Precision diagnosis and therapy for pediatric central nervous system tumors: consensus from the Brazilian Society of Pediatric Oncology (SOBOPE)

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Summary

Precision medicine has reshaped the classification and management of pediatric central nervous system tumors, enabling more accurate diagnoses and targeted therapies. However, access to molecular diagnostics and precision treatments remains uneven in many low- and middle-income countries, including Brazil. To address this gap, the Brazilian Society of Pediatric Oncology (SOBOPE) convened a national expert panel to develop consensus recommendations adapted to the Brazilian healthcare context. Using a structured literature overview and a modified Delphi process involving pediatric oncologists, neuropathologists, and laboratory medicine specialists, the panel proposed a tiered molecular testing strategy prioritizing essential and actionable biomarkers. Recommendations were tailored to both public and private healthcare settings and aligned with therapeutic guidance when targeted options are feasible. This consensus provides a practical framework to standardize molecular testing, support clinical decision-making, and promote equitable implementation of precision medicine in pediatric neuro-oncology in Brazil.

Keywords: Pediatric neuro-oncology; Precision medicine; Targeted therapy; Consensus

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Introduction

Central nervous system (CNS) tumors are the most prevalent solid tumors in children and adolescents, comprising 20% of childhood cancers worldwide.[1] Current multimodal therapy depends on histopathological diagnosis, tumor molecular characteristics, disease stage, and the child's age.[2] Advances in tumor biology knowledge have led to the identification of molecular markers that are significant for diagnosis, risk stratification, and targeted therapy. These markers have the potential to impact clinical practice by enabling more effective and potentially less toxic treatments.

Molecular classification is now considered standard practice in pediatric CNS tumor diagnosis and risk stratification. In the fifth edition of the World Health Organization (WHO) Classification of Tumors of the CNS (WHO CNS5)[3] genetics and epigenetics were embedded into disease definitions. However, molecular testing is often a challenge, especially in low-middle income countries (LMICs).

In Brazil, most tertiary pediatric oncology centers are hospital-based and heterogeneous in terms of available resources, with marked regional disparities and differences between public and private healthcare coverage. Many centers lack access to molecular diagnostics and targeted therapies. As part of an initiative led by the Brazilian Committee of Precision Medicine in Pediatric Oncology (BC-PMPO) of the Brazilian Society of Pediatric Oncology (SOBOPE), this study presents a national consensus to guide professionals in the incorporation and prioritization of molecular biomarkers and targeted therapy in clinical practice.

Methods

The study comprised two main phases: an initial evidence overview followed by subsequent modified Delphi rounds to generate consensus.

Evidence sources, search strategy and selection criteria

Preliminary recommendations were informed by two complementary evidence sources. First, the Memorial Sloan Kettering Cancer Center's Precision Oncology Knowledge Base (OncoKB)[4,5] was used to support tissue-agnostic targeted therapy recommendations. Second, an overview of reviews was conducted to identify molecular biomarkers and targeted agents with potential clinical applicability in pediatric CNS tumors.

Literature search was intentionally designed to support clinical prioritization rather than to provide an exhaustive assessment of diagnostic or prognostic biomarkers. A PubMed search was performed using predefined strings combining pediatric CNS tumor entities and molecular targeted therapy, restricted to review articles ("Pediatric AND Glioma AND Molecular Targeted Therapy AND Review"; "Pediatric AND Ependymoma AND Molecular Targeted Therapy AND Review"; "Pediatric AND Medulloblastoma AND Molecular Targeted Therapy AND Review"; "Pediatric AND Brain Neoplasms AND Molecular Targeted Therapy AND Review"). The search strategy included studies published up to October 31, 2024. A five-year publication window was selected to prioritize contemporary evidence syntheses and avoid the redundant inclusion of older secondary literature. Earlier reviews were referenced to prevent omission of foundational evidence and to provide appropriate historical and conceptual context regarding the evolution of molecular biomarkers and targeted therapies. Study selection was performed independently by two reviewers using Rayyan®,[6] with disagreements resolved by discussion and consensus. The reporting of this overview was aligned with selected PRISMA-ScR items.[7] Details are provided in the Supplementary Material, Appendix 1.

Data were extracted using a predefined standardized form capturing publication details, tumor histologies, molecular biomarkers, targeted therapies, and reported therapeutic and prognostic impact. Extraction was performed independently by two reviewers, with discrepancies resolved by consensus and third-reviewer adjudication. The synthesized data informed preliminary recommendations, which were subsequently refined through a modified Delphi process.

