The 2016 WHO classification of central nervous system tumors: what neurologists need to know

John C. DeWitt*a, Andreas Mock*a,b,c,* and David N. Louis*a

Purpose of review
The 2016 WHO classification of tumors of the central nervous system (2016 CNS WHO) features many changes that are relevant to neurologists treating patients with brain tumors as well as neurologists involved in basic, clinical, and epidemiological research. This review summarizes what neurologists need to know and will need to know in the next years.

Recent findings
The 2016 CNS WHO introduces diagnostic terms that ‘integrate’ histological and molecular information and suggests presenting diagnoses in a four-layered reporting format. In addition, it utilizes a ‘not otherwise specified’ designation to identify diagnostic categories that are not precisely defined. A better understanding of the biology of entities further led to changes in the tumor nosology, for example, diffuse gliomas based on IDH gene status. Meaningful molecular subgroups could also be identified in embryonal tumors and other entities. Given the pace of change in the field of brain tumor classification, there will likely be additional practical advances that emerge over the next few years. A new initiative entitled Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy intends to formulate recommendations between WHO updates.

Summary
The 2016 CNS WHO includes major changes in the way brain tumors are classified, with molecular parameters being incorporated into diagnostic criteria for a substantial number of such entities.

Keywords
brain tumors, glioma, WHO

INTRODUCTION
The 2016 WHO classification of tumors of the central nervous system (2016 CNS WHO) is markedly different from its 2007 predecessor, with major changes relevant to neurologists treating patients with brain tumors as well as neurologists involved in basic, clinical, and epidemiological research [1*]. The current review outlines those changes and adumbrates additional developments likely to affect brain tumor classification over the next few years (see Table 1 for a summary of the major changes).

BASIC PRINCIPLES
The 2016 CNS WHO differs from the past four CNS WHO classifications in that, in addition to adding and deleting histologically defined tumor entities just as the 1979, 1993, 2000, and 2007 classifications did, it also formulates tumor entities on the basis of both histological and molecular grounds. Prior to incorporating molecular parameters into tumor classification, the WHO Working Group had access to the results of two surveys with good response rates that supported the decision to incorporate molecular characteristics into the classification: one to the Society for Neuro-Oncology and one to the International Society of Neuropathology (ISN). The Society for Neuro-Oncology survey, with about 400 respondents that covered the breadth of neuro-oncological disciplines, demonstrated that all specialties believed that the field had progressed to the point at which use of molecular diagnostic

*Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. aDivision of Experimental Neurosurgery, Department of Neurosurgery and †Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany
Correspondence to David N. Louis, MD, Room 225, Warren Building, 55 Fruit Street, Boston, MA 02114, USA. Tel: +1 617 726 2966; e-mail: dlouis@mgh.harvard.edu
John C. DeWitt and Andreas Mock contributed equally to this article.

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Integrated diagnoses

The 2016 CNS WHO attempts to classify tumors on the basis of both histological and molecular parameters, at least for those tumors for which there is clinically and biologically relevant known molecular information. To do so, it has followed the so-called ISN-Haarlem guidelines and the approaches used by the hematological malignancy classification community: the use of diagnostic terms that ‘integrate’ histological and molecular information. For example, tumor entities such as diffuse gliomas are designated both by their histological and molecular features, for example, diffuse astrocytoma, IDH-mutant. In other words, the official WHO designation is no longer simply diffuse astrocytoma.

Layered diagnoses

The ISN-Haarlem guidelines proposed a four-layered reporting format that allows preservation of a traditional histological diagnosis and histological grade in addition to listing of molecular information and generation of an integrated diagnosis (Table 2).

It is important for neurologists to be aware of this format as they will likely see diagnoses being rendered in this format. It is also essential to realize that, because the molecular information may only come back after a few days to weeks, the integrated diagnosis may appear after the original histological diagnosis, meaning that the pathologist may render an integrated diagnosis of “pending” prior to the molecular information being available. Such an approach makes it clear that an integrated diagnosis will be rendered, and is far safer than including the integrated diagnosis in an addendum that may or may not be seen weeks after the original diagnosis. The layered diagnosis is thus a safety feature in the era of molecular classification.

