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RESEARCH LETTER

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cIMPACT-NOW update 11: Proposal on adaptation of diagnostic criteria for IDH- and H3-wildtype diffuse high-grade gliomas and for posterior fossa ependymal tumors

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Abstract

The Consortium to Inform Molecular and Practical Approaches to Central Nervous System Tumor Taxonomy (cIMPACT-NOW) updates provide guidelines for the diagnosis of central nervous system (CNS) tumors and suggestions for future World Health Organization (WHO) classification. Following publication of the fifth edition WHO Classification of CNS Tumors (WHO CNS5) in 2021, the cIMPACT-NOW working group "Clarification" reviewed WHO CNS5 and prioritized two topics for further elucidation: (a) distinction of *Glioblastoma, IDH-wildtype* from *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* and (b) clarification of subgroups of posterior fossa (PF) ependymal tumors. Recommendations regarding the IDH- and H3-wildtype diffuse high-grade gliomas include: (1) use caution assigning CNS WHO grade 4 (diagnosis of *Glioblastoma, IDH-wildtype*) to a "*TERT* promoter only", histologically low-grade, IDH-wildtype tumor; (2) *EGFR* gene amplification and +7/−10 chromosome copy number alterations should not be used as solitary defining features for diagnosing high-grade gliomas as *Glioblastoma, IDH-wildtype* in patients <40 years of age; (3) *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* should be considered in the differential diagnosis in adults, especially those <40 years of age; (4) *PDGFRA* alteration, *EGFR* alteration, or *MYCN* amplification count as key molecular features of *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* only in patients <25 years. Guidelines for improved diagnosis of posterior fossa ependymal tumors include: (1) immunohistochemical demonstration of nuclear EZHIP supports classification as *PF group A ependymoma*; (2) a PF ependymoma with retained nuclear H3 K27me3 expression and no nuclear EZHIP overexpression for which DNA methylation profiling is not performed should be considered as PF ependymoma, "not otherwise specified"; (3) for emerging tumors not included in WHO CNS5, "not elsewhere classified" (NEC) can be added to the diagnosis. Of note, these recommendations are not formal changes to the WHO definitions and diagnostic criteria but are intended to provide diagnostic guidance in advance of WHO CNS6.

KEYWORDS
cIMPACT-NOW; clarification; diffuse pediatric-type high-grade glioma; Glioblastoma, IDH-wildtype; posterior fossa ependymoma; WHO classification

1 | INTRODUCTION

Over the years, new technologies have been applied to clarify certain aspects of tumor types, including electron microscopy, immunohistochemistry, molecular genetics, and, most recently, broad molecular profiling approaches. These methods can be divided into those that recognize patterns of diverse features (e.g., histology, DNA methylation profiling) and those that detect specific molecular changes (e.g., immunohistochemistry, gene sequencing). Molecular genetic characteristics became part of the definition of particular central nervous system (CNS) tumor types for the first time in the revised fourth edition of the World Health Organization (WHO) CNS tumor classification (WHO CNS4R; published in 2016) [1,2]. Meanwhile, DNA methylation profiling emerged as a powerful tool for the classification of CNS tumors, and the "methylation fingerprint" of a tumor often explicitly suggests particular diagnoses, coupled with confidence scores for the different possible diagnoses [3,4]. At the same time, this diagnostic tool raised additional questions about how CNS tumors are defined and how the DNA methylation profiling results affect the interpretation of more traditional diagnostic approaches in routine clinical neuropathology settings [5].

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was established in late 2016 by a group of neuropathology and neuro-oncology experts to provide practical recommendations (published as cIMPACT-NOW updates) to improve the diagnosis and classification of CNS tumors in advance of the publication of the next WHO Classification of CNS tumors. Between the publication of WHO CNS4R and the fifth edition of the classification (WHO CNS5, published in 2021) [6], seven cIMPACT-NOW updates were published [7], and virtually all recommendations were incorporated into WHO CNS5, either in their original or modified forms. Following the publication of WHO CNS5, cIMPACT-NOW

began a new series of updates. As with the initial round, the cIMPACT-NOW Steering Committee created working groups to report recommendations separately. In 2024, the "Meningioma" working group published cIMPACT-NOW update 8 with clarifications on molecular risk parameters and recommendations for improved WHO grading of meningiomas [8]. In 2025, cIMPACT-NOW update 9 featured the recommendations of the "Methylation" working group on the role of DNA methylation profiling in the diagnosis of CNS tumors [5]. An update from the "New entities" cIMPACT-NOW working group summarized recommendations on criteria to be used for the identification and definition of new CNS tumor types [9]. Finally, a fourth cIMPACT-NOW working group was convened to look at whether clarifications were needed for any individual tumor types included in WHO CNS5.

This last working group solicited input on tumor definitions and tables of essential and desirable diagnostic criteria in WHO CNS5 that might require clarification, resulting in >50 initial suggestions. The group observed that there was more variability in the definitions between chapters than in prior editions, probably because of the newly modified editorial process that was used for the generation of WHO CNS5. Also, the information in the tables with essential and desirable diagnostic criteria at times contained (generally minor) conflicting and/or confusing statements. The working group collected these but felt that such suboptimal aspects, as long as they were minor and did not clearly jeopardize patient care, should be addressed in the next edition of the WHO classification rather than by cIMPACT-NOW. The group also felt that suggesting updated definitions or criteria on a large array of tumor types so soon after publishing WHO CNS5 will generate more confusion in daily clinical practice. Instead, the group focused on topics for clarification in which practically useful interpretations could help pathologists work within the broader WHO CNS5 guidelines. These included recommendations on how recent findings could be applied to improve diagnosis of particular CNS tumors. Importantly, such recommendations are not formal changes to WHO definitions because that would require confirmation by WHO. Based on discussions of the multiple suggestions for possible clarification, the working group prioritized two topics: (a) the distinction of *Glioblastoma, IDH-wildtype* from *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, and (b) clarification of subgroups of posterior fossa ependymal tumors.

2 | GLIOBLASTOMA, IDH-WILDTYPE VERSUS DIFFUSE PEDIATRIC-TYPE HIGH-GRADE GLIOMA, H3-WILDTYPE AND IDH-WILDTYPE

WHO CNS5 distinguishes two diffuse high-grade glioma types that are genetically characterized predominantly by lack of IDH and H3 mutations rather than by a specific tumorigenic alteration: *Glioblastoma, IDH-wildtype* (belonging to the family of adult-type diffuse gliomas), and *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* (belonging to the pediatric-type diffuse high-grade glioma family). The need to more clearly separate these molecularly heterogeneous groups of diffuse high-grade gliomas primarily affecting distinct age groups has been felt for a long time, and the elucidation of molecular, in particular epigenetic, differences has now made this possible. Importantly, however, while these "adult-type" and "pediatric-type" tumors primarily occur in adults and children, respectively, pediatric-type tumors may also present in adults and vice versa [10].

