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COMMENTARY

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Announcing the Asian Oceanian Society of Neuropathology guidelines for Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Restrained Regions (AOSNP-ADAPTR)

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In 2023, molecular evaluation contributes significantly to classifying many central nervous system (CNS) tumors and offers prognostic and predictive information [1]. Following the WHO 2016 [2], the 2021 WHO classification (WHO CNS5) further advanced the integration of molecular diagnostics into CNS tumor diagnosis and grading [3]. Methylation profiling is now also recognized as a powerful molecular diagnostic technique for CNS tumors, which can aid in diagnosing challenging cases and defining some tumor types and subtypes/subgroups [4].

The increasing impact of molecular approaches in diagnosing CNS tumors has created significant practical challenges in implementing WHO CNS5, especially in low- and middle-income countries, including those in the Asian Oceanian region. This is mainly attributable to the restricted availability of molecular testing facilities in these resource-restrained regions, owing to the high cost combined with a lack of technological infrastructure facilities and skilled technical human resources. Another challenge in implementing the current WHO classification is the shortage of trained neuropathologists.

Further, the relevance and real added value of several molecular markers in clinical management are unclear at the current stage. Thus, the available therapeutic options for many CNS tumors still remain limited, and very few molecular advances have translated to therapeutic molecular targets in CNS tumors, such as BRAF inhibitors for *BRAF* mutations and TRK inhibitors for *NTRK* fusions [5]. Adults diagnosed with high-grade gliomas, the most common primary CNS tumor, typically undergo maximal surgical tumor removal, followed by radiotherapy and chemotherapy as the standard treatment [6]. The recently announced results of a phase III study of vorasidenib in IDH-mutant grade 2 gliomas [7] give hope that more targeted therapies will emerge in the future.

The above challenges have mandated the generation of practical and economical guidelines for diagnosing CNS

tumors in resource-restrained regions. Pathologists in various countries have proposed practical adaptations of the previous WHO 2016 classification to address this issue in the past [8, 9]. The present initiative termed ADAPTR (pronounced Adapter), spearheaded by the Asian Oceanian Society of Neuropathology (AOSNP), aims to adapt the current WHO CNS5 classification to make it suitable for routine diagnostic practices in resource-limited settings, with a specific focus on the Asian-Oceanian region. The ultimate objective is to benefit all patients with brain tumors worldwide with varying resource restraints. ADAPTR does not seek to alter the definition of tumor types or diagnostic criteria outlined in the WHO CNS5. Instead, its purpose is to offer practical information that can be effectively utilized in patient care and treatment within the available diagnostic resources of each medical setting. This cannot completely align with the WHO CNS5 criteria in all cases but will be clinically relevant and practically applicable, focusing primarily on benefiting patients (Table 1).

This commentary outlines the broad principles and framework of the ADAPTR guidelines. Separate guidelines on critical tumor categories written by each working committee of ADAPTR, including adult-type diffuse gliomas, pediatric-type diffuse low- and high-grade gliomas, circumscribed astrocytic gliomas, ependymomas, and embryonal tumors, are being developed and will be published in due course following this announcement, with the support of the clinical and international advisory board.

The implementation of different diagnostic testing methods, including molecular testing, and the prioritization of testing infrastructure are influenced by several interconnected factors. These include the capability of diagnostic infrastructure, technical expertise, cost considerations, and understanding the clinical significance of specific tests in influencing management decisions. Given the diverse range of local resource availability, a hierarchy of resource levels has been defined, with recommendations tailored to each level. This allows ADAPTR to be utilized in various settings in resource-limited countries.

Resource level I (RL I)—At this level, the available resources for diagnostic testing include conventional histology techniques and some special stains (e.g., reticulin, Periodic Acid-Schiff).

Resource level II (RL II)—This level encompasses the use of standard immunohistochemical (IHC) markers such as GFAP, synaptophysin, vimentin, EMA, OLIG2, CD34, and Ki-67/MIB-1. Standard histologic and immunohistochemical techniques are widely available in most healthcare institutions.

Resource level III (RL III)—Advanced immunohistochemical (IHC) markers are available at this level which are specific or surrogate markers for key molecular events, such as IDH1 p.R132H, ATRX, p53, BRAF VE1, EZHIP, H3K27me3, H3K27M, L1CAM, NFkB, YAP1, INI-1, BRG1, Lin28A, pHH3, and MTAP.

Resource level IV (RL IV)—This level includes basic molecular testing methods such as FISH (Fluorescence In-Situ Hybridization) for chromosomal alterations and single gene sequencing for specific mutations, such as 1p/19q, EGFR, MYC, MYCN, PTEN, and CDKN2A/2B. Test for TERT promoter mutation and MGMT promoter methylation status can be included. These methods may allow the appropriate classification of many CNS tumors to WHO CNS5 standards.

Resource level V (RL V)—This level represents fully integrated advanced molecular diagnostics, including targeted gene sequencing panels, whole exome sequencing, and DNA methylation arrays. These advanced molecular techniques are typically performed in highly specialized centers. Although they come with higher cost implications, they provide the most cost-efficient approach regarding the amount of information obtained per unit cost. Centralizing Resource level V molecular testing in specialized labs can strategically optimize limited resources by establishing service agreements between lower-resource and higher-resource laboratories.

At RL I and II, where diagnostic capabilities are limited, the guidelines allow for a general diagnosis, such as "diffuse glioma," either histologically high-grade or low-grade. This provides a broad understanding of the tumor type based on histopathologic characteristics supplemented with basic IHC markers. At RL III, using mutation-specific antibodies, a diagnosis of "IDH-mutant astrocytoma" can be made without WHO CNS5 grading but with an assigned histological grade. At RL IV, by detecting CDKN2A/B copy number status, a diagnosis of "IDH-mutant astrocytoma" with WHO CNS5 grade can be made, incorporating molecular and histologic information. Finally, at RL V, with advanced molecular diagnostics such as next-generation sequencing (NGS) and DNA methylation array, nearly all WHO CNS5 diagnoses can be accurately made. By structuring the guidelines to cater to the different resource levels, we aim to ensure that clinically appropriate diagnoses are achievable regardless of the available diagnostic technology in each region.

In resource-limited settings, the histopathology-oriented approach for accurate tumor diagnosis is fundamental. To facilitate this approach, we have recommended an "integrated resource stratified histopathology-oriented diagnosis" in a layered format at each resource level. The examples of parameters included in this layered format are shown in Table 1. By integrating these parameters into the diagnostic process, we aim to provide a comprehensive and practical approach that can be implemented in resource-limited settings.

Radiological information plays an important role in AOSNP-ADAPTR guidelines. Location and imaging features can help certain tumors, such as distinguishing subgroups 3 and 4 of Non-WNT/Non-SHH medulloblastoma, and location is essential information for the classification of ependymoma; supratentorial, posterior fossa, and spinal. The use of advanced MRI sequences has also

TABLE 1 Example of adult glioma at resource level III—advanced immunohistochemistry level.

Age of the patient	35 years
Tumor location*	Frontal lobe
Imaging features*	A non-enhancing mass with an indistinctive border without a T2-FLAIR mismatch sign
Histopathological features	Moderately cellular, well-differentiated classic oligodendroglioma with nodularity without anaplasia; mitosis <6/10HPFs, no microvascular proliferation, nor necrosis
Histologic grade	II
Histopathological diagnosis	Oligodendroglioma
Immunohistochemistry (basic diagnostic markers)	Positive for Olig2/HIP1R and negative for vimentin; Ki-67 labeling index <10%
Immunohistochemistry (surrogate molecular markers)	IDH1 p.R132H and -positive, H3K27 me3-lost ATRX-retain, p53-negative
Molecular information	Not available except for IDH1-mutation
WHO CNS 5 diagnosis	Diffuse glioma, NOS
CNS WHO grade	Compatible with WHO CNS grade 2
AOSNP-ADAPTR conclusion: Diffuse glioma, NOS, compatible with oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2, cerebral hemisphere	
AOSNP-ADAPTR recommendations for resource-restricted settings: (i) AOSNP- ADAPTR conclusion is based on histopathological and immunohistochemical features (basic and surrogate molecular markers) in conjunction with the patient's age and radiological findings. (The tumor location* and the imaging features* are quoted from imaging reports.) (ii) For confirmation of the WHO CNS5 diagnosis and molecular grading, molecular workup, particularly for 1p/19q codeletion, should be carried out at a center of higher resource level. (iii) However, based on the AOSNP-ADAPTR conclusion, the patient can be treated as oligodendroglioma in a resource-restricted setting.	

improved the accuracy of diagnosis. In centers where molecular markers are unavailable, imaging can be an important correlate to histopathology diagnoses. Ordinary CT and MRI are affordable and feasible in the most resource-restricted area. For example, a tumor located in the frontal lobe exhibiting calcification, a vague margin, and heterogeneous intensities on MRI without T2-FLAIR mismatch strongly suggests oligodendroglioma [10]. In such cases, if the classical histology of oligodendroglioma without anaplastic features is observed, along with positive IDH1 p.R132H and retained ATRX IHC, it would be sufficient to make the AOSNP-ADAPTR conclusion of oligodendroglioma and assign a histological grade 2 (Table 1). However, if the tumor has a discrete margin and uniform intensity on MRI, the same histology findings would not be sufficient to diagnose oligodendroglioma. In such cases, assessing 1p/19q codeletion is recommended to confirm the diagnosis. Similarly, the T2-FLAIR mismatch sign, characteristic of IDH-mutant astrocytomas, can also provide valuable information alongside histology and IHC. Imaging information is derived from radiological reports, and where possible, close communication between pathologists and radiologists will enhance the value of this information in contributing to the AOSNP-ADAPTR conclusion. As shown in Table 1, the AOSNP-ADAPTR conclusion and recommendations are clearly distinguished from the WHO CNS5 grading and diagnosis. We consistently advocate for conducting relevant molecular testing to attain a formal WHO diagnosis. The final responsibility to use this information relies on clinicians, identical to the traditional histopathological diagnosis.

The AOSNP-ADAPTR guidelines also provide a comprehensive list of IHC markers for each histological tumor type, including mandatory and optional markers. Literature reviews supporting the use of surrogate IHC markers instead of molecular techniques are provided as evidence for the recommendations. Hopefully, these lists may also aid in obtaining reimbursements for tests and securing funds for pathology departments.

Diagnostic flowcharts are also included in the AOSNP-ADAPTR guidelines to provide stepwise algorithms for diagnosis, which is particularly useful in resource-limited centers and for general pathologists. The flowcharts are based on simple histopathology and immunohistochemistry approaches, with FISH and single gene sequencing (RL IV) being optional.

While the primary goal of these guidelines is to achieve an appropriate diagnosis to guide patient care, the initiative holds significance for other reasons, such as epidemiological studies and funding considerations. It also serves as an educational effort, particularly for general pathologists. Implementing these guidelines requires effective communication between neuropathologists and oncologists in each institution, with regular tumor board meetings playing a vital role.

AUTHOR CONTRIBUTIONS

All the authors contributed equally and approved the final version of the manuscript.

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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