Paradigm shifts in tumor nosology

Basing diagnoses on biological relationships in addition to histological similarities has required some
notable shifts in the overall organization of the classification. The most notable examples of this are closer grouping of all diffuse gliomas (whether astrocytic or oligodendroglial in appearance) based on IDH gene status rather than closer grouping of gliomas with an astrocytic phenotype, and the use of both histological subdivisions as well as genetic subdivisions of medulloblastomas.

Expressing uncertainty and ‘not otherwise specified’ diagnoses

Because specific combined histological and molecular information may not be available for a certain tumor or tumor type, the 2016 CNS WHO utilizes the NOS designation to identify those diagnostic categories that are not precisely defined. An NOS designation implies that there is insufficient information to assign a more specific code. NOS suffixes (e.g., diffuse astrocytoma, NOS) have been added to the classification in those places where such diagnoses are possible. NOS in general refers to tumors that have not been fully tested for the key genetic features, but may also include lesions that have been tested but do not show the diagnostic genetic alterations. Most important to realize is that the NOS diagnosis does not define a specific entity; rather it designates a group of lesions that cannot be classified into the more precisely defined groups. These entities require further study prior to the next WHO classification.

WHAT THE NEUROLOGIST NEEDS TO KNOW

Diffuse gliomas

One of the major areas in which the new classification incorporates both histologic and genetic characteristics is the diffuse gliomas (Fig. 1). The presence or absence of IDH1 and IDH2 gene mutations now separates astrocytomas and glioblastoma into IDH-mutant and IDH-wildtype categories. Genetic features are also required for the diagnosis of the common type of oligodendroglioma: in addition to IDH mutation, combined whole arm losses of the short (p) arm of chromosome 1 and the long (q) arm of chromosome 19 (1p/19q codeletion) are necessary. In the absence of documentation of IDH mutation or 1p/19q codeletion, only a diagnosis of oligodendroglioma, NOS is possible. These new classifications not only separate entities in a more logical manner based on their phenotype and genotype, but also into groups that share similar prognostic outcomes and treatment strategies.

For IDH, approximately 90% of mutations occur in the form of the R132H IDH1 variant, a variant reliably screened for by use of R132H-IDH1-specific
immunohistochemistry (IHC). In those cases that do not stain for R132H IDH1, the 2016 WHO recommends evaluation of all grade II and grade III astrocytomas and oligodendrogliomas with sequencing to look for noncanonical IDH1 and IDH2 mutations. However, because of the rare occurrence of noncanonical IDH1 and IDH2 mutations in older glioblastoma patients, sequencing of an R132H IDH1 immunonegative result is only recommended in patients less than 55 years of age [5,6*].

In addition to these major changes in the more common diffuse gliomas, there are new approaches to some rarer types. Epithelioid glioblastoma is now a recognized variant of IDH-wildtype glioblastoma that often harbors a BRAFV600E mutation, making recognition of this subtype and its potentially targetable mutation an important part of glioblastoma evaluation and possibly treatment [7]. Glioblastoma with primitive neuronal component was added as a clinically relevant pattern to recognize in glioblastoma, as these tumors are prone to craniospinal fluid dissemination and therefore from a clinical perspective may prompt evaluation of the craniospinal axis for tumor seeding [8]. A new entity in the 2016 WHO is the diffuse midline glioma, H3 K27M-mutant. This diffusely infiltrating tumor often found in a midline location [spinal cord, brain stem (i.e., what used to be termed diffuse intrinsic pontine glioma or brain stem glioma), or thalamus] occurs primarily in pediatric patients and is characterized by mutation of the histone H3 gene H3F3A [9]. Knowledge of genetically defined entities such as these is important as they represent unique opportunities for possible therapeutic targeting and involvement in clinical trials.

**Embryonal tumors**

The classification of embryonal tumors, including medulloblastomas, has undergone substantial changes with the incorporation of genetic information into tumor classification. There has long been prognostic implications of the different histologic subtypes of medulloblastoma, and with advances in molecular techniques, there are now generally accepted genetic subtypes with their own prognostic and therapeutic implications [10]. In the 2016 WHO, rather than list all the possible combinations of histologic and genetic subtypes, two categories of variants of medulloblastoma are listed: those histologically defined and those genetically defined, with the expectation that the pathologist will communicate both pieces of information in an integrated diagnostic format (see Table 3).