2.1 | Glioblastoma, IDH-wildtype

In WHO CNS5, *Glioblastoma, IDH-wildtype* is defined as "a diffuse, astrocytic glioma that is IDH-wildtype and H3-wildtype and has one or more of the following histological or genetic features: microvascular proliferation, necrosis, *TERT* promoter mutation, *EGFR* gene amplification, +7/−10 chromosome copy number changes (CNS WHO grade 4)." Also, WHO CNS5 lists three histological subtypes of *Glioblastoma, IDH-wildtype*: giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma. Strictly speaking, the diagnosis of *Glioblastoma, IDH-wildtype* thus requires exclusion of IDH and H3 mutations. However, for WHO CNS4R, a practical consensus was reached for IDH mutation testing: IDH1 p.R132H immunonegativity is sufficient to diagnose *Glioblastoma, IDH-wildtype* in a patient aged >55 years at diagnosis with classic histological features of glioblastoma and without history of a pre-existing lower grade glioma [2]. So far, a corresponding consensus for which cases require H3 testing (either via immunohistochemistry or molecular testing) has been lacking.

"H3-wildtype" in WHO CNS5 refers to the absence of mutations at two hotspots in the family of H3 genes: H3 p.K28 (K27) and H3.3 p.G35 (G34). For the sake of brevity and simplicity, these hotspots will be referred to in the rest of this manuscript as H3 K27 and H3 G34, respectively. H3 K27 mutations are a typical feature of *Diffuse midline glioma, H3 K27-altered*. These tumors develop in midline structures, in particular, in the brain stem, thalamus, spinal cord, pineal region, or cerebellum. Only rarely are these mutations detected in more lateral cerebral hemispheric tumors, which by definition would not qualify as *Diffuse midline glioma, H3 K27-altered*. As a practical approach, H3 K27 testing is generally not needed in a patient >55 years of age with a non-midline diffuse glioma. In contrast, assessment of H3 K27 alteration should be undertaken for all diffuse astrocytic gliomas of midline location in all ages. In a rigorously controlled setting, immunohistochemistry demonstrating retained nuclear H3 lysine 27 trimethylation (H3 K27me3) in tumor cells may be used

as a surrogate approach as this is a strong indicator of H3 K27-wildtype status [11]. However, the opposite is not true: loss of nuclear H3 K27me3 staining in tumor cells does not equal H3 K27-mutant status of the tumor. Also, in this context, finding ambiguous nuclear H3 K27me3 staining of tumor cells is a good reason to assess the H3 K27M status by immunohistochemistry or by molecular analyses including DNA sequencing.

H3 G34 mutations in the *H3-3A* (*H3F3A*) gene are a defining feature of *Diffuse hemispheric glioma, H3 G34-mutant*. These tumors characteristically occur in younger patients than those with *Glioblastoma, IDH-wildtype*, and only a few have been reported in patients >55 years [12–15]. Practically, therefore, a diffuse astrocytic glioma can be considered H3 G34-wildtype if the patient is >55 years of age even without further molecular testing. ATRX and OLIG2 immunohistochemistry may serve as additional immunohistochemical indicators in this setting, as the majority of *Diffuse hemispheric gliomas, H3 G34-mutant*, lack nuclear expression of these markers. Moreover, mutant-specific antibodies against H3 G34R or H3 G34V proteins are available to directly assess the presence or absence of these variants by immunohistochemistry.

The molecular definition of *Glioblastoma, IDH-wildtype*, however, has become more complex since cIMPACT-NOW update 3 and WHO CNS5 were published [6,16]. First, the clinical behavior of "*TERT* promoter mutation-only" IDH-wildtype diffuse gliomas is variable [17–22]. Diagnostic interpretation of *TERT* promoter mutation in an IDH-wildtype diffuse glioma lacking necrosis and microvascular proliferation requires careful consideration of clinical and radiological features (patient age; tumor location; contrast enhancement and presence of necrosis on imaging indicating "undersampling") and of histological features (diffuse growth pattern; anaplasia) before establishing a diagnosis of *Glioblastoma, IDH-wildtype*. If possible, especially in histologically low-grade tumors, further molecular analyses should be performed. For tumors in which the additional presence of either *EGFR* amplification or +7/−10 chromosome copy number changes is demonstrated, or for which a diagnostic DNA methylation profile is found, the diagnosis of *Glioblastoma, IDH-wildtype* can be made [16,23].

Of note, *TERT* promoter mutations identical to those found in *Glioblastoma, IDH-wildtype* have (rarely) been detected in glial tumors that, in small biopsies, may be difficult to distinguish from *Glioblastoma, IDH-wildtype*. Examples of such tumors include *Pleomorphic xanthoastrocytoma* [24], *Subependymoma* [25], *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* [26], and *FGFR3*::*TACC3* fusion-positive diffuse gliomas [27,28], with the latter not representing a distinct tumor type in WHO CNS5. Some of these tumors carry molecular alterations that represent potential candidates for targeted therapy, such as mitogen-activated protein kinase pathway inhibition in *Pleomorphic xanthoastrocytoma* or fibroblast growth factor receptor (FGFR) inhibitors for *FGFR3*::*TACC3* fusion-positive tumors [29]. In case targeted therapy is considered, ultimate proof of the presence of the molecular alteration(s) of interest must be provided by DNA or RNA sequencing, or by immunohistochemistry for the specific druggable protein variant, for example, the BRAF p.V600E mutant protein [30].

Furthermore, the DNA methylation profile of some IDH-wildtype, diffuse, histologically low-grade and/or gliomatosis cerebri-like gliomas matches a novel methylation cluster designated as "Adult-type diffuse high-grade glioma, IDH-wildtype, subtype F" (HGG-F), which, despite a high prevalence of *TERT* promoter mutations, has been associated with a less aggressive clinical course than *Glioblastoma, IDH-wildtype* [19,20] (Figure 1). Based on the available data, the working group recommends that *TERT* promoter mutation should not be used as the sole defining factor for *Glioblastoma, IDH-wildtype*, in histologically low-grade, IDH-wildtype, diffuse astrocytic tumors. Such tumors—as well as tumors with higher-grade features that do not meet histological criteria for Glioblastoma—are best diagnosed descriptively ("NEC") and treatment approaches depend on careful discussions of the combined histological and molecular findings with the treating oncologists.

EGFR gene amplification is not specific for *Glioblastoma, IDH-wildtype* either, as it can be found in a small subset of other tumor types such as *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* [26] and *Diffuse hemispheric glioma, H3 G34-mutant* [12,31]. Especially in children and younger patients the proportional frequency of *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* and *Diffuse hemispheric glioma, H3 G34-mutant* is higher than *Glioblastoma, IDH-wildtype*. Based on the available experience, the working group, therefore, recommends that *EGFR* amplification should not be used as a sole defining molecular feature for *Glioblastoma, IDH-wildtype* in a patient <40 years, and that ideally, further molecular analyses such as methylation profiling or DNA next generation sequencing (NGS) should be performed to resolve the differential diagnosis in light of other types of IDH-wildtype and H3-wildtype diffuse high-grade gliomas in this age group.