Modified Delphi rounds

Recommendations were evaluated through three iterative modified Delphi rounds. Experts in pediatric neuro-oncology, genetics and laboratory medicine were invited to participate, ensuring diverse geographic and professional representation. Invitations were sent through the BC-PMPO to 30 experts actively involved in this field across all five of Brazil's geographic regions (Southeast, South, Central-West, Northeast, and North). In total, 9 pediatric oncologists, 1 medical geneticist, and 5 pathology/laboratory medicine specialists accepted the invitation and participated in all rounds. The panel included experts from three of the five geographic regions (Southeast, South, and Central-West), with a higher concentration of participants from the Southeast, reflecting the regional distribution of pediatric oncology centers in the country. All 15 panelists evaluated biomarker-related recommendations, whereas therapeutic recommendations were evaluated only by physicians (n = 13), as the therapeutic section was not applicable to non-physician specialists. Details on Delphi outputs, patterns of disagreement, and revision rationales are provided in Supplementary Material, Appendix 1. Each round involved anonymous surveys where participants rated their level of agreement with each recommendation using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). Participants were also encouraged to provide qualitative feedback and additional recommendations based on their experience.

Consensus was predefined as at least 75% of participants rating a recommendation as "agree" or "strongly agree" (scores of 4 or 5). Recommendations not achieving consensus were revised based on participant feedback and re-evaluated in subsequent rounds or excluded. The process continued until consensus was achieved or no further revisions were feasible.

Results

Results of the literature overview

The initial search retrieved 208 publications; 119 remained after duplicate removal. Following manual inclusions, 75 reviews met the eligibility criteria and were used for data extraction. All included studies were compiled into a dedicated reference library to support panelist consultation throughout the consensus process (Supplementary Material, Appendix 2). Final recommendations were organized into tissue-agnostic Onco-KB based recommendations and histology-specific recommendations. The latter was organized in three panels, for each tumor category: (i) essential biomarker panel; (ii) expanded biomarker panel; (iii) therapeutic recommendations, and subjected to medical professional review during the consensus process.

Delphi panel results

The whole process of searches, preliminary recommendations elaboration and recommendation selection were schematically described in Fig. 1.

General principles

The first element evaluated concerned the general principles guiding the recommendations, all of which were approved with 100% consensus in the first round. Principle one stated that recommendations would be organized into tissue-agnostic and histology-specific categories for the following tumor types: low-grade gliomas, high-grade gliomas, midline gliomas, ependymomas, and medulloblastomas. Other CNS tumors were not included in this first consensus. Principle two stated that, for biomarkers, two parallel lines of recommendations would be provided, where applicable: (i) biomarkers considered essential for clinical management and (ii)