Advances in molecular information have also led to the consolidation of a number of rare embryonal tumors, as it has become increasingly recognized that many of these tumors harbor amplifications of the C19MC region on chromosome 19. These tumors include the former embryonal tumor with abundant neuropil and true rosettes, ependymoblastoma, and most medulloepitheliomas, now collectively known in the 2016 WHO as embryonal tumor with multilayered rosettes, C19MC-altered. Furthermore, atypical teratoid/rhabdoid tumor is now defined by loss of expression of INI-1, or more rarely BRG-1, with both alterations able to be screened for by IHC [12]. In those tumors lacking this genetically defined characteristic, the term CNS embryonal tumor with rhabdoid features is now used.

**Other neoplasms**

The incorporation of advances in the molecular understanding of CNS tumors has not only impacted diffuse gliomas and embryonal tumors. Among ependymomas, a genetically defined entity, ependymoma, RELA-fusion-positive is now recognized [13,14]. Although the classification of meningiomas was largely unchanged, the presence of brain invasion was added as a sufficient criterion for classification as a WHO grade II atypical meningioma, as clinical outcomes such as recurrence and mortality rate are known to be poorer in these cases compared with grade I meningiomas [15].

Another entity undergoing changes in the 2016 WHO is the newly combined entity of solitary fibrous tumor (SFT)/haemangiopericytoma (HPC). These entities share the same genetic alteration, with fusion of the NAB2 and signal transducer

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**Table 3. 2016 WHO classification of medulloblastomas**

<table>
<thead>
<tr>
<th>Medulloblastoma, genetically defined</th>
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<tr>
<td>Medulloblastoma, WNT-activated</td>
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<tr>
<td>Medulloblastoma, SHH-activated and TP53-mutant</td>
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<tr>
<td>Medulloblastoma, SHH-activated and TP53-wildtype</td>
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<td>Medulloblastoma, non-WNT/non-SHH</td>
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<tr>
<td>Medulloblastoma, group 3</td>
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<td>Medulloblastoma, group 4</td>
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<table>
<thead>
<tr>
<th>Medulloblastoma, histologically defined</th>
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<tr>
<td>Medulloblastoma, classic</td>
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<tr>
<td>Desmoplastic/nodular medulloblastoma</td>
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<tr>
<td>Medulloblastoma with extensive nodularity</td>
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<td>Large cell/anaplastic medulloblastoma</td>
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Medulloblastoma, NOS

Genetically and histologically defined medulloblastomas. Genetic and histologic diagnoses come together to form a single integrated diagnosis. NOS, not otherwise specified.

Adapted with permission [11].
and activator of transcription (STAT)6 genes leading to accumulation of STAT6 protein in the nucleus, and likely represent a spectrum along a single entity [16]. Given the spectrum of clinical behavior inherent in this new single entity, grading breaks from the traditional grading of CNS neoplasms with three distinct grades (WHO grade I, II, and III) within this single entity. Clinically, grade I lesions should be expected to behave more similar to the historically defined SFT, grade II lesions to historically defined HPC, and grade III lesions to historically defined anaplastic HPC.

**WHAT THE NEUROLOGIST WILL NEED TO KNOW**

**Grading astrocytomas**

The 2007 CNS WHO divided diffuse gliomas into grades II, III, and IV based on histological features because all prior studies had been based on histological grading systems. As such, it is unclear whether such grades are accurate estimates for combined histological and molecular classifications; in other words, grades need to be redefined by repartitioning cohorts according to the 2016 CNS WHO integrative diagnosis. Most strikingly, work in astrocytomas suggests that the former prognostic differences were primarily because of different distributions of IDH mutations. Notably, the prognosis of IDH-mutant astrocytomas appears to be more favorable than their wild-type counterparts. Within the IDH-mutant group, however, virtually no survival difference could be observed between grade II, III, and IV tumors [17,18]. In addition, mitotic index, which has been a key feature for histological grading, could not be confirmed as prognostic in IDH-mutant astrocytomas [19]. In IDH-wildtype astrocytomas, grade II and IV tumors were found to be distinct regarding overall survival, but not grade III and IV tumors [18], suggesting that IDH-wildtype anaplastic astrocytomas might be undersampled IDH-wildtype glioblastomas. Nonetheless, not all studies have found such discrepancies [20] and the 2016 CNS WHO did not feel that there was sufficient evidence to change grading at this time, but a recasting of prognostic grades is likely in the near future and will have a major impact on treatment regimes and clinical trials.