According to cIMPACT-NOW update 3 and a summary of WHO CNS5, the combination of gain of whole chromosome 7 with loss of whole chromosome 10 can be used as a molecular criterion for CNS WHO grade 4 in histologically lower grade, IDH- and H3-wildtype diffuse gliomas in adults [10,16]. Combinations including partial gain of chromosome 7 and/or partial loss of chromosome 10 are less frequent and less thoroughly investigated; however, Stichel et al. [23] showed that such latter combinations have a prognostic value similar to that of the complete +7/−10 signature. Importantly, +7/−10 chromosome copy number changes are also not completely

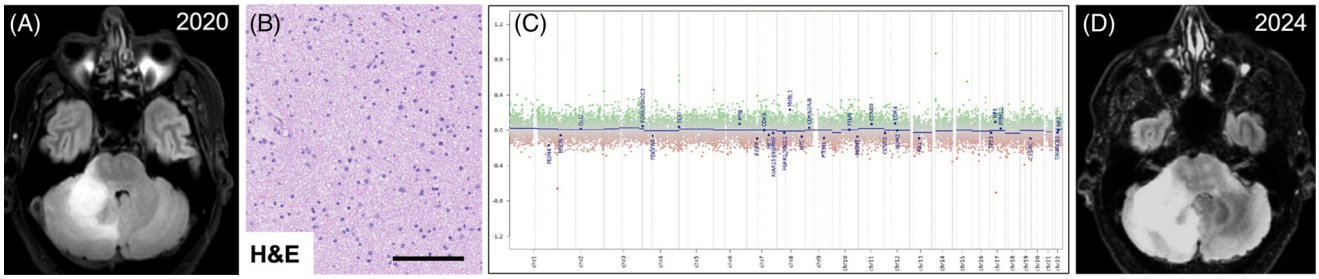

FIGURE 1 Histologically low-grade, IDH- and H3-wildtype diffuse glioma with *TERT* promoter mutation and with prolonged survival as compared to mean survival of patients with classic *Glioblastoma, IDH-wildtype*. (A) A 60-year-old male was diagnosed with a non-enhancing tumor in the right cerebellar hemisphere that was hyperintense on T2-FLAIR magnetic resonance imaging. (B) On biopsy, the tumor histologically resembled a diffuse, low-grade glioma, with a Ki-67 labeling index of <2% (not shown). DNA next generation sequencing revealed an IDH- and H3-wildtype status, but the presence of mutations in the *TERT* promoter (c.-146 C>T "C250T"; mutant allele frequency 56.2%) and in *PIK3CA* (c.1624G>A (p.Glu542Lys); mutant allele frequency 26.6%). With RNA sequencing no oncogenic variants (including no *MYB*/*MYBL1* alteration) were detected. (C) Using DNA methylation profiling, no match with a calibrated score >0.3 was obtained with the Heidelberg Brain Tumor Classifier version 11b4 (i.e., the most recent version available at that time), and the copy number variation profile was flat. In the next couple of years, a wait-and-scan policy was followed and the neurological signs and symptoms only slowly worsened. (D) On follow-up T2-FLAIR magnetic resonance images 4 years after the initial diagnosis, the treatment-naïve tumor had increased in size but remained non-enhancing post-contrast (not shown). Re-analysis of the DNA methylation profile with a more recent version (v12.6) of the Heidelberg Classifier as well as the Bethesda v2 Classifier now assigned the tumor with very high confidence scores (>0.99) to the category "adult-type diffuse high-grade glioma, IDH-wildtype, subtype F (HGG-F)," which is known to encompass *TERT* promoter mutant, IDH- and H3-wildtype diffuse gliomas with a more favorable prognosis than *Glioblastoma, IDH-wildtype* [19,20]. Scale bar in (B) = 100 μm. H&E, hematoxylin and eosin.

specific for *Glioblastoma, IDH-wildtype*, given that this pattern has been observed in some *Pleomorphic xanthoastrocytomas* and *Diffuse hemispheric gliomas, H3 G34-mutant* as well [12,24,32]. Caution is thus required particularly in younger patients, who have higher rates of these latter tumors. It is therefore recommended not to use the +7/−10 signature as a solitary defining molecular factor for *Glioblastoma, IDH-wildtype* in patients <40 years. Rather, in this situation, additional analysis of the *TERT* promoter status and *EGFR* amplification, exclusion of *BRAF* mutation plus/minus DNA methylation profiling should be undertaken. A high-confidence match to the *Glioblastoma IDH-wildtype* methylation family strongly supports this diagnosis, and even sub-threshold scores can still contribute to a diagnosis, especially when ancillary molecular findings, as just mentioned, are supportive. Meanwhile, and as with all diagnostic testing modalities, classifier predictions from methylation profiling data in clinical diagnostics require critical review and integration with clinical, radiological, histological, and genomic data [5].

According to WHO CNS5, most DNA methylation profiles of *Glioblastomas, IDH-wildtype* in adults fall into one of three methylation subclasses: receptor tyrosine kinase 1 (RTK1), RTK2, and mesenchymal (MES). Additionally (and currently not recognized in WHO CNS5), glioblastoma with primitive neuronal component has been described as yet another methylation subclass of *Glioblastoma, IDH-wildtype* [33]. The RTK1, RTK2, and MES methylation subclasses have reportedly been associated with particular pathobiological and clinical characteristics, for example, an increased immune cell presence in MES tumors [34,35], and a relatively high frequency of *EGFR* amplification and of preoperative and long-term seizures in RTK2 tumors [36]. However, in most studies, no clear survival differences among these methylation subclasses were found [34,37,38]. Also, one study reported a survival benefit from maximized extent of resection in newly diagnosed and recurrent glioblastomas of the RTK1 and RTK2 subclasses, but not the MES subclass [37], but independent confirmation is missing.

So far, the clinical impact of the assessment of the methylation subclasses of *Glioblastoma, IDH-wildtype* is thus very limited. Moreover, not infrequently in a case of *Glioblastoma, IDH-wildtype*, unequivocal methylation subclass assignment is not possible as the classifier identifies distinct subclasses with too low scores for each. Also, it has been reported that the methylation subclass assignment of a *Glioblastoma, IDH-wildtype* can shift over time and that even at a single time point, different *Glioblastoma, IDH-wildtype* methylation subclasses can be present within different regions of the same tumor [5,39,40]. Furthermore, subclass assignment may vary depending on the CNS tumor classifier versions used. At present, as long as a high-confidence match to the *Glioblastoma IDH-wildtype* methylation family is obtained, the score(s) for the methylation subclass(es) do not affect the WHO CNS5 integrated diagnosis nor the therapeutic management. However, in a subset of adult patients, the DNA methylation profile of tumors otherwise qualifying as *Glioblastoma, IDH-wildtype* does not align with the adult glioblastoma methylation family but is classified as *Diffuse pediatric-type high-grade glioma* (see below) [41,42]. Of note, in a situation that (e.g., because of limited resources) a choice needs to be made between DNA methylation profiling and NGS for further work-up of the case, the latter diagnostic tool should be prioritized in case identification of targetable alterations is considered important [30].

TABLE 1 Suggested diagnostic criteria for *Glioblastoma, IDH-wildtype* (changes compared to WHO CNS5 in bold).

Essential
An IDH-wildtype **and**[a] H3-wildtype,[b] diffuse astrocytic glioma AND One or more of the following: • Microvascular proliferation • Necrosis • *TERT* promoter mutation **(not as solitary defining factor in histologically low-grade tumors)** • *EGFR* gene amplification **(not as solitary defining factor in patients <40 years)** • +7/−10 chromosome copy number alterations **(not as solitary defining factor in patients <40 years)**
Desirable
DNA methylation profile of *Glioblastoma, IDH-wildtype*

[a]Comma replaced by "and."
[b]As a practical approach, in a patient >55 years of age: IDH can be considered wildtype if IDH1 R132H immunohistochemistry is negative; H3 K27 testing is generally not needed for a non-midline diffuse glioma; a diffuse astrocytic glioma can be considered H3 G34-wildtype, especially so when tumor cell nuclei have retained ATRX expression and are OLIG2 immunopositive.