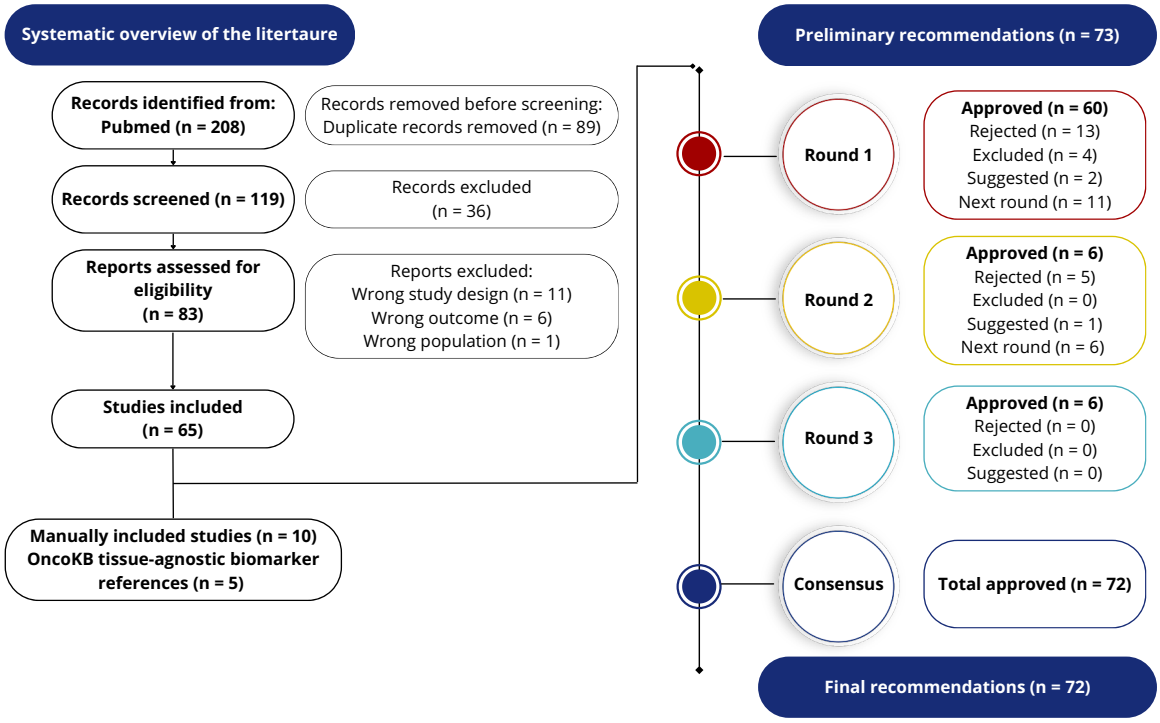

***Fig. 1:* Flow diagram of the study selection and recommendation process.** Reviews were identified through PubMed (n = 208), with duplicates removed (n = 89), resulting in 119 records screened. Of these, 83 underwent full-text eligibility assessment, and 65 studies were included from the database search. An additional 10 key references were manually included, yielding a total of 75 studies considered in the evidence overview. Five OncoKB tissue-agnostic biomarker sources (n = 5), defined as evidence entries supporting biomarker-driven therapies across tumor types, were additionally included to inform tissue-agnostic recommendations. Preliminary recommendations (n = 73) underwent three rounds of review. In Round one, 60 recommendations were approved, 13 rejected, four excluded, two new suggestions added, and 11 moved to the next round. Round two led to six approvals, five rejections, one suggestion, and six moved forward. Round three resulted in six additional approvals. Consensus was achieved, yielding a total of 72 final recommendations.

additional biomarkers that may complement diagnostic or therapeutic decision-making. Principle three stated that levels of clinical applicability would be assigned using a framework modeled after the OncoKB[4,5] levels of evidence, modified to reflect the Brazilian context and developed specifically for this work. This framework was adapted to align with the regulatory context of the Brazilian Health Regulatory Agency (ANVISA) and public drug access through the Brazilian Health System (SUS), and is described in Table 1.

Recommendations

Recommendations are presented along with their level of agreement achieved and their corresponding level of clinical applicability attributed by the researchers. A comprehensive summary of all recommended biomarkers is provided in Fig. 2.

Tissue-agnostic recommendations

Tissue-agnostic biomarkers (Table 2) were considered clinically relevant in the Brazilian context primarily in the setting of recurrent or refractory disease, where conventional treatments are no longer effective and the patient maintains a good performance status. Although tissue-agnostic targeted therapies have received FDA approval for alterations such as *NTRK* fusions, MSI-high, TMB-high, and *BRAF* V600E mutations, access to both molecular testing and targeted agents remains limited in Brazil. Furthermore, some agents such as pembrolizumab or BRAF inhibitors are available for specific tumor types but are not approved by ANVISA for tissue-agnostic indications. Larotrectinib received regulatory approval for NTRK fusion–positive tumors only recently, supported by emerging efficacy data, including a Brazilian pediatric series that contributed to the evidence base evaluated by regulatory authorities.[8]

For these reasons, performing tissue-agnostic testing upfront was not considered either feasible or clinically beneficial for most patients with brain tumors. Nevertheless, in specific histological contexts (refer to tissue-specific recommendations below) or in carefully selected refractory cases, such therapies may represent a viable treatment option when both molecular testing and drug access are available.

DNA methylation profiling was recommended by the group for cases with diagnostic uncertainty. Access to this methodology is expanding in Brazil. Current evidence indicates that methylation profiling has a significant impact on confirming or revising diagnoses, particularly when histopathology is inconclusive or the clinical course is atypical.[9]

Low-grade gliomas

Maximal safe surgical resection remains the cornerstone of treatment for low-grade gliomas (LGG).[10] However, precision medicine strategies can inform prognosis and therapeutic decision-making, especially in cases of progressive or recurrent disease.