**Pediatric low-grade glioma**

Seminal work over the past few years has shown that the majority of pediatric low-grade gliomas harbor a genetic alteration in the mitogen-activated protein kinase pathway (reviewed in [21*]). Although current histological groupings fail to capture the observed molecular heterogeneity, some histological entities are enriched for particular molecular alterations (e.g., BRAF alterations in pilocytic astrocytomas) and it is, therefore, expected that employing an integrative diagnosis as suggested by the ISN-Haarlem guidelines [4*] will be instrumental in defining entities in the near future. Given the current evidence for putatively targetable alterations, a basic molecular workup currently includes assessments for BRAF V600E mutation and BRAF fusion, but this list could grow quickly in the future and the list of assayed genes is already much longer at pediatric brain tumor centers.

**Ependymoma**

Histological grading of ependymoma has been controversial, without consistent prognostic capability and confounded by the anatomical location of the tumor. Hence, the current consensus on the clinical management of ependymomas is to refrain from grading-based treatment decisions [22**]. Instead, nine molecular subgroups have been proposed with three entities per location (supratentorial, posterior fossa, and spine); this approach outperforms histological grading with respect to risk stratification [23]. One supratentorial ependymoma group could be identified to harbor a RELA fusion protein and is already included in the 2016 CNS WHO; another is tightly associated with a YAPI fusion protein. With these changes in classification, clinical studies will need to identify entity-specific treatment recommendations.

**Meningioma**

The current WHO grading of meningiomas based on histopathology has been imperfect in predicting the 20% of tumors that recur and prognostic biomarkers are yet to be established [24*]. A comprehensive recent study suggests that meningiomas can be more accurately stratified for clinical behavior by DNA methylation profiling [25*]. Critically assessing the feasibility of DNA methylation profiling in routine pathology workups will be instrumental to determine its role for clinical decision-making in the next years.

**Consortium to Inform Molecular and Practical Approaches to Central Nervous System Tumor Taxonomy**

The current pace of identifying genetic alterations in human brain tumors and understanding their
Clinical correlates is faster than the cycle of WHO classifications, as WHO classifications relate to a wide variety of clinical, experimental, and epidemiological stakeholders[1,4] and therefore cannot be updated too frequently. For example, extensions of the diagnostic algorithm for diffuse glioma by ATRX and TERT[26] mutation status and the definition of new pediatric tumor entities[27] have been proposed very recently. As a result, a new initiative has begun, entitled the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (or cIMPACT )[28,29]. This is not an official WHO process, but is intended to complement the longer interval WHO updates. cIMPACT has recently begun and intends to publish consensus recommendations on some of the upcoming challenges mentioned above.

CONCLUSION

The 2016 CNS WHO represents a large step forward in CNS tumor classification, both from conceptual and practical points of view, and features many changes that neurologists should understand. Nonetheless, with the rapid ongoing changes in the field, it is likely that neurologists will also need to be attentive to practical advances in brain tumor classification that emerge over the next few years, potentially well ahead of future WHO classifications.

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None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

4. The publication shows the availability of molecular methods and the use of biomarkers for brain tumor diagnostics across 48 countries.
6. The publication proposed guidelines for the molecular classification of brain tumors as well as a layered reporting system for brain tumor diagnoses.
19. The publication reclassifies a large French cohort of cases with high-grade glioma according to the 2016 WHO classification and shows there is significantly greater prognostic value in the updated classification when incorporating molecular information.
23. The publication summarizes the findings of a consensus conference on the impact of molecular genetics on pediatric low-grade glioma classification and treatment. Recommendations for integration of molecular information into diagnoses and treatment are supported.
25. The publication suggests treatment for ependymoma (outside of clinical trials) should be independent of grade, and that molecular subgrouping should be a part of all subsequent clinical trials.
The publication reviews the evolving strategies for diagnosis and treatment of meningiomas, including surgery, radiosurgery, radiotherapy, and emerging pharmacologic approaches.

The publication suggests that meningiomas can be more accurately stratified using DNA methylation profiling.


The publication shows molecular profiling can identify well defined CNS-PNET entities and identifies four novel entities based on their unique molecular profiles.