As a result of the issues discussed above, the working group suggests clarifications of the diagnostic criteria for *Glioblastoma, IDH-wildtype*, which are listed in Table 1.

2.2 | Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Acknowledging that diffuse, high-grade, H3- and IDH-wildtype gliomas in children, adolescents and young adults often differ in biological features compared to their older adult counterparts, *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* has been introduced in WHO CNS5 as a new type with the following definition: "A diffuse glioma with histological features of malignancy, typically occurring in children, adolescents or young adults, which is wildtype for histone H3, *IDH1*, and *IDH2* (CNS WHO grade 4)." In this context, the term "pediatric-type" reflects that these tumors occur primarily in children but may occasionally occur in adults as well [10]. Recent studies indicate, however, that the age overlap between *Glioblastoma, IDH-wildtype* and *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* is greater than previously anticipated, with the latter occurring in adults up to 70 years of age [41,42].

Unequivocal separation of *Glioblastoma, IDH-wildtype, and Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, based on their histopathological features is not possible. In addition, both tumor types may share several molecular features such as *PDGFR* or *EGFR* alterations. Thus, the current diagnostic approaches for malignant gliomas in adults, which are mostly histology- and immunohistochemistry-driven, can be expected to result in an underdiagnosis of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* in these patients. Several factors might hint at the differential diagnosis of a *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* in adult patients, such as tumor development <40 years of age, loss of ATRX expression and/or a negative OLIG2 stain (which has been reported in a subset of these tumors; [43]), lack of *TERT* promoter mutation (although bona fide *Glioblastomas, IDH-wildtype* not infrequently are *TERT* promoter-wildtype as well), glioma developing after brain irradiation, or a personal or family history suggesting an underlying replication repair deficiency (RRD) syndrome. The presence of such features might prompt the pathologist to pursue additional diagnostic testing. Regardless, the clinical impact of recognizing *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* especially in adult patients needs further elucidation.

In WHO CNS5, three subtypes of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* are mentioned, characterized respectively by *PDGFRA* amplification (pediatric high-grade glioma [pHGG], RTK1 subtype), *EGFR* amplification (pHGG, RTK2 subtype), and *MYCN* amplification (pHGG, MYCN subtype) [26,41]. However, these alterations are neither constantly observed in these three subtypes, nor are they specific to each subtype. In fact, DNA methylation profiling has emerged as the only reliable approach for making the diagnosis of *Diffuse pediatric-type high-grade gliomas, H3-wildtype and IDH-wildtype* as a whole and of the respective subtypes. Meanwhile, and as also indicated in the section on *Glioblastoma, IDH-wildtype* above, in case of limited resources, one may choose to perform NGS over DNA methylation profiling, as NGS allows for identification of targetable alterations of (potential) clinical relevance [30].

The vast majority of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, occur in the supratentorial compartment. Infratentorial tumors are slightly more likely to be the pHGG RTK1 and pHGG MYCN subtypes compared to the pHGG RTK2 subtype [26]. pHGGs RTK1 are associated with RRD syndromes, in particular constitutional mismatch repair deficiency (CMMRD) or Lynch syndrome, and with prior cranial irradiation [44,45]. pHGGs RTK2 were recently reported to be associated with a gliomatosis cerebri phenotype on imaging [43,46]. pHGGs MYCN have been described to be associated with an embryonal phenotype and nodular growth pattern of the tumor cells, with *MYCN* and/or *ID2* amplification, and with *TP53* mutation (+/− Li-Fraumeni syndrome) [47,48]. Additional subtypes for *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, are likely to be recognized in the future, as the current version of the Heidelberg CNS Tumor Classifier (v12.8) already lists three

methylation subclasses for pHGG RTK1 (A, B, and C), two for pHGG RTK2 (A, B), as well as two additional, novel methylation subtypes (subtype A and B). At present, however, information on the biology and potential clinical importance of these subclasses is very limited.

Especially in adults, the implications of a *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* diagnosis for clinical management need further research. Reporting the relevant pathological (i.e., histological and molecular) findings in a layered diagnosis format may help to decide in a multidisciplinary setting if an individual patient should be treated as a *Glioblastoma, IDH-wildtype* (+/− inclusion in a trial for these tumors) despite the different diagnosis (see, e.g., Figure 2). Meanwhile, the association of pHGGs with genetic tumor syndromes is of clinical relevance. For example, patients with RRD high-grade gliomas may be eligible for targeted therapy such as immune checkpoint blockade, and there may be additional implications for the patient's family [42,49,50]. In the study of Hadad et al. [42], 9 out of 459 cases (2%) of adult patients with tumors otherwise

