27:851–852
17. Louis DN, von Deimling A (2017) Grading of diffuse astrocytic gliomas: broders, Kernohan, Zulch, the WHO... and Shakespeare. *Acta Neuropathol* 134:517–520
18. Louis DN, Giannini C, Capper D et al (2018) cIMPACT-NOW update 2: diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant. *Acta Neuropathol* 135:639–642
19. Louis DN, Wesseling P, Paulus W et al (2018) cIMPACT-NOW update 1: not otherwise specified (NOS) and not elsewhere classified (NEC). *Acta Neuropathol* 135:481–484
20. Louis DN, Wesseling P, Aldape K et al (2020) cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol* 30:844–856
21. Louis DN, Wesseling P, Brandner S et al (2020) Data sets for the reporting of tumors of the central nervous system: recommendations from the International Collaboration on Cancer Reporting. *Arch Pathol Lab Med* 144:196–206
22. Louis DN, Perry A, Wesseling P et al (2021) The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol* 23:1231–1251
23. Sturm D, Pfister SM, Jones DTW (2017) Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. *J Clin Oncol* 35:2370–2377
24. WHO Classification of Tumors Editorial Board (2021) Central nervous system tumours, 5th edn. International Agency for Research on Cancer, Lyon

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.