Received: 27 June 2025 | Accepted: 19 September 2025

DOI: 10.1111/bpa.70046

RESEARCH ARTICLE

Brain Pathology

AOSNP-ADAPTR resource level-based recommendations on practical diagnostic strategies for WHO CNS5 adult-type diffuse gliomas

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Abstract

The fifth edition of the WHO classification of CNS Tumors (WHO CNS5) has revised the diagnostic and grading criteria for Adult-type Diffuse Gliomas (ADGs) by integrating molecular parameters with histologic features. Conducting molecular testing for most ADGs is now crucial in fulfilling the WHO CNS5 diagnostic criteria. However, due to additional costs and technical barriers, implementing molecular diagnostics is often not feasible in Low-Income Countries (LICs) and Lower Middle-Income Countries (LMICs). Therefore, practical approaches are needed for diagnosis in resource-restrained settings. Hence, the Asian Oceanian Society of Neuropathology (AOSNP), through the 'ADAPTR' (Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Restrained Regions) initiative, aimed to provide resource-stratified recommendations for diagnosing ADGs based on available resources while adhering to the WHO guidelines as much as possible. ADAPTR identified different resource levels (RLs) of diagnostic pathology services, ranging from RL I to RL V, with RL I to RL IV being applicable to the LMICs, and provides recommendations for a 'Histology-oriented integrated diagnosis format' for each tumor type at different RLs. In addition, diagnostic flow charts for ADGs have been generated to suit these RLs. The emphasis is mainly on using histopathological approaches with immunohistochemistry, while molecular testing recommendation is categorized as 'can be considered', 'highly recommended' or 'obligatory', to reach the next level diagnosis. In each RL, either a WHO CNS5 diagnosis with an accompanying CNS WHO grade or an ADAPTR descriptive diagnosis with an associated ADAPTR histologic grade is provided, depending on the context. ADAPTR recommendations are therefore a practical adaptation of the WHO CNS5 guidelines that will suit routine diagnostic practices in resource-restrained regions.

KEYWORDS

adult-type diffuse gliomas, AOSNP-ADAPTR, LMICs, recommendations, resource-restrained regions

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1 | INTRODUCTION

In the fifth edition of the WHO Classification of Central Nervous System Tumors (WHO CNS5), Adult-type Diffuse Gliomas (ADGs) include three tumor types: Astrocytoma, IDH-mutant (A, IDH-mut); Oligodendroglioma, IDH-mutant and 1p/19q-codeleted (O, IDH-mut & 1p/19q-codel), and Glioblastoma, IDH-wildtype (GBM, IDH-wt) [1]. For many such tumors, molecular testing has become essential for achieving a formal WHO CNS5 diagnosis. However, many countries and centers have encountered significant challenges in implementing WHO CNS5. The deficiency is seen mainly in the Low-Income Countries (LICs) and Lower Middle-Income Countries (LMICs) and is attributed to under-resourced laboratories, high costs, and technical barriers [2–5]. Therefore, it is necessary to generate practical recommendations for the WHO guidelines that are appropriate for resource-restrained settings. Similar recommendations were proposed previously by a few groups in the Asian Oceanian region after the WHO 2016 classification of CNS tumors [6–8].

A, IDH-mut is defined by key molecular alterations such as mutations in *IDH1* or *IDH2*, *ATRX*, and *TP53* genes and lacking 1p/19q codeletion. These tumors are graded as CNS WHO grades 2, 3, and 4 (A, IDH-mut, grades 2, 3, and 4). O, IDH-mut and 1p/19q-codel is graded as CNS WHO grades 2 and 3 (O, IDH-mut and 1p/19q-codel, grades 2 and 3). GBM IDH-wt is defined by its IDH-wildtype and H3-wildtype status, corresponds to CNS WHO grade 4 (GBM, IDH-wt, grade 4), and can be histologically or molecularly defined.

Diagnostic evaluations for ADGs start with histology and immunohistochemistry (IHC) for markers like Glial Fibrillary Acidic Protein (GFAP), vimentin, and OLIG2. Ki-67 serves as an ancillary marker in the assessment of tumor grade. Ki-67 labeling index (LI) is typically below 4% for A, IDH-mutant, CNS WHO grade 2, ranges between 5% and 10% for grade 3, and can be variably elevated in grade 4 tumors [9]. However, there is an observed overlap in Ki-67 LI values among histological grades [10–12], and reported values differ across studies [12]. This overlap may be attributed in part to interobserver variability and the differing methodologies used to estimate Ki-67 LI [13]. A definitive cutoff for Ki-67 LI therefore remains undetermined, and while digital quantification in gliomas has been attempted, it still requires validation [14].

Molecular testing for ADGs can partly be performed using IHC surrogate molecular markers such as IDH1 p.R132H, ATRX, and p53. IDH1 p.R132H serves as a highly sensitive and specific surrogate for its corresponding mutation [15]. Most IDH-mutant astrocytomas are positive for IDH1 p.R132H and demonstrate loss of ATRX expression alongside p53 immunopositivity. *ATRX* mutations are mainly truncating mutations with occasional missense mutations in the highly conserved region of the helicase domain of the gene. These are associated with loss of ATRX nuclear expression by IHC [16]. Most alterations in the *TP53* gene are associated with p53 immunopositivity. Missense variants of *TP53* lead to an increased half-life of the p53 protein, which is reflected by prominent immunoreactivity present in most tumor cell nuclei, as opposed to scattered nuclear positivity or faint nuclear staining [17]. Nuclear positivity exceeding 10% has been demonstrated to correlate with the presence of an underlying *TP53* mutation [18]; however, a threshold of greater than 40% p53 immunopositivity in tumor cells is considered more reliable for practical applications. Additionally, truncating mutations in *TP53*, including nonsense, splice site, or frameshift variants, are typically associated with absent or minimal p53 protein expression ("null phenotype"). Consequently, negative p53 staining does not rule out a *TP53* mutation and should be interpreted cautiously [19].

DNA (Sanger) sequencing for the other *IDH1* and all the *IDH2* mutations is essential to diagnose A, IDH-mut and O, IDH-mut and 1p/19q-codel tumors that are negative for IDH1 p.R132H, and for GBM IDH-wt in patients under 55 years [1]. *CDKN2A/B* (cyclin-dependent kinase inhibitor 2A/B) homozygous deletion (HD) status can be evaluated by fluorescence in situ hybridization (FISH) and other techniques, such as multiplex ligation-dependent probe amplification (MLPA) and polymerase chain reaction (PCR), and is required for the identification of CNS WHO grade 4 neoplasms that otherwise would be diagnosed as A, IDH-mut, grade 2 or 3 [16, 18, 20–22]. 1p/19q codeletion evaluation is essential for the diagnosis of O, IDH-mut and 1p/19q-codel and can be assessed by FISH and other techniques [21, 22]. IDH status in GBM IDH-wt is routinely evaluated either by IHC or Sanger sequencing [22]. In addition, an IDH-wt lower-grade diffuse glioma is also designated as GBM IDH-wt if it has one or more of the following molecular features: *TERT* promoter mutation, *EGFR* amplification, and +7/−10 chromosome copy number changes [23–25]. These are assessed usually by Sanger sequencing, FISH or next generation sequencing (NGS). O^6 methylguanine DNA methyl transferase (*MGMT*) promoter

methylation, which is a predictive marker for the efficacy of temozolomide treatment in patients with GBM, IDH-wt, is usually evaluated by techniques such as methylation-specific PCR (MS-PCR), quantitative PCR (qPCR), methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) or pyrosequencing [26, 27]. Broadly, therefore, some of the testing platforms for molecular markers of ADG include IHC, Sanger sequencing, FISH, PCR, MLPA, pyrosequencing and NGS. DNA methylation profiling is advocated in unresolved cases and the methylation profile of any of the ADGs remains a desirable diagnostic criterion in WHO CNS5 [28–30].