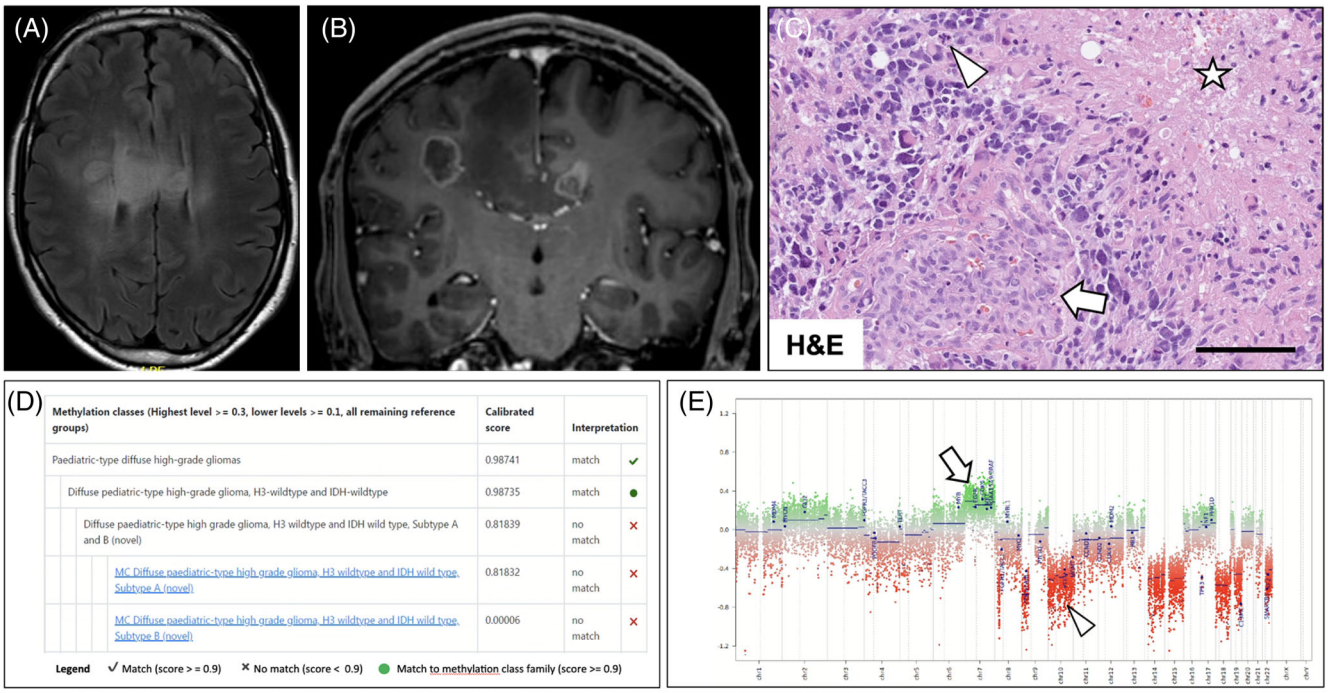

FIGURE 2 Example of a layered diagnosis for a high-grade, diffuse, IDH- and H3-wildtype glioma with the DNA methylation profile of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* in a 60-year-old male. (A) T2-weighted magnetic resonance image revealing a right frontal lobe tumor that crossed the corpus callosum. (B) In this T1-weighted post-contrast image, several ring-enhancing foci are evident. (C) On biopsy, the tumor histologically showed astroglial cytology, high cellularity, marked nuclear pleomorphism, multiple mitoses (including abnormal mitotic figures, arrowhead), necrosis (star) and florid microvascular proliferation (arrow). (D) Using the Heidelberg Brain Tumor Classifier version 12.8 and the Bethesda classifier v2, the DNA methylation profile of the tumor matched with a (very) high score with *Diffuse pediatric-type high-grade glioma* (and within that methylation family with subgroup A (novel) and ped_HGG RTK2, respectively). (E) The copy number variation profile of the tumor obtained by DNA methylation profiling revealed multiple chromosomal alterations, including a whole chromosome 7 gain (arrow) and whole chromosome 10 loss (arrowhead), but no *EGFR* amplification. (F) In this case, the integrated diagnosis of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* was made, and the layered format of the diagnosis is shown. Scale bar in (B) = 100 μm. CNS, central nervous system; H&E, hematoxylin and eosin; pHGG, pediatric high-grade glioma; WHO, World Health Organization.

qualifying as *Glioblastoma, IDH-wildtype* were found to have an RRD high-grade glioma, and four out of five of these cases that could successfully be analyzed by DNA methylation profiling belonged to the pHGG RTK1 class (subclass A). These tumors were found to occur at a younger age and often lack the molecular hallmarks (e.g., *EGFR* amplification, +7/−10, and *TERT* promoter mutation) of classical glioblastomas.

Importantly, however, methylation profiling is not a reliable method for the definitive diagnosis of RRD in gliomas. In cases in which this is suspected (e.g., based on the clinical context, classification by methylation profiling as pHGG RTK1, and/or presence of bizarre and multinucleated tumor giant cells either focally or diffusely throughout the tumor), immunohistochemistry for the mismatch repair (MMR) proteins MSH2, MSH6, MLH1, and PMS2, and molecular analysis to pinpoint the underlying defect is advised for optimal guidance of the patients and their families. Acknowledging that MMR deficiency is more common in gliomas of especially children, adolescents, and young adults than previously reported, as a practical approach, MMR testing by immunohistochemistry should be considered in patients <18 years with H3-wildtype high-grade gliomas (including IDH-mutant astrocytomas), as well as in adult patients between 18 and 40 years with H3- and IDH-wildtype high-grade gliomas that do not fit the histological and molecular criteria for classic *Glioblastoma, IDH-wildtype* [42,51,52].

In conclusion, a definitive diagnosis of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* requires DNA methylation profiling. When DNA methylation profiling is unavailable and tissue or extracted tumor DNA cannot be sent to centers with access to DNA methylation technology, single gene analyses for key alterations targeting *EGFR*, *PDGFR*, or *MYCN* can be used as molecular surrogate markers to support this diagnosis in patients <25 years. However, the working group recommends to then add a *"not otherwise specified"* (NOS) designation to the diagnosis to clarify that this diagnosis was not based on DNA methylation profiling analysis, for example: *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, *MYCN*-amplified, NOS. Although we recognize that "NOS" is generally not used after defined WHO type diagnoses, it does serve as a shorthand notation that not all testing has been done. The alternative would be to designate the tumor as "Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, *MYCN*-amplified, not confirmed by methylation profiling" but such a diagnostic term seems more cumbersome.

In light of these issues, the working group suggests clarifications for the diagnostic criteria for *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, which are listed in Table 2.

TABLE 2 Suggested diagnostic criteria for *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* (changes compared to WHO CNS5 in bold).

Essential
A diffuse glioma with mitotic activity **typically** occurring in a child or young adult
AND
Absence of mutations in *IDH1* **and**[a] *IDH2*
AND
Absence of mutations in H3 genes
AND
DNA methylation profile aligned with one of the methylation subtypes of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* (such as pHGG RTK1, pHGG RTK2, or pHGG MYC).
Desirable
• Microvascular proliferation
• Necrosis, typically palisading
• H3 p.K28me3 (K27me3) retained
• **In cases for which DNA methylation profiling is not available, key molecular features (*PDGFRA* alteration, *EGFR* alteration, or *MYCN* amplification) may be assessed as surrogate markers to support the diagnosis in children or young adults <25 years; it is recommended to then add "not otherwise specified" (NOS) to the diagnosis to clarify that this diagnosis is not based on methylation class assignment**.

[a]"or" replaced by "and."

3 | POSTERIOR FOSSA EPENDYMAL TUMORS

WHO CNS5 distinguishes three types of ependymal tumors of the posterior fossa: *posterior fossa group A (PFA) ependymoma*, with a preferential manifestation in infants and young children; *posterior fossa group B (PFB) ependymoma*, with a predilection for older children, adolescents, and adults; *subependymoma* originating in the posterior fossa and preferentially presenting in adults. Based on a review of the essential and desirable diagnostic criteria of these tumor types and of more recent findings on a few other ependymal tumors originating in the posterior fossa, the cIMPACT-NOW working group generated the following recommendations for the improved diagnosis of these neoplasms.

3.1 | Posterior fossa group A ependymoma

PFA ependymoma is defined by WHO CNS5 as "a circumscribed posterior fossa glioma aligned with the PFA molecular group of ependymomas, demonstrating pseudorosettes or ependymal rosettes and comprising uniform small cells with round nuclei embedded in a fibrillary matrix. An ependymoma can be classified as PFA by identifying a loss of nuclear H3 K27me3 expression in tumor cells or by DNA methylation profiling."

The loss of nuclear H3 K27me3 expression is generally a reliable method for classifying a posterior fossa ependymoma as *PFA ependymoma*, provided appropriate optimization of antibody concentration and laboratory tissue processing has been done. The non-neoplastic cells (e.g., endothelial and inflammatory cells) retain nuclear H3 K27me3 expression and serve as important internal controls. WHO CNS5 states that "global reduction" of H3 K27me3 expression in tumor cell nuclei serves as an essential diagnostic criterion without providing a definite percentage of tumor cells showing this alteration. While most cases indeed demonstrate complete loss of H3 K27me3 expression in tumor cell nuclei by immunohistochemistry, the working group recognized that there may be cases with excessive stromal elements that could raise doubts when evaluating this marker.