Recommendations (Table 3) were divided into an essential biomarker panel and an additional biomarker panel. In the upfront setting, testing for *BRAF* V600E mutations and *BRAF* fusions was highlighted as the most important priority. *BRAF* represents the most frequently altered gene in pediatric LGGs, with

Therapeutic applicability

T1-BR: Therapy formally approved by ANVISA, established as standard of care in SUS and/or private guidelines, and supported by consolidated clinical recommendations.

T2-BR: Therapy supported by robust evidence, with approval from international regulatory agencies or endorsement in international guidelines, but without ANVISA approval or SUS incorporation.

T3-BR: Therapy supported by evidence from phase II studies or other promising clinical results.

T4-BR: Therapy supported only by limited data (e.g., case reports, preclinical or translational studies). Use is strictly experimental and not recommended outside of research settings.

R1/R2-BR: Markers that confer resistance to a given therapy.

R1-BR: Supported by consolidated evidence demonstrating resistance.

R2-BR: Supported by limited or emerging evidence of resistance.

Prognostic applicability

P1-BR: Strongly supported by high-quality evidence (e.g., large prospective cohorts or robust meta-analyses) and recognized as having a significant impact on clinical management.

P2-BR: Supported by robust evidence and endorsed in international guidelines; however, its clinical impact and accessibility remain limited.

P3-BR: Supported by preliminary or inconsistent data (e.g., small cohorts or retrospective series), without solid mention in guidelines, and largely based on anecdotal evidence.

P4-BR: Supported only by very limited evidence (e.g., preclinical models or isolated case reports).

Diagnostic applicability

D1-BR: Diagnostic marker strongly supported by high-quality evidence and required for classification under the 2021 WHO CNS5 criteria.

D2-BR: Diagnostic marker supported by robust evidence, relevant for disease diagnosis or for associated conditions, but not required for classification under the 2021 WHO CNS5 criteria.

D3-BR: Diagnostic marker supported by preliminary or moderate-quality evidence (e.g., small cohorts, retrospective studies), with promising utility but lacking consistent inclusion in diagnostic guidelines.

D4-BR: Diagnostic marker supported only by very limited evidence (e.g., case reports, preclinical or translational studies), without consensus or mention in diagnostic guidelines; use remains exploratory.

Table 1: **Framework for molecular biomarker applicability in pediatric CNS tumors adapted to the Brazilian regulatory and healthcare context.**