Despite traditional classifications, age boundaries between adult-type and pediatric-type diffuse gliomas are increasingly blurred. Adult-type diffuse gliomas, such as GBM IDH-wt, are typically observed in older adults but can also be found in children and adolescents [25]. Similarly, pediatric-type diffuse gliomas, including low- and high-grade gliomas, may occur in adults [31]. Among low-grade gliomas, distinguishing diffuse astrocytoma, *MYB*- or *MYBL1*-altered, from adult-type diffuse low-grade gliomas in patients under 40 is essential [32]. OLIG2 is generally negative in *MYB*- or *MYBL1*-altered tumors, though rare cases complicate diagnosis when it is positive [33]. Diffuse hemispheric glioma, H3G34-mutant, may present in young adults and can closely resemble A, IDH-mut, CNS WHO grades 3 and 4, due to shared features such as ATRX loss and p53 positivity. However, the typical negativity for OLIG2 in diffuse hemispheric glioma, H3G34-mutant, generally distinguishes it from IDH-mutant astrocytomas at the IHC level [34]. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, has also been identified in adults up to 70 years old, indicating that these tumors, while more commonly found in children, can occur in adults as well (and are therefore designated as 'pediatric-type' rather than 'pediatric') [35, 36]. For a definitive diagnosis of such complex cases, advanced molecular diagnostics, such as DNA methylation profiling, may be necessary.

2 | LIMITATIONS OF MOLECULAR TESTING FOR ADGs IN RESOURCE-RESTRAINED REGIONS

In resource-restrained regions, molecular testing for ADG to reach a WHO CNS5 diagnosis faces several challenges. Healthcare systems in most LMICs vary, with diagnostic services dependent on each center's resources. A survey conducted by the ADAPTR (Adapting Diagnostic Approaches for Practical Taxonomy in Resource-restrained regions) group of the AOSNP (Asian Oceanian Society of Neuropathology) [37] documented the availability of technologies for CNS tumor classification in 19 countries of the Asian Oceanian region comprising varied socioeconomic status [38]. The survey indicated that 97.6% of centers in LMICs have magnetic resonance imaging (MRI) available. Most IHC surrogate molecular markers are available in-house/locally in slightly over half of diagnostic histopathology laboratories in the LMICs, but fewer centers offer molecular tests such as FISH (29%) and Sanger sequencing (10.7%). Advanced techniques such as NGS for DNA/RNA sequencing are available in only 9.4% of centers, and in-house/local DNA methylation profiling is unavailable in any LMICs. DNA methylation profiling is accessible only in a limited number of centers, even in high-income countries within the Asian Oceanian region (12.5%). This service thus may remain financially inaccessible for numerous individuals caused by economic limitations [38]. Our survey revealed that 28.9% of LMICs do not even have local access to basic diagnostic IHC markers for routine diagnosis. Nepal (100%), Bangladesh (86%), and Indonesia (73%) showed the highest non-availability [38]. Some LMIC centers collaborate with more advanced diagnostic centers, both domestically and internationally, to obtain final diagnoses [39]. Therefore, according to the survey results, which indicated a lack of availability of advanced diagnostic pathology services, particularly in LMICs, the ADAPTR group convened to provide recommendations tailored to different resource levels for the routine evaluation of ADGs. These recommendations were designed to adapt the WHO CNS5 guidelines suitable for resource-restrained regions. The ADAPTR recommendations emphasize the use of alternative approaches, including IHC surrogate molecular markers that include well-established and newer markers, and consider clinical and radiological features as supportive evidence—all to provide the most optimal and economically feasible diagnosis.

2.1 | Imaging features of ADGs suitable for ADAPTR recommendations

On MRI, As, IDH-mut are hypointense on T1-weighted (T1W) images and hyperintense on T2-weighted (T2W) images but with a relative hypointensity on fluid-attenuated inversion recovery (FLAIR) sequences. This T2–FLAIR mismatch or discordance sign is considered a characteristic feature and often used as a radiological surrogate for IDH-mutant astrocytomas [40, 41]. However, one of the pitfalls of this sign is that some pediatric-type low-grade gliomas which can also present in adults, such as diffuse astrocytoma *MYB*- or *MYBL1*-altered or pediatric-type low-grade gliomas with or *FGFR1::TACC1* fusion, and a few others, may present with this alteration on imaging [42, 43], which hence has to be interpreted with caution. Whilst As, IDH-mut, grade 2 are usually non-enhancing, grades 3 and 4 tumors show variable degrees of enhancement, with focal necrosis in grade 4. Os, IDH-mut and 1p/19q-codel, grades 2 and 3 are T1W-hypointense and T2W-hyperintense masses, with indistinct tumor margins and without the T2-FLAIR mismatch sign [44]. While many of the grade 2 tumors are non-enhancing, grade 3 tumors exhibit varying

degrees of post-contrast enhancement. GBM, IDH-wt is often a ring-enhancing lesion on MRI with a central dark area of necrosis, which can be helpful in supporting the diagnosis of molecularly defined GBM when histology shows features of IDH-wildtype lower-grade diffuse glioma [45]. In summary, ADG imaging features can be useful to the pathologist since they provide supportive diagnostic evidence.

2.2 | Additional IHC surrogate markers for ADGs suitable for ADAPTR recommendations

2.2.1 | IHC surrogates for *CDKN2A/B* homozygous deletion

Recent studies have validated p16 and MTAP (Methylthioadenosine Phosphorylase) as IHC surrogate markers for *CDKN2A/B* homozygous deletion (HD). Loss of p16 expression has been shown to correlate with *CDKN2A* HD in both pediatric and adult gliomas. p16 loss in over 95% of tumor cells predicts *CDKN2A* HD with high sensitivity and negative predictive value (NPV) [46]. Some authors have shown that p16 positivity in equal to or less than 5% of tumor cells demonstrated 100% specificity for *CDKN2A* HD, while scores above 20% consistently indicated the absence of *CDKN2A* HD; scores between 6% and 20% were considered inconclusive [47]. In GBM, IDH-wt, p16 loss shows good sensitivity and NPV, supporting its use as a screening tool for *CDKN2A* deletion status [48]. These studies indicate that widespread loss of p16 is thus a strong indicator of *CDKN2A/B* HD.