Loss of nuclear H3 K27me3 expression in *PFA ependymoma* is the consequence of nuclear overexpression of the EZHIP protein (enhancer of zest homologs inhibitory protein) or rarely H3 K27M mutations [53–56]. The EZHIP protein conformationally mimics the structure of the oncogenic driver H3 K27M and disrupts the activity of the PRC2 complex [54,57]. Antibodies are available for the H3 K27M mutant protein and the EZHIP protein (Figure 3). For cases with ambiguous staining patterns for H3 K27me3, additional testing by DNA methylation analysis can resolve the diagnosis. Additional staining for EZHIP expression can be helpful in cases with ambiguous H3 K27me3 staining for which DNA methylation profiling is not available, as strong and diffuse nuclear EZHIP expression lends support for the diagnosis *PFA ependymoma* in tumors that are H3-wildtype [58,59].

The working group, therefore, suggests clarifications for the diagnostic criteria for *PFA ependymoma*, which are listed in Table 3.

3.2 | Posterior fossa group B ependymoma

WHO CNS5 defines *PFB ependymoma* as "a circumscribed posterior fossa glioma aligned with the PFB molecular group of ependymomas, demonstrating pseudorosettes or ependymal rosettes and comprising uniform small cells with round nuclei embedded in a fibrillary matrix. An ependymoma can be classified as PFB by DNA methylation profiling. Retention of nuclear H3 K27me3 is observed but is not specific for PFB ependymomas."

In cases in which staining for H3 K27me3 remains inconclusive, additional staining for EZHIP may be

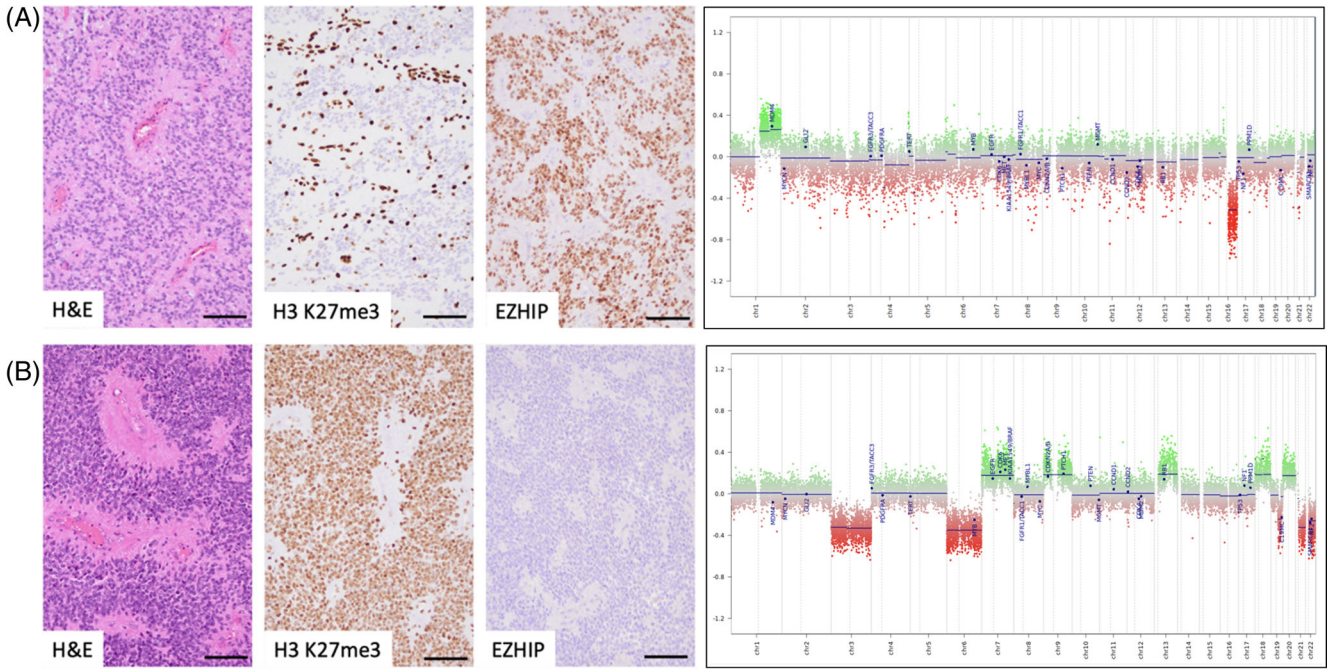

FIGURE 3 Examples of immunohistochemistry of posterior fossa group A (PFA) and posterior fossa group B (PFB) ependymomas. (A) Histology shows a hypercellular tumor with perivascular pseudorosettes; immunohistochemistry demonstrates loss of nuclear H3 K27me3 (the strong staining of non-neoplastic nuclei serves as a positive internal control); EZHIP expression in the nuclei of the tumor cells is strong and diffuse (the nuclei of non-neoplastic cells now serve as a negative internal control); copy number profiling demonstrates gain of chromosome 1q and loss of chromosome 16q; this tumor was assigned with a high confidence score to the PFA ependymoma methylation class. (B) Histology shows a hypercellular ependymal neoplasm with strong and diffuse nuclear H3 K27me3 immunoreactivity and no EZHIP expression; copy number profiling in this tumor reveals a genomically unstable tumor with losses of chromosomes 3, 6, 19, 21, and 22, as well as gains of chromosomes 7, 9, 13, 18, and 20; the tumor was assigned with a high confidence score to the PFB ependymoma methylation class. Scale bars in (A) and (B) = 100 μm. H&E, hematoxylin and eosin.

TABLE 3 Suggested diagnostic criteria for *posterior fossa group A (PFA) ependymoma* (changes compared to WHO CNS5 in bold).

Essential
Posterior fossa tumor with morphological and immunohistochemical features of ependymoma
AND
Loss of H3 K27me3 expression[a] in tumor cell nuclei
OR
DNA methylation profile aligned with PFA ependymoma
Desirable
i. Stable genome on genome-wide copy number analysis[b]
ii. **Strong and diffuse nuclear expression of EZHIP**

[a]"Global reduction of H3 K27me3" replaced by "Loss of H3 K27me3 expression."
[b]Presence of chromosome 1q gain and/or chromosome 6q loss are associated with worse survival [60].

TABLE 4 Suggested diagnostic criteria for *posterior fossa group B (PFB) ependymoma* (changes compared to WHO CNS5 in bold).

Essential
Posterior fossa tumor with morphological and immunohistochemical features of ependymoma
AND
DNA methylation profile aligned with PFB ependymoma.
Desirable
i. Chromosomal instability and aneuploidy on genome-wide copy number analysis
ii. Retained nuclear expression of H3 K27me3
iii. **No EZHIP expression in tumor nuclei**

performed to help resolve the distinction between *PFA ependymoma*, which typically shows strong and diffuse EZHIP expression in the nuclei of tumor cells, and *PFB ependymoma*, which is typically EZHIP negative (Figure 3) [58]. However, definite classification of *PFB ependymoma* requires DNA methylation profiling, also because there is a posterior fossa subependymoma (PFSE) methylation class associated with classic ependymoma histology or with a mixed ependymoma/subependymoma phenotype that shows retained H3 K27me3 expression and lack of EZHIP expression as well (see below) [25,61]. Without conclusive DNA methylation profiling, a posterior fossa tumor demonstrating the histomorphology of ependymoma, retained nuclear expression of H3 K27me3 and no nuclear EZHIP overexpression should be considered as a *Posterior fossa ependymoma, NOS*, which especially in a situation of limited resources is an acceptable diagnosis as well.

The working group thus suggests clarifications for the diagnostic criteria for *PFB ependymoma*, which are listed in Table 4.

3.3 | Other ependymal tumors of the posterior fossa

Next to *PFA ependymoma*, *PFB ependymoma*, and *subependymoma* as distinguished by WHO CNS5, some other ependymal tumors originating in the posterior fossa have emerged. For the diagnosis of those tumors, "not elsewhere classified" (NEC) can be added to the diagnosis, thereby highlighting that the necessary diagnostic testing was successfully performed, but that the results do not allow for a specific diagnosis per WHO CNS5 [10,62].

DNA methylation profiling of posterior fossa tumors with classic ependymoma histology, retained nuclear expression of H3 K27me3 and no nuclear expression of EZHIP revealed a subset of tumors that were assigned with a high confidence score to a methylation class originally designated as "posterior fossa subependymoma" because some of the tumors also showed subependymoma-like histology [63–65]. Further experience has shown that a pure ependymoma or mixed ependymoma–subependymoma histologic pattern for the tumors in this PFSE methylation class is common. In a study in seven different centers, assignment of the PFSE methylation class to posterior fossa tumors with ependymoma histology in adults was found in all institutions, the frequencies ranging between 29% and 67% [25]. WHO CNS5 does not specify how such tumors should be classified.

In 2021, Thomas et al. reported on posterior fossa ependymal tumors with *TERT* promoter mutation, loss of chromosome 6, and the PFSE DNA methylation class assignment. Most of these tumors had a combination of chromosome 6 (or in an individual case 6q) loss, *TERT* promoter mutation, and classic ependymoma features without any subependymoma component (Figure 4), while in other cases a mixed ependymoma–subependymoma phenotype or, rarely, a pure subependymoma phenotype was found [61]. Importantly, these molecular alterations and the classical ependymoma phenotype were found to be associated with shorter progression-free survival than expected for prototypical subependymomas presenting in the posterior fossa [25,61]. For the time being, for these tumors the descriptive label "*Posterior fossa ependymal tumor with TERT promoter mutation and/or chromosome 6 loss and with PFSE methylation class assignment, NEC*" is proposed. As the available evidence suggests that the expected clinical behavior of these neoplasms aligns with that of CNS WHO grade 2 tumors, more frequent radiological follow-up may be indicated than for bona fide subependymomas, especially in the case of subtotal resection. Further discussion in the context of WHO classification is needed to determine what the best name and position in the CNS tumor taxonomy is for these neoplasms.

Furthermore, according to WHO CNS5, *Supratentorial ependymoma, ZFTA fusion-positive* is a distinct type of ependymal tumor [10]. However, rare cases of ependymoma with *ZFTA* fusion have also been reported in the posterior fossa [66,67], accounting for up to 6% of

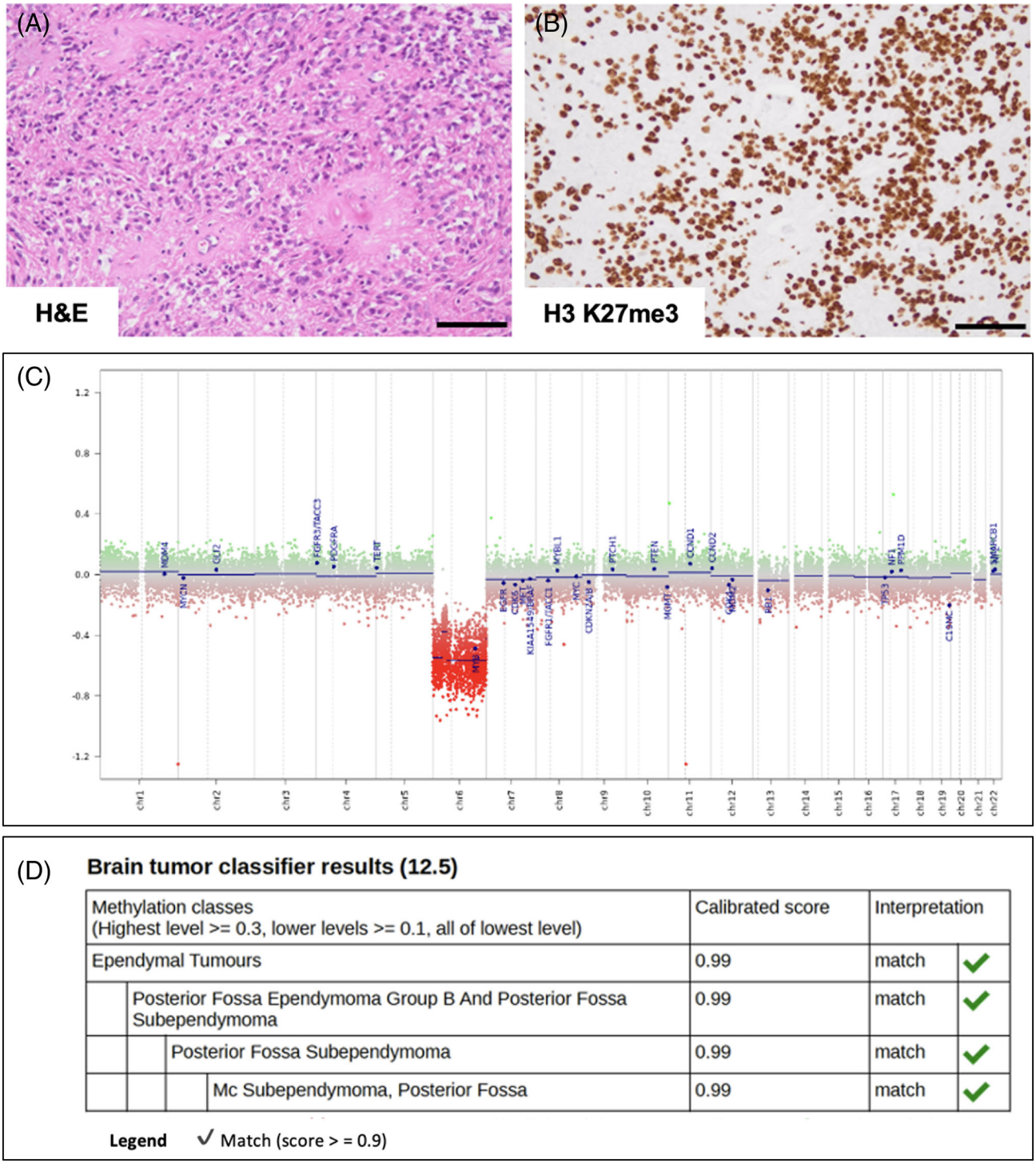

FIGURE 4 Posterior fossa ependymal tumor with *TERT* promoter mutation and/or chromosome 6 loss and with posterior fossa subependymoma (PFSE) methylation class assignment, "not elsewhere classified" (NEC) in a 50-year-old female patient. (A and B) Histology shows ependymoma features with perivascular pseudorosettes and retained nuclear expression of H3 K27me3. (C) The tumor's DNA copy number profile shows isolated loss of chromosome 6. (D) The tumor's methylome profile was assigned by the Heidelberg Brain Tumor Classifier (version 12.5) to the methylation class PFSE with a calibrated score of 0.99. In addition, digital duplex polymerase chain reaction (ddPCR) analysis revealed a c.-146 C>T ("C250T") variant in the *TERT* promoter (not shown). The available evidence suggests that the expected clinical behavior of such neoplasms aligns with that of CNS WHO grade 2 tumors, in contrast to classic subependymomas. Scale bar in (A) and (B) = 100 μm. H&E, hematoxylin and eosin.

the tumors in a recent large meta-analysis cohort [60]. Posterior fossa ependymomas with *ZFTA* fusion share the DNA methylation class and a typically flat DNA copy number profile with their supratentorial counterparts, with chromosome 9 losses being less common in posterior fossa compared to supratentorial tumors [60].

These posterior fossa tumors typically present in infants and children and are rare in adolescents and adults [60]. Survival data on patients with *ZFTA* fusion-positive ependymoma in the posterior fossa are limited by small patient numbers, but available data suggest that these tumors are associated with frequent relapse and worse progression-free and overall survival compared to patients with supratentorial *ZFTA* fusion-positive ependymoma [60]. Acknowledging that in WHO CNS5, *ZFTA* fusion-positive ependymomas are only listed as supratentorial ependymomas, in line with the recommendations in cIMPACT-NOW update 1 [62] the posterior fossa counterpart of these tumors can, for the time being, be designated as *Posterior fossa ependymoma, ZFTA fusion-positive, NEC*. For the next edition of the WHO CNS classification, removal of the site designation "supratentorial" for *ZFTA* fusion-positive ependymomas will help to avoid too much splitting of tumor types (similar to what happened for, e.g., *Rosette-forming glioneuronal tumor* [of the fourth ventricle] in previous WHO CNS tumor classifications).

Recently, yet another unique subgroup of posterior fossa ependymomas has been reported, characterized by somatic heterozygous coding point mutations in the activin receptor type I (*ACVR1*) gene and retained H3 K27me3 expression [68]. The clinicopathologic features of these *ACVR1*-mutant posterior fossa ependymomas show some overlap with PFB ependymomas. For now, such tumors can be signed out as *Posterior fossa ependymoma, ACVR1-mutant, NEC*; but further elucidation of the biologic and clinical implications of this diagnosis is needed.

4 | SUMMARY OF RECOMMENDATIONS

Glioblastoma, IDH-wildtype and *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* are both tumor types in WHO CNS5 that are predominantly characterized genetically by lack of IDH and H3 mutations, rather than by presence of specific tumorigenic alterations. As such, these two types represent heterogeneous groups of neoplasms that may include multiple distinct molecular/methylation types and subtypes. In addition, and importantly, at present the clinical impact of a more refined characterization of these tumor types is still limited and the clinical importance of distinguishing *Glioblastoma, IDH-wildtype* from *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* in adult patients is unclear. Based on currently available information, cIMPACT-NOW suggests the following diagnostic recommendations for these high-grade, IDH-wildtype and H3-wildtype diffuse gliomas:

1. Caution should be used in assigning a diagnosis of *Glioblastoma, IDH-wildtype*, CNS WHO grade 4 to "*TERT* promoter only," histologically low-grade IDH-wildtype diffuse gliomas, and alternative diagnoses should be considered, such as *Pleomorphic xanthoastrocytoma, Subependymoma*, *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype*, or emerging tumor (sub)types or groups of tumors such as "gliomatosis-like glioma" [19,20] and "*FGFR3::TACC3* fusion-positive gliomas" [27,28];
2. *EGFR* gene amplification and +7/−10 chromosome copy number alterations should also not be used as solitary defining features for diagnosing an IDH-wildtype diffuse glioma as *Glioblastoma, IDH-wildtype* in patients <40 years of age, since these alterations can occur in other tumors that are relatively frequent in younger patients (*EGFR* amplification in *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype* and *Diffuse hemispheric glioma, H3 G34-mutant*; +7/−10 in some *Pleomorphic xanthoastrocytomas*);
3. *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, should be considered in the differential diagnosis of a malignant glioma, especially when occurring in adults <40 years of age, when tumor cell nuclei are immunohistochemically negative for ATRX and/or OLIG2, in cases that are *TERT* promoter-wildtype, in neoplasms that have arisen post-irradiation, and in patients with features or a family history of RRD syndrome;
4. In contrast, *PDGFRA* alteration, *EGFR* alteration, or *MYCN* amplification should be considered key molecular features of *Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* only in children or adults <25 years.

With regard to posterior fossa ependymal tumors, cIMPACT-NOW suggests the following:

1. Demonstration of nuclear EZHIP expression by immunohistochemistry can support the classification of a posterior fossa ependymoma as PFA ependymoma, especially in cases of ambiguous nuclear H3 K27me3 expression and when DNA methylation profiling analysis cannot be performed;
2. A posterior fossa ependymoma with retained nuclear expression of H3 K27me3 and without nuclear EZHIP overexpression for which DNA methylation profiling is not performed should be considered as posterior fossa ependymoma, NOS;
3. For emerging posterior fossa ependymal tumor types, "not elsewhere classified" can be added to the diagnosis to emphasize that these tumors are not (yet) listed in the most recent WHO classification; an example is: "Posterior fossa ependymal tumor with *TERT* promoter mutation and/or chromosome 6 loss and with PFSE methylation class assignment, NEC".

These recommendations are based on a current review of the field and are meant to provide additional guidance to practicing pathologists and neuro-oncologists. Of note, the age cut-offs mentioned in this update are current best estimates based on our reviews and experiences and will likely need adjustment as more information becomes available. Furthermore, with the field changing quickly, problems will continue to arise when a diagnosis based on histology (+/− other molecular findings) does not match with a diagnosis suggested by DNA methylation profiling with a high confidence score. There is unfortunately no "ground truth" solution that can be universally applied yet in such cases, and a layered diagnosis remains the best way to report such divergent diagnostic findings. Depending on the weight that is given to the DNA methylation profile in an individual case, a more "conservative" approach can be followed in which the histological information is leading, or a diagnosis can be rendered in which the DNA methylation profiling results are given more weight (see example in Figure 2) [4]. Also, for emerging tumor types (such as the posterior fossa ependymal tumors "NEC" discussed above), application of the criteria as presented in cIMPACT-NOW update 10 will help to decide if they are mature enough for incorporation as a distinct tumor type (or tumor grade) in the next WHO CNS tumor classification [9].

As with all cIMPACT-NOW updates, these recommendations are not official changes to WHO definitions as that would require discussion and confirmation by the next WHO committee. In addition, most of the above comments serve to highlight advances in the field that have been published since WHO CNS5, and further refinements may precede the sixth edition of the WHO CNS tumor classification. Nonetheless, it is hoped that this update indeed provides practical guidance with regard to the diagnosis of *Glioblastoma, IDH-wildtype* versus *Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype*, as well as the diagnosis of ependymal tumors in the posterior fossa.

AUTHOR CONTRIBUTIONS

All authors of this manuscript participated in consensus discussions, contributed to writing, and approved the manuscript, and none of the authors received funding pertaining to working on this cIMPACT-NOW update.

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CONFLICT OF INTEREST STATEMENT

David Capper holds a patent on the diagnostic use of the IDH mutation-specific antibody clone H09 and receives license fees from Dianova GmbH, Hamburg, Germany. David Capper and Stefan M. Pfister are co-founders, advisors, and shareholders of Heidelberg Epignostix GmbH, a company for the development and application of methylation array-based technologies in tumor classification. No conflicts of interest for the other authors.

DATA AVAILABILITY STATEMENT

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

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