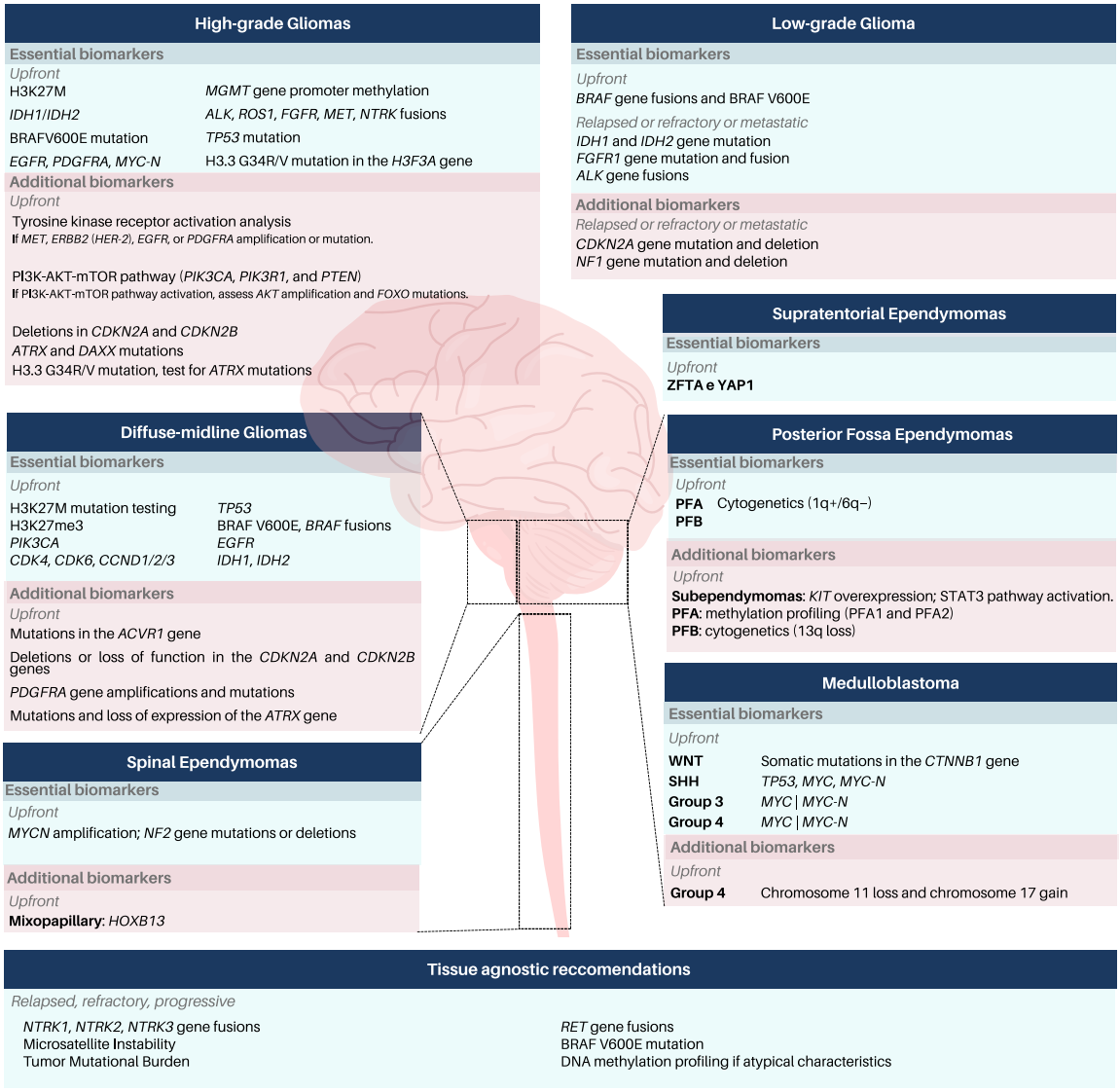

***Fig. 2:* Summary of essential and additional biomarkers recommended for molecular evaluation of pediatric central nervous system (CNS) tumors.** The figure synthesizes key biomarkers categorized by tumor type, including low-grade gliomas, high-grade gliomas, diffuse midline gliomas, ependymomas (supratentorial, posterior fossa, and spinal), and medulloblastomas, and stratified according to clinical context (e.g., upfront testing vs. relapsed/refractory/metastatic disease). Biomarkers are further classified as essential (those with direct diagnostic, prognostic, or therapeutic implications) or additional (markers with emerging or context-dependent clinical utility). Tissue-agnostic recommendations are also presented, highlighting alterations with potential therapeutic relevance across tumor types.

alterations present in up to 50% of cases. These alterations include single nucleotide variants, most commonly the *BRAF* V600 hotspot mutation found in roughly 15% of tumors, and *BRAF* fusions seen in approximately 35% of cases with various partner genes, most often *KIAA1549*.[11] In both contexts, these somatic events lead to constitutive activation of the RAS/MAPK pathway. However, LGGs with a *BRAF* fusion are generally more indolent, while tumors with *BRAF* V600E mutations present a higher risk of progression or recurrence.[12]

For subependymal giant cell astrocytoma (SEGA), it was also considered important to assess TSC1 and TSC2 mutations, even in the absence of clinical criteria for tuberous sclerosis complex (TSC), as somatic alterations in these genes may occur and activate the mTOR/PI3K pathway, which is amenable to mTOR inhibition.[13] Furthermore, investigation of *IDH1*, *IDH2*, *FGFR* mutations, and *ALK* fusions was considered essential in the management of refractory disease, where targeted therapies may represent a viable treatment option.[14,15]