MTAP is located on 9p21, only 165 kb telomeric to *CDKN2A/2B*, and is often deleted in association with *CDKN2A/B* HD. Loss of MTAP expression by IHC has been shown to predict *CDKN2A/B* HD higher for As, IDH-mut (sensitivity, 88%; specificity, 98%) and GBM, IDH-wt (sensitivity, 89%; specificity, 100%), than for Os, IDH-mut and 1p/19q-codel (sensitivity 67%; specificity 57%) [49]. Of note, MTAP loss as assessed by IHC has been shown to be highly specific for *CDKN2A/B* HD in malignant mesothelioma [50]. Studies have evaluated MTAP and p16 together and separately as surrogate markers for *CDKN2A/B* HD in gliomas. One study reported that complete loss of MTAP was 100% sensitive and 97% specific for *CDKN2A/B* HD, while p16 loss showed lower sensitivity and specificity [51]. Another report indicated p16 positivity in less than 5% tumor cells combined with loss of MTAP staining predicted *CDKN2A/B* HD in over 87% of IDH-mutant astrocytomas. Conversely, p16 positivity in more than 20% cells with retained MTAP pointed to *CDKN2A/B* retained cases. Ambiguous results were observed in cases with 5–20% cells showing p16 staining and mosaic MTAP patterns. The authors report that MTAP immunostaining is an effective, reliable, and affordable method for evaluating gliomas caused by its close association with *CDKN2A/B* status but recommend caution when interpreting p16 results [52]. In a separate study, the combination of p16 nuclear staining of <1% and MTAP cytoplasmic staining of ≤30% demonstrated high specificity (96%) and sensitivity (86%) for *CDKN2A/B* HD in pleural mesotheliomas [53].

2.2.2 | IHC surrogates for 1p/19q codeletion

Huntingtin interacting protein 1-related (HIP1R) overexpression, loss of vimentin expression, and loss of H3 p.K28me3 (K27me3) have been identified as predictors of 1p/19q codeletion status in IDH-mutant gliomas [54]. HIP1R, which induces cellular transformation, is related to cell survival and is overexpressed in some cancers like colonic and prostate cancers [55]. Mass spectrometry-based proteomic analysis demonstrated high HIP1R and low vimentin levels in Os, IDH-mut & 1p/19q-codel compared to low HIP1R and high vimentin levels in As, IDH-mut. By IHC, HIP1R and vimentin predicted 1p/19q codeletion accurately in more than 90% of the cases. These two markers combined with retained nuclear ATRX expression increased the sensitivity to 96% and the specificity to 100% [56]. A meta-analysis on gene expression in diffuse low-grade gliomas identified HIP1R to be a downregulated gene in A, IDH-mut when compared to O, IDH-mut & 1p/19q-codel.

Trimethylation at lysine 27 of histone 3 (H3 p.K27me3) is a repressive histone mark, important for epigenetic gene regulation and CNS tumor classification [57]. Among ADGs, its loss is more frequent in O, IDH-mut and 1p/19q codel compared to A, IDH-mut, but it also occurs in some A, IDH-mut, up to 75% in one study [54], with others reporting 13% and 27%, respectively [58, 59]. Also, H3 p.K27me3 loss is seen with IDH1R132H mutations, but not with those having other *IDH1* and *IDH2* mutations [58]. Moreover, retention of H3 p.K27me3 occurs in 25% of oligodendrogliomas, showing that its loss alone is not fully sensitive or specific for diagnosis [59].

Furthermore, strong and widespread nuclear staining for p53 has been proposed as a sufficient criterion to rule out 1p/19q deletion [60]. In summary, using a combined approach with p16 and MTAP for *CDKN2A/B* HD and HIP1R/vimentin/H3 p.K27me3 alongside ATRX and p53 for 1p/19q codeletion may serve as IHC surrogates for routine application, particularly in resource-limited areas. These markers provide a reliable and cost-effective alternative to more complex techniques such as FISH. Nevertheless, it is essential to validate these markers in other cohorts, and caution should be exercised when employing them.

3 | ADAPTR RECOMMENDATIONS FOR THE EVALUATION OF ADGs

ADAPTR categorized three components for its recommendations: (i) identifying resource levels of diagnostic

pathology services; (ii) providing recommendations for 'Histology-oriented integrated diagnosis' format for each tumor type at different resource levels; (iii) generating diagnostic flow charts that suit these resource levels.

3.1 | Resource levels of diagnostic pathology services (Table 1)

According to our previous reports, ADAPTR stratified five resource levels (RLs) of diagnostic pathology services for ADGs, ranging from RL I to RL V [37, 38]. A similar stratification of RLs has also been suggested for other tumors, such as breast cancer in Asia [61]. Table 1 presents the RLs of diagnostic pathology services for assessing ADGs along with the list of IHC/molecular tests that are available at each RL. Briefly, RL I includes centers with basic facilities such as H&E staining performed on squash/smear preparations or frozen sections and formalin-fixed, paraffin-embedded (FFPE) tissues, along with a few histochemical stains such as reticulin. At RL II, a center has the ability to run IHC for basic diagnostic markers such as GFAP, vimentin, OLIG2, and others. Reporting of gliomas is often carried out by a general pathologist at these two RLs. RL III has the additional availability of IHC surrogate molecular markers such as IDH1 p.R132H, ATRX, p53, and others. A pathologist skilled in interpreting these markers is needed at this RL. RL IV laboratories are equipped to carry out basic molecular techniques such as FISH, Sanger sequencing, and PCR, as well as a few others. This resource level needs a neuropathologist proficient in interpreting molecular tests for an integrated diagnosis. RL V is the highest resource level, where advanced molecular tests such as DNA and RNA sequencing by NGS as well as DNA methylation profiling are performed, which are mostly unavailable in LICs and LMICs.

3.2 | ADAPTR recommendations for 'Histology-oriented integrated diagnosis' format for ADGs at different resource levels (Tables S1–S5 and Figures 1–5)

ADAPTR proposes a 'Histology-oriented integrated diagnosis' format for the different RLs (RL I to RL IV); note that RL V, being the highest resource level, is not included in the recommendations. These recommendations rely on histopathology and IHC, whereas molecular information is categorized as 'can be considered', 'highly recommended', or 'obligatory' to reach the next level diagnosis, depending on the situation. Clinical and imaging features are also considered as supportive evidence for the diagnosis. ADAPTR recommendations address adults with suspected diffuse low- or high-grade glioma, but they can also be applied to adolescents and children likely to have ADGs based on clinical and radiological evidence. ADAPTR recommendations are given for each tumor type at different resource levels and may be used by the pathologist depending on the individual patient and available resources.

Table S1 illustrates ADAPTR 'Histology-oriented integrated diagnosis' format for a typical case of A, IDH-mut, CNS WHO grade 2. First, the baseline clinical information, such as age, tumor location, clinical and imaging features common for all RLs, is considered. The next parameters include histopathologic features (based on H&E staining ± other histochemical stains), IHC information (basic diagnostic/surrogate molecular markers), and molecular test information. Based on these parameters, the diagnosis rendered is either a WHO CNS5 diagnosis with an associated CNS WHO grade or an ADAPTR descriptive diagnosis accompanied by an ADAPTR histologic grade, as applicable. The ADAPTR descriptive diagnosis (an NOS [Not Otherwise Specified] diagnosis) is provided when a WHO CNS5 diagnosis cannot be determined at a certain RL. The ADAPTR comment includes an opinion based on histopathological and IHC features, clinical data, and imaging parameters, depending on the RL. ADAPTR descriptive diagnosis is accompanied by ADAPTR histologic grade. A point to note is that Roman numerals (II–IV) are used to depict the ADAPTR histologic grade for situations in which not all tests could be performed for assigning a malignancy grade according to WHO CNS5 standards. The use of Roman numerals (the WHO approach for CNS tumors prior to 2021) helps to distinguish this grading from the CNS WHO grading approach using Arabic numerals following 2021 (when many of the molecular testing requirements were added).

The diagnosis provided (either WHO CNS5 diagnosis or ADAPTR descriptive diagnosis, with ADAPTR comment) and ADAPTR recommendations for A, IDH-mut, CNS WHO grade 2, at different RLs are shown in Table S1 and Figure 1. At RL I and RL II, an ADAPTR descriptive diagnosis (Diffuse low-grade glioma, NOS) and ADAPTR histologic grade (grade II) are provided as the WHO CNS5 diagnosis cannot be reached. The ADAPTR comment would indicate that the features are suggestive of 'Diffuse low-grade astrocytic glioma', based on the histopathological assessment ± basic IHC markers and available clinical and radiological information. At these RLs, referral to an RL III center (where histopathologic findings can be correlated with IHC surrogate molecular markers and the available radiological features) is 'highly recommended' by ADAPTR to arrive at the most probable diagnosis. If resources permit, referral to an RL IV center for molecular testing 'can be considered' for reaching a WHO CNS5 diagnosis. If referral to a higher RL center is not feasible, ADAPTR suggests managing the patient according to ADAPTR descriptive diagnosis and histologic grade. Approximately 30% of centers in LMICs are at RL III [38], making RL III facilities with IHC surrogate molecular markers valuable for

TABLE 1 ADAPTR-Stratification of resource levels of diagnostic pathology services for adult-type diffuse gliomas (ADGs). The IHC surrogate molecular markers and diagnostic molecular assays relevant for each RL are listed.

Resource levels	Resource level 1 (RL I)	Resource level II (RL II)	Resource level III (RL III)		Resource level IV (RL IV)		Resource level V (RL V)
Available resources	Histology only	+ Basic diagnostic IHC markers	+ Surrogate IHC molecular markers		+ Basic molecular tests		+ Advanced molecular tests
Pathology services	Material (i) FFPE sections (ii) Frozen tissue/ squash smear	Material (i) and (ii)	Material (i) and (ii)		Material (i) and (ii) (iii) Fresh tissue		Material (i), (ii) and (iii)
	Techniques 1. H&E 2. Other histochemical stains	Techniques 1. and 2. 3. Basic IHC markers	Techniques 1. to 3. 4. Surrogate IHC molecular markers		Techniques 1. to 4. 5. Sanger sequencing 6. FISH 7. RT-PCR (qPCR) 8. MSP 10. MLPA 11. MS-MLPA		Techniques 1. to 11. 12. DNA/RNA sequencing by NGS for diagnosis 13. DNA Methylation profiling for methylation-based diagnosis
Basic diagnostic IHC markers	Nil	GFAP, Vimentin, OLIG2, S100, Ki-67 and others	Same as RL II		Same as RL II		Same as RL II
IHC Surrogate molecular markers	Nil	Nil	Markers IDH1 p.R132H, ATRX, p53	For diagnosis/grading of: All ADGs	Same as RL III		Same as RL III
			MTAP, p16	A, IDH-mut, grades 2&3			
			HIP1R	O, IDH-mut & 1p/19q-codel, grades 2&3			
			BRAF p.V600E, H3 p.G35R/V(G34R/V)	GBM, IDH-wt in younger adults			
			H3 p.K28M(K27M)	To exclude Diffuse midline glioma, H3 K27-altered			
			H3 p.K28me3(K27me3)	O, IDH-mut & 1p/19q-codel, and Diffuse midline glioma, H3 K27-altered			
Diagnostic molecular assays	Nil	Nil	Nil		1. Sanger sequencing (a) *IDH1* & *IDH2* mutations (in cases where IHC for IDH1 p.R132H is negative)	For diagnosis of: (i) A, IDH-mut (ii) O, IDH-mut & 1p/19q-codel (iii) GBM, IDH-wt in patients <55 years	Same as RL IV and 1. Targeted NGS using (glioma) panel for diagnosis

TABLE 1 (Continued)

Resource levels	Resource level 1 (RL I)	Resource level II (RL II)	Resource level III (RL III)	Resource level IV (RL IV)		Resource level V (RL V)
				(b) *BRAF* p.V600E mutations	For diagnosis of: Epithelioid GBM in younger adults where IHC for BRAF p.V600E is inconclusive	2. Methylation profiling for methylation-based diagnosis
				(c) *TERT*p mutations	For diagnosis of: molecularly defined GBM	
				2. FISH or MLPA		
				(a) 1p/19q codeletion	For diagnosis of: O, IDH-mut & 1p/19q-codel	
				(b) *CDKN2A/B* homozygous deletion	For grading of: A, IDH-mut, grades 2&3	
				(c) *EGFR* amplification, +7/−10 status	For diagnosis of: Molecularly defined GBM	
				3. MSP, MS-MLPA and qPCR		
				(a) *MGMT* promoter methylation	GBM, IDH-wt (especially in elderly/frail patients)	
Personnel/ Pathologist	General pathologist	General pathologist	Pathologist skilled in interpreting the IHC surrogate molecular markers	Neuropathologist proficient in interpretation of molecular tests and providing an integrated diagnosis		Neuropathologist proficient in interpretation of molecular tests and providing an integrated diagnosis

Abbreviations: A, IDH-mut: Astrocytoma, IDH-mutant; GBM, IDH-wt: glioblastoma, IDH-wildtype; FISH: fluorescence in situ hybridization; HIP1R: Huntingtin interacting protein 1 related; IHC: immunohistochemistry; MLPA: multiplex ligation-dependent probe amplification; MSP: methylation specific PCR; MS-MLPA: methylation-specific MLPA; MTAP: methylthioadenosine phosphorylase; NGS: next generation sequencing; O, IDH-mut & 1p/19q-codel: oligodendroglioma, IDH-mutant and 1p/19q-codeleted; RT-PCR: real-time PCR.

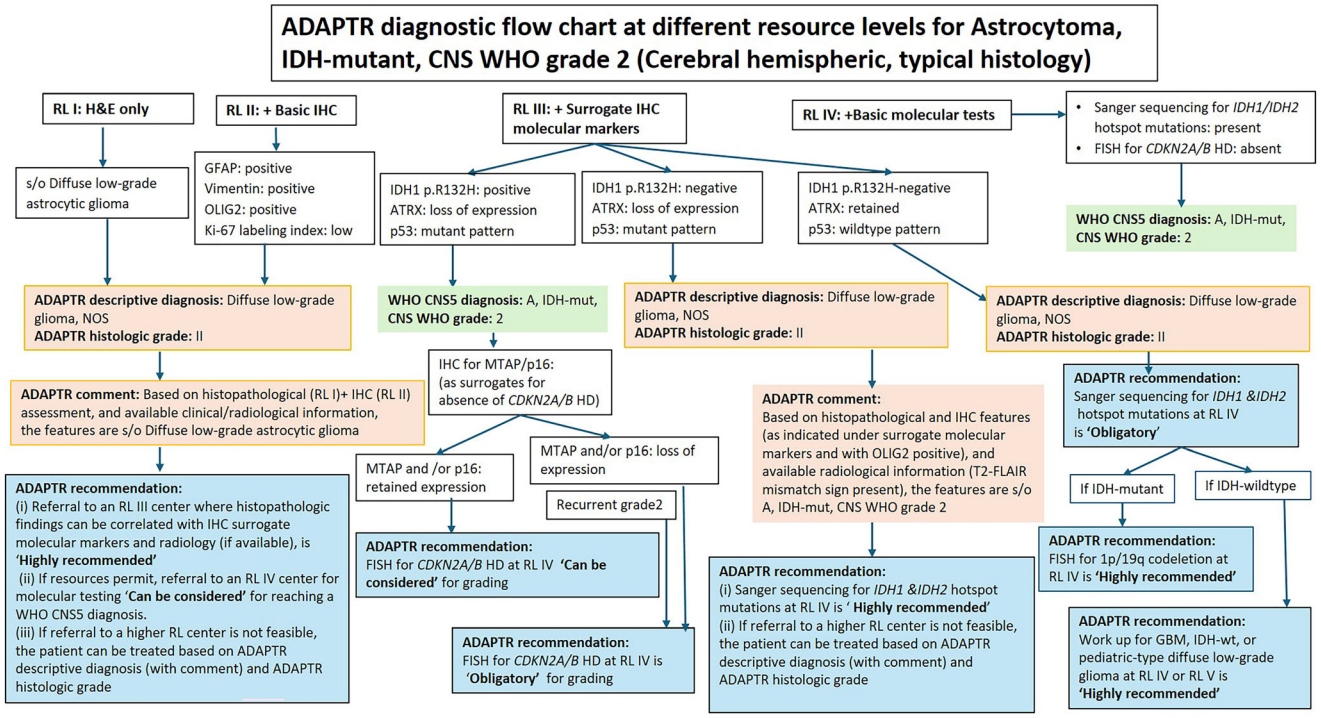

FIGURE 1 ADAPTR diagnostic flow chart for A, IDH-mut, CNS WHO grade 2 at resource levels-RL I to RL IV. (i) WHO CNS5 diagnosis can be established at RL III using IHC surrogate molecular markers or at RL IV through molecular testing. If WHO CNS5 diagnosis cannot be determined, ADAPTR descriptive diagnosis and ADAPTR histologic grading are provided. ADAPTR recommendations—'Can be considered', 'Highly recommended', and 'Obligatory'—are based on histopathological and IHC findings at various resource levels. (ii) p53 mutant expression pattern is typically characterized by strong immunopositivity of >40% of tumor cell nuclei; however, truncating *TP53* mutations can result in complete lack of p53 staining of tumor cell nuclei. Therefore "unmatching p53-ATRX profiles" should be cautiously interpreted. (iii) If IDH is wildtype, work up for GBM, IDH-wt (in older adult), or pediatric-type diffuse low-grade glioma (in younger adult), at RL IV or RL V is 'highly recommended'. (iv) MTAP and p16 are IHC surrogate markers for *CDKN2A*/*B* HD. A, IDH-mut: Astrocytoma, IDH-mutant; GBM, IDH-wt: Glioblastoma, IDH-wildtype; FISH: Fluorescence in situ hybridization; *CDKN2A*/*B* HD: Cyclin Dependent Kinase A/B homozygous deletion; MTAP: Methylthioadenosine phosphorylase.

RL I and RL II institutions. At an RL III center, the pathologist can provide a WHO CNS5 diagnosis or ADAPTR descriptive diagnosis based on the IHC profile using surrogate molecular markers, including comments and recommendations. Molecular testing is classified as 'can be considered', 'highly recommended', or 'obligatory', depending on the IHC profile, as shown in Table S1 and Figure 1.

For instance, while molecular testing for *CDKN2A*/*B* HD is necessary for further grading of A, IDH-mut (grades 2 and 3), studies show that *CDKN2A*/*B* HD is rare in A, IDH-mut, CNS WHO grade 2 [62, 63]. Thus, for a typical grade 2 IDH-mutant astrocytoma at RL III, ADAPTR advises utilizing IHC surrogate markers such as p16 and MTAP. If MTAP and/or p16 show retained expression, ADAPTR indicates that FISH for assessing *CDKN2A*/*B* HD 'can be considered'. If either MTAP or p16 shows loss of expression, or in the case of a recurrent grade 2 tumor, FISH for *CDKN2A*/*B* HD would become 'obligatory'. These recommendations will assist RL III pathologists in providing the most appropriate diagnoses (given the circumstances), thus enabling effective patient treatment. In LMICs, fewer RL IV centers (i.e., centers that have basic molecular testing facilities at their disposal) are available, and such centers may represent tertiary referral centers. Most ADG cases can be diagnosed with an integrated WHO CNS5 at RL IV.

The 'histology-oriented integrated diagnosis' format for A, IDH-mut, CNS WHO grades 3 and 4 is illustrated in Tables S2 and S3 and in Figures 2 and 3, respectively. If resources are limited and further tests (IHC or molecular) cannot be performed at RL I and RL II, patient treatment can proceed based on ADAPTR descriptive diagnosis and ADAPTR histologic grade. Similarly, for O, IDH-mut and 1p/19q-codel, CNS WHO grades 2 and 3, the ADAPTR descriptive diagnosis and ADAPTR histologic grade, along with comments and recommendations, are determined based on the RL. IHC surrogate approaches using markers such as HIP1R, vimentin, H3 p.K28me3 (K27me3), p53, and ATRX are recommended in lieu of testing for 1p/19q codeletion in resource-restrained settings (Table S4 and Figure 4).

Table S5 and Figure 5 illustrate an example of the 'histology-oriented integrated diagnosis' format for GBM, IDH-wt, CNS WHO grade 4 that includes the ADAPTR recommendations based on the RL. Glioblastoma, NOS,

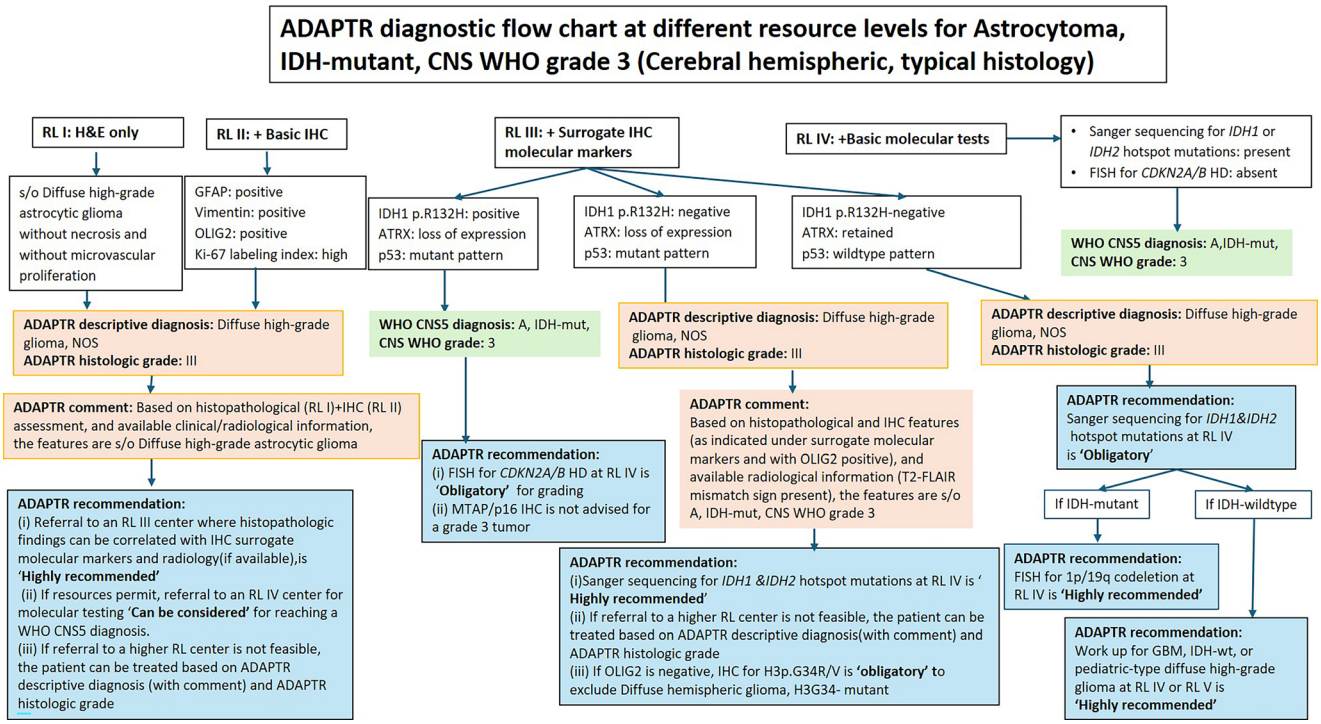

FIGURE 2 ADAPTR diagnostic flow chart for A, IDH-mut, CNS WHO grade 3 at resource levels RL I to RL IV. (i) For grade 3 tumors, MTAP/p16 IHC is not recommended; FISH for *CDKN2A*/*B* HD at RL IV is 'obligatory' for grading. (ii) If OLIG2 and IDH1p.R132H are negative, with ATRX loss and p53 mutant expression pattern, H3p.G34R/V IHC is obligatory to rule out diffuse hemispheric glioma, H3G34-mutant (in younger adults). A, IDH-mut: Astrocytoma, IDH-mutant; FISH: Fluorescence in situ hybridization; *CDKN2A*/*B* HD: Cyclin Dependent Kinase A/B homozygous deletion; MTAP: Methylthioadenosine phosphorylase.

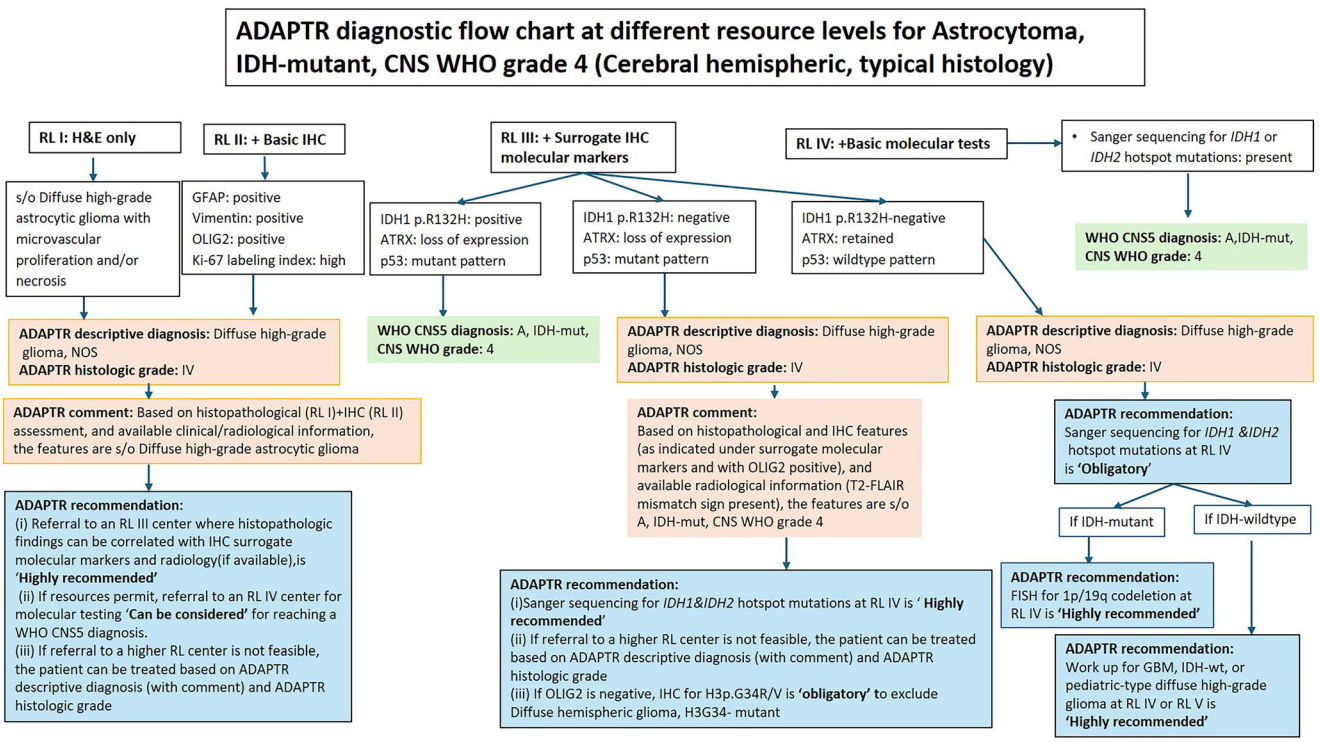

FIGURE 3 ADAPTR diagnostic flow chart for A, IDH-mut, CNS WHO grade 4 at resource levels RL I to RL IV. If OLIG2 and IDH1p.R132H are negative, with ATRX loss and p53 mutant expression pattern, H3p.G34R/V IHC is obligatory to rule out diffuse hemispheric glioma, H3G34-mutant (in younger adults). A, IDH-mut: Astrocytoma, IDH-mutant.

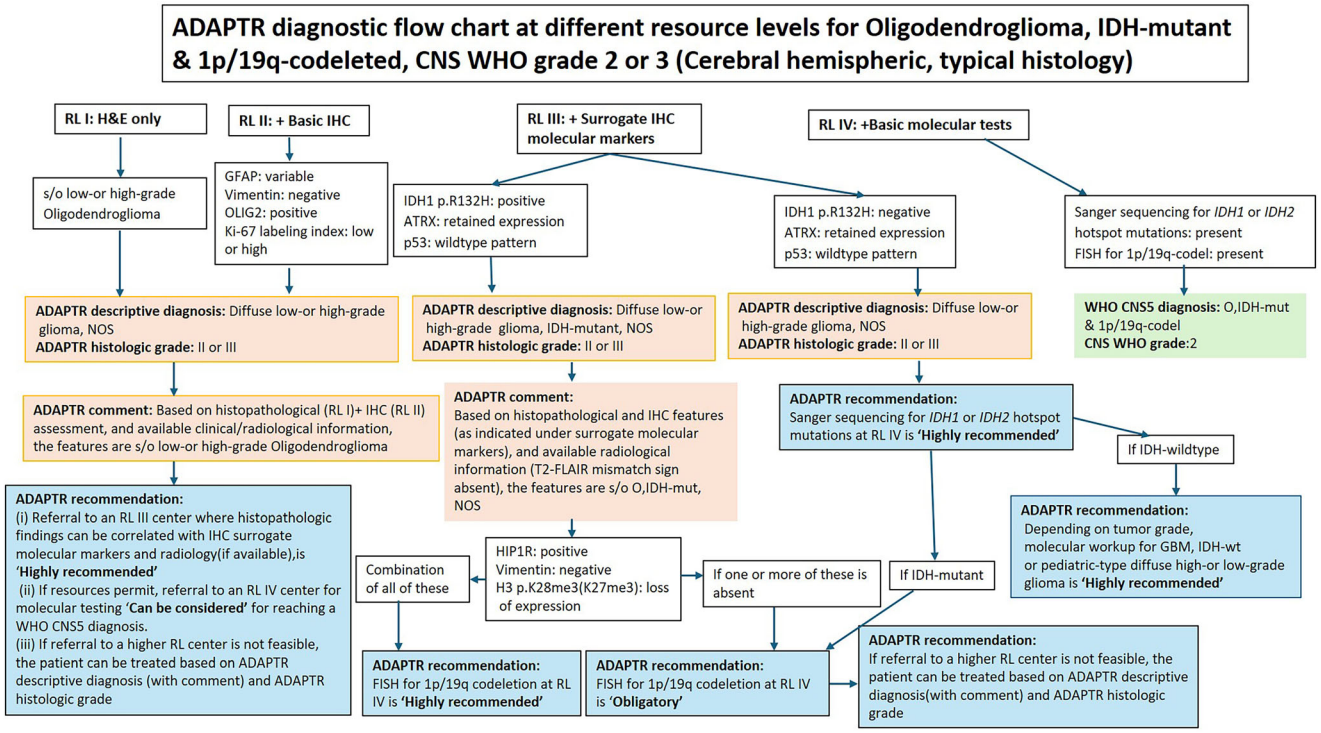

FIGURE 4 ADAPTR diagnostic flow chart for O, IDH-mut & 1p/19q codel, CNS WHO grade 2 and 3 at resource levels—RL I to RL IV. WHO CNS5 diagnosis can be established at RL III using IHC surrogate molecular markers or at RL IV through molecular testing. If WHO CNS5 diagnosis cannot be determined, ADAPTR descriptive diagnosis and ADAPTR histologic grading are provided. ADAPTR recommendations—'Can be considered', 'Highly recommended', and 'Obligatory'—are based on histopathological and IHC findings at various resource levels. HIP1R, vimentin and H3 p.K28me3 (K27me3) serve as IHC surrogates for 1p/19q codeletion. p53 wildtype pattern is characterized by the tumor cell nuclei being typically negative for p53 with occasionally scattered variably positive nuclei. If IDH is wildtype, work up for GBM, IDH-wt (in older adult), or pediatric-type diffuse low-or high-grade glioma (in younger adult) at RL IV or RL V is 'highly recommended'. O, IDH-mut & 1p/19q-codel: Oligodendroglioma, IDH-mutant & 1p/19q-codeleted; FISH: Fluorescence in situ hybridization; HIP1R: Huntingtin interacting protein 1-related; GBM, IDH-wt: Glioblastoma, IDH-wildtype.

histologic grade IV, can be diagnosed at RL I and RL II in older adults based on characteristic histopathological features. If further testing is not feasible, the patient can be managed using ADAPTR descriptive diagnosis and ADAPTR histologic grade. For patients aged 55 and over with classic GBM histology, a non-midline tumor location, no prior low-grade glioma, and negative IDH1 p.R132H immunoreactivity, a diagnosis of GBM, IDH-wt, CNS WHO grade 4 can be made as per WHO CNS5 guidelines [64]. For patients under 55 years, if IDH1 p.R132H is negative, the diagnosis 'Diffuse high-grade glioma, NOS', histologic grade IV is provided by ADAPTR. For patients aged 40–55, if IDH1 p.R132H is negative by IHC, with retained ATRX expression and either wildtype or mutant p53 expression, along with classic GBM histopathology and imaging features, the ADAPTR comment indicates that the features are 'suggestive of GBM, IDH-wt' and Sanger sequencing for *IDH1 and 2* mutations is 'highly recommended'. On the other hand, for adult patients under 40 years, Sanger sequencing for *IDH1* and *IDH2* mutations becomes 'obligatory' to reach the next level diagnosis (Table S5 and Figure 5) since they fall within the Adolescent and Young Adult (AYA) group (ages 15–39), bridging pediatric and adult cohorts. They may present with pediatric-type high-grade gliomas, as well as with IDH-mutant astrocytomas and oligodendrogliomas and with GBM, IDH-wt [65]. For this reason, Sanger sequencing is required for accurate classification. IDH-wildtype cases are recommended to undergo further molecular analysis to exclude pediatric-type high-grade gliomas. These procedures are important for prognosis and treatment planning. At RL III or RL IV, in cases where WHO CNS5 diagnosis of GBM, IDH-wt is reached, ADAPTR recommends considering analysis of the *MGMT* promoter methylation status for elderly and frail patients.

For adult-type diffuse gliomas (grades 2 and 3) that are IDH-wildtype, molecular testing at RL IV or V is necessary to differentiate them from GBM, IDH-wt (in older adults), or pediatric-type diffuse low- or high-grade gliomas (in younger adults), because this determines treatment planning (Figures 1–4 legends, footnotes Tables S1–S4). Diagnosis of molecular GBM, IDH-wt relies on the demonstration of one or more of the following: *TERT* promoter mutation, *EGFR* amplification, and +7/−10 copy number changes [23–25]. However, caution is needed with IDH-wildtype grade 2 gliomas

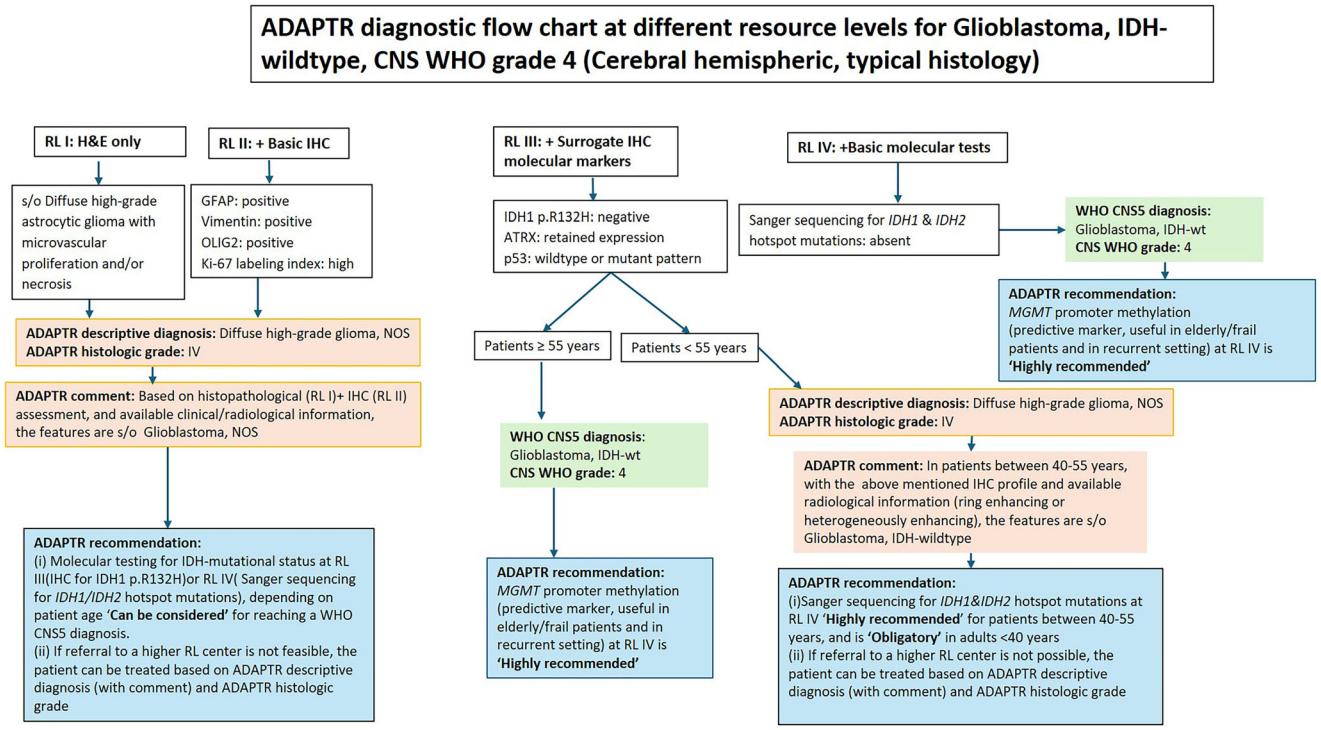

FIGURE 5 ADAPTR diagnostic flow chart for GBM, IDH-wt, CNS WHO grade 4 at resource levels- RL I to RL IV. WHO CNS5 diagnosis can be established at RL III using IHC surrogate molecular markers or at RL IV through molecular testing. If WHO CNS5 diagnosis cannot be determined, ADAPTR descriptive diagnosis and ADAPTR histologic grading are provided. ADAPTR recommendations—'Can be considered', 'Highly recommended', and 'Obligatory'—are based on histopathological and IHC findings at various resource levels. p53 mutant expression pattern is typically characterized by strong immunopositivity of >40% of tumor cell nuclei; however, truncating TP53 mutations can result in complete lack of p53 staining of tumor cell nuclei. p53 wildtype pattern is characterized by the tumor cell nuclei being typically negative for p53 with occasionally scattered variably positive nuclei. For adults under 40, Sanger sequencing for *IDH* mutations is 'obligatory' if IDH1p.R132H is negative, to identify IDH-wildtype tumors and rule out pediatric-type high-grade gliomas. If midline structures are involved, histone H3 mutation should be excluded by checking at least H3 p.K27me3 expression. GBM, IDH-wt: Glioblastoma, IDH-wildtype; *MGMT*: O6 methylguanine DNA methyl transferase.

showing only a *TERT* promoter mutation, as these are often associated with longer survival [66], and some may be reclassified as diffuse pediatric-type low-grade glioma. *TERT* promoter mutations also appear in other tumors, such as pleomorphic xanthoastrocytoma, subependymoma, pediatric-type high-grade glioma, and diffuse gliomas that are *FGFR3::TACC3* fusion positive, thereby complicating diagnosis, especially in small biopsies. Additionally, in patients under 40 years, *EGFR* amplification or +7/−10 copy number changes are not specific, caused by overlaps with pediatric-type high-grade gliomas, H3-wildtype and IDH-wildtype. DNA methylation profiling at RL V is usually required in this age group for definitive diagnosis [67].

As depicted in Tables S1–S5 and Figures 1–5, based on the situation, the ADAPTR descriptive diagnosis often remains as an NOS diagnosis at different RLs because the necessary molecular tests were not performed, thereby indicating the necessity for further workup of the case. Simultaneously, ADAPTR's 'Histology-oriented Integrated Diagnosis' format presents the pathologist's findings of the case. This, coupled with the accompanying comments, can aid the clinician in determining the expected prognosis and most appropriate therapeutic management for patients with ADGs based on the available resources.

3.3 | Diagnostic flow charts

ADAPTR diagnostic flow charts are created for each tumor type at different RLs to ensure clarity. Diagnostic flow charts for A, IDH-mut, CNS WHO grades 2, 3, and 4 are shown in Figures 1–3, respectively. Charts for O, IDH-mut & 1p/19q-codel, CNS WHO grades 2 and 3 are depicted in Figure 4, and a chart for GBM, IDH-wt, CNS WHO grade 4 is shown in Figure 5. These diagnostic flow charts outline scenarios at different RLs where WHO CNS5 diagnosis is possible and circumstances where WHO CNS5 diagnosis is not attainable. In the latter, ADAPTR descriptive diagnosis with comments and ADAPTR histologic grade are provided along with suitable recommendations. The ADAPTR recommendations for referring molecular testing to a higher RL are categorized as 'can be considered', 'highly recommended', and 'obligatory' in the diagnostic flow charts, based on available resources. When resource limitations occur that preclude reaching a WHO CNS5 diagnosis, ADAPTR

advises patient management using ADAPTR descriptive diagnosis and histologic grade.

4 | MOLECULAR DIAGNOSTICS AND TREATMENT OF ADGs: IMPLICATIONS IN LICs AND LMICs

The role of molecular markers in clinical care is expanding, with new treatments emerging, especially in high-income countries (HICs). Advances such as FDA-approved IDH inhibitors for certain gliomas are reflected in guidelines [68, 69], but remain largely inaccessible in LICs and LMICs caused by limitations in availability and financial constraints. In fact, in many such countries, access to standard treatments like radiation and chemotherapy may itself be unaffordable or unavailable. Thus, RL I and II centres should prioritize basic oncology care over advanced diagnostics and refer patients to at least an RL III centre for more comprehensive testing when possible. As resources improve, molecular diagnostics can be gradually integrated, supporting ongoing neuro-oncology development in LICs and LMICs.

5 | CONCLUSION

Expert neuropathologists from the Asian Oceanian region have developed ADAPTR recommendations to adapt WHO CNS5 guidelines for diagnosing ADGs routinely at various RLs. These recommendations are designed to assist multidisciplinary teams globally, particularly in resource-restrained settings, in developing the most accurate diagnoses and optimal management strategies for patients with ADGs.

AUTHOR CONTRIBUTIONS

V.S. contributed to the study concept, design, and manuscript writing. C.S. contributed equally to the study design and manuscript editing. D.N.L and P.W. extensively revised the guidelines and edited the manuscript. T.K. provided insights and assisted in editing. S.R. helped with editing and bibliography. All authors contributed to AOSNP guidelines and approved the final manuscript.

ACKNOWLEDGMENTS

We thank Prof. David N. Louis and Prof. Pieter Wesseling for sparing their valuable time and for their advice, guidance, and significant contributions to this study. We thank Prof. David N. Louis for coining the acronym 'ADAPTR'. We also appreciate the ADAPTR Advisory Board members and the executive members of the International Society of Neuropathology (ISN) for approving this manuscript. Prof. Rakesh Jalali, Neuro-oncology Advisor for ADAPTR, is acknowledged for providing insights on therapy implications. C.S. thanks the Indian National Science Academy (INSA) for the Distinguished Professor position.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Santosh V, Sarkar C, Rao S, Ng H-K, Shibahara J, Al-Hussaini M, et al. AOSNP-ADAPTR resource level-based recommendations on practical diagnostic strategies for WHO CNS5 adult-type diffuse gliomas. Brain Pathology. 2025. e70046. https://doi.org/10.1111/bpa.70046