Tissue agnostic recommendations
TA1: For central nervous system tumors–especially diffuse gliomas refractory to conventional treatment or relapsed, with no possibility of new therapies with curative potential, when the patient maintains good performance status–investigation of gene fusions in the *NTRK1*, *NTRK2* and *NTRK3* genes is recommended as part of the molecular evaluation. **Methods:** RNA-NGS (preferred); FISH or RT-PCR as alternative. **Level of Agreement:** 100%. **Level of Clinical Applicability:** T1-BR.
TA2: For central nervous system tumors refractory to conventional treatment or recurrent, with no possibility of new therapies with curative potential, when the patient maintains good performance status, perform microsatellite instability (MSI) testing as part of the molecular evaluation. **Methods:** PCR-based MSI testing (preferred); IHC for MMR proteins or NGS as alternatives. **Level of Agreement:** 85%. **Level of Clinical Applicability:** T2-BR.
TA3: For central nervous system tumors refractory to conventional treatment or recurrent, with no possibility of new therapies with curative potential, when the patient maintains good performance status, tumor mutational burden (TMB) assessment is recommended as part of the molecular evaluation. **Method:** NGS-based TMB assessment. **Level of Agreement:** 93%. **Level of Clinical Applicability:** T2-BR.
TA4: For central nervous system tumors refractory to conventional treatment or recurrent, with no possibility of new therapies with curative potential, when the patient maintains good performance status, *RET* gene fusions research is recommended as part of the molecular evaluation. **Methods:** RNA-NGS (preferred); FISH or RT-PCR as alternatives. **Level of Agreement:** 93%. **Level of Clinical Applicability:** T2-BR.
TA5: For central nervous system tumors refractory to conventional treatment, or recurrent, with no possibility of new therapies with curative potential, when the patient maintains good performance status, *BRAF* V600E mutation testing should be performed. **Methods:** NGS or PCR. **Level of Agreement:** 100%. **Level of Clinical Applicability:** T2-BR.
TA6: For central nervous system tumors with atypical histological, epidemiological, radiological, or genomic characteristics, DNA methylation profiling is recommended to improve diagnostic accuracy **Method:** DNA methylation array. **Level of Agreement:** 80%. **Level of Clinical Applicability:** D2-BR.

Table 2: **Tissue agnostic recommendations.**

The additional biomarker panel for LGGs included *NF1* mutations,[16] which may correlate with a potential response to MEK inhibitors, and *CDKN2A*[17] deletions, which are associated with a poorer prognosis.[18,19] Patients with NF1 have a predisposition to brain tumors, with gliomas occurring in approximately 15–20% of individuals.[20] Pathogenic and likely pathogenic germline *NF1* mutations lead to constitutive activation of the RAS/MAPK pathway, creating an opportunity for targeting glioma. Different MEK inhibitors were tested in the setting of LGGs in patients with NF1, with overall good responses.[21] Already completed Phases 1/2 trials include selumetinib[12] and binimetinib.[22] A phase II study with trametinib for patients with refractory brain tumors and activation of the MAPK/ERK pathway, including a group of patients with NF1, is ongoing (NCT03363217). Also, a clinical Phase 1/2 study of oral mirdametinib plus endovenous vinblastine for newly diagnosed/previously untreated pediatric LGG with activation of MAPK, which will include patients with NF1, is expected to start recruitment (NCT06666348). Due to the general favorable results for this approach in treating LGGs in patients with NF1, a Phase III study randomizing standard chemotherapy treatment (carboplatin/vincristine) and selumetinib is ongoing (NCT03871257). Given the current uncertainty regarding their direct clinical benefit, the inclusion of these markers in an additional panel may support future research efforts and facilitate patient enrollment in clinical trials. Because the association between low-grade gliomas and several RASopathies is well documented and may affect clinical outcomes, genetic testing for these conditions and appropriate follow-up and counseling are recommended according to clinical judgment.

Therapeutic recommendations were also formulated, with *BRAF* mutations and fusions representing the most relevant actionable targets. Although current literature supports the use of dabrafenib and trametinib as upfront therapy for inoperable, residual, or refractory LGGs harboring *BRAF* V600 mutations, access to these agents remains limited in LMICs. Nevertheless, their use should be considered in such scenarios, based on evidence from a randomized phase II trial demonstrating superior response rates, longer progression-free survival, and a more favorable toxicity profile compared with conventional chemotherapy.[23] Monotherapy targeting the BRAF V600 mutation with vemurafenib or dabrafenib alone may be considered depending on local availability and access to medication.[24]

Importantly, the panel recommended against the use of type I *BRAF* inhibitors (such as dabrafenib or vemurafenib) when a *KIAA1549-BRAF* fusion is

Low-grade gliomas

Essential biomarkers

Upfront

LGG1 | For low-grade gliomas, regardless of histological subtype, *BRAF* gene fusions and *BRAF* V600E mutation testing should be performed as part of the molecular evaluation.

Methods: RNA-NGS or FISH for BRAF fusions; PCR or NGS for BRAF V600E.

Level of Agreement: 100%.

Level of Clinical Applicability: D1-BR.

LGG2 | For subependymal giant cell astrocytomas, test for mutations in the *TSC1* and *TSC2* genes, even in the absence of diagnostic criteria for tuberous sclerosis.

Method: NGS.

Level of Agreement: 80%.

Level of Clinical Applicability: D2-BR.

Relapsed or refractory or metastatic tumors

LGG3 | For low-grade gliomas refractory to conventional treatment or metastatic, regardless of histological subtype, perform *IDH1* and *IDH2* gene mutation testing.

Methods: PCR or NGS.

Level of Agreement: 87%

Level of Clinical Applicability: D2-BR.

LGG4 | For low-grade gliomas refractory to conventional treatment or metastatic, regardless of histological subtype, perform *FGFR1* gene mutation and fusion testing as part of the molecular evaluation.

Methods: RNA-NGS or FISH for *FGFR1* fusions; PCR or NGS for *FGFR1* mutations.

Level of Agreement: 93%

Level of Clinical Applicability: D2-BR.

LGG5 | For low-grade gliomas refractory to conventional treatment, especially in infants, regardless of histological subtype, consider testing for *ALK* gene fusions as part of the molecular evaluation.

Methods: RNA-NGS (preferred).

Level of Agreement: 84%.

Level of Clinical Applicability: D2-BR.

Additional biomarkers

Relapsed or refractory or metastatic tumors

LGG6 | For low-grade gliomas refractory to conventional treatment or metastatic, regardless of histological subtype, perform *CDKN2A* gene mutation and deletion testing as part of the molecular evaluation.

Methods: NGS, MLPA or FISH.

Level of Agreement: 87%

Level of Clinical Applicability: P3-BR.

LGG7 | For low-grade gliomas refractory to conventional treatment or metastatic, regardless of histological subtype, perform *NF1* gene mutation and deletion testing.

Methods: NGS or MLPA.

Level of Agreement: 80%.

Level of Clinical Applicability: P3-BR.

Therapeutic recommendations

LGG8 | For low-grade gliomas with *BRAF* V600 mutations, inoperable or with residual lesion, or refractory/relapsed, consider combination therapy with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).

Level of Agreement: 85%.

Level of Clinical Applicability: T2-BR.

LGG9 | For low-grade gliomas with *KIAA1549-BRAF* fusion or wild-type *BRAF*, DO NOT use type 1 BRAF inhibitors (such as dabrafenib or vemurafenib).

Level of Agreement: 85%.

Level of Clinical Applicability: R1-BR.

LGG10 | For patients with low-grade gliomas that present with the *KIAA1549-BRAF* fusion, consider using tovorafenib as a therapeutic option.

Level of Agreement: 85%.

Level of Clinical Applicability: T3-BR.

LGG11 | For low-grade gliomas with *ALK* gene fusion, consider treatment with the ALK inhibitor alectinib.

Level of Agreement: 77%.

Level of Clinical Applicability: T3-BR.

LGG12 | For low-grade gliomas with *TSC1* or *TSC2* mutations, especially inoperable or progressive Subependymal Giant Cell Astrocytomas, consider treatment with mTOR inhibitors.

Level of Agreement: 80%.

Level of Clinical Applicability: T1-BR.

(Table 3 continues on next page)

Low-grade gliomas

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LGG13 | For symptomatic, progressive optic pathway gliomas refractory to standard treatment, consider using bevacizumab as a therapeutic option.

Level of Agreement: 80%.

Level of Clinical Applicability: T3-BR.

LGG14 | For recurrent or conventional treatment-refractory low-grade gliomas with PI3K-AKT-mTOR pathway alterations, the use of mTOR inhibitors, such as everolimus, is recommended.

Level of Agreement: 92%.

Level of Clinical Applicability: T3-BR.

High-grade gliomas

Essential biomarkers

Upfront

HGG1 | For high-grade gliomas, H3K27M mutation screening is recommended, with evaluation of the H3F3A, HIST1H3B, and HIST1H3C genes.

Methods: PCR or NGS; IHC for H3K27M as a screening alternative.

Level of Agreement: 80%.

Level of Clinical Applicability: D1-BR.

HGG2 | For high-grade gliomas, especially in adolescents and young adults, test for IDH1/IDH2 mutation.

Methods: PCR or NGS (preferred).

Level of Agreement: 100%.

Level of Clinical Applicability: D1-BR.

HGG3 | For high-grade gliomas, regardless of histology, test for *BRAF* V600E mutation.

Methods: PCR or NGS.

Level of Agreement: 100%.

Level of Clinical Applicability: P1-BR.

HGG4 | For high-grade gliomas, testing for mutations in the *EGFR*, *PDGFRA*, and *MYC-N* genes, including copy number variation (CNV) analysis, is recommended.

Methods: NGS; MLPA or FISH for CNV analysis as alternatives.

Level of Agreement: 93%.

Level of Clinical Applicability: P2-BR.

HGG5 | For pediatric high-grade gliomas, consider testing for *MGMT* gene promoter methylation.

Methods: MSP (preferred); MLPA or methylation array as alternatives.

Level of Agreement: 100%.

Level of Clinical Applicability: P1-BR.

HGG6 | For high-grade gliomas, especially hemispheric and in infants, consider testing for fusions in *ALK*, *ROS1*, *FGFR*, *MET*, and *NTRK* genes.

Methods: RNA-NGS (preferred); FISH or RT-PCR as alternatives.

Level of Agreement: 93%.

Level of Clinical Applicability: P2-BR.

HGG7 | For high-grade gliomas, test for mutations in the *TP53* gene.

Method: NGS.

Level of Agreement: 100%.

Level of Clinical Applicability: P1-BR.

HGG8 | For pediatric high-grade gliomas, especially hemispheric ones in adolescents and young adults, testing for the H3.3 G34 R/V mutation in the *H3F3A* gene is recommended.

Methods: PCR or NGS; IHC as a screening alternative.

Level of Agreement: 100%.

Level of Clinical Applicability: D1-BR.

HGG9 | For pediatric high-grade gliomas, especially in infants, *ALK* gene fusion testing is recommended.

Methods: RNA-NGS; FISH or RT-PCR as alternatives.

Level of Agreement: 100%.

Level of Clinical Applicability: P2-BR.

Additional biomarkers

Upfront

HGG10 | For high-grade gliomas with *MET*, *ERBB2* (*HER-2*), *EGFR*, or *PDGFRA* amplification or mutation, consider concomitant tyrosine kinase receptor activation analysis.

Method: NGS.

Level of Agreement: 78%.

Level of Clinical Applicability: P3-BR.

HGG11 | For high-grade gliomas, investigate mutations and deletions in genes of the PI3K-AKT-mTOR pathway, including *PIK3CA*, *PIK3R1*, and *PTEN*.

Method: NGS.

(Table 3 continues on next page)

High-grade gliomas

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Level of Agreement: 93%.
Level of Clinical Applicability: P3-BR.
HGG12 | For high-grade gliomas with PI3K-AKT-mTOR pathway activation, assess *AKT* amplification and *FOXO* mutations.
Method: NGS.
Level of Agreement: 78%.
Level of Clinical Applicability: P3-BR.
HGG13 | For high-grade non-brainstem gliomas, investigate deletions in *CDKN2A* and *CDKN2B*.
Method: NGS.
Level of Agreement: 93%.
Level of Clinical Applicability: P3-BR.
HGG14 | For high-grade gliomas, consider testing for *ATRX* and *DAXX* mutations.
Method: NGS.
Level of Agreement: 85%
Level of Clinical Applicability: P3-BR.
HGG15 | For pediatric high-grade gliomas with H3.3 G34 R/V mutation, test for *ATRX* mutations.
Method: NGS.
Level of Agreement: 78%.
Level of Clinical Applicability: P3-BR.

Therapeutic recommendations

HGG16 | For high-grade gliomas with *BRAF* V600E mutation, consider combination therapy with dabrafenib and trametinib.
Level of Agreement: 92%.
Level of Clinical Applicability: T2-BR.
HGG17 | For pediatric high-grade gliomas (pHGG) with *NTRK* fusions, consider the use of TRK inhibitors, such as larotrectinib and entrectinib.
Level of Agreement: 92%.
Level of Clinical Applicability: T1-BR.
HGG18 | For pediatric high-grade gliomas with *MET* amplification, consider MET inhibitors such as volitinib.
Level of Agreement: 77%.
Level of Clinical Applicability: T3-BR.
HGG19 | For high-grade gliomas with *ALK* gene alterations, consider the use of second-generation ALK inhibitors.
Level of Agreement: 85%.
Level of Clinical Applicability: T3-BR.
HGG20 | For refractory pediatric high-grade gliomas with mutations or amplifications in the *FGFR* gene, the use of FGFR inhibitors, such as erdafitinib or cabozantinib, should be considered with caution, due to the risk of adverse effects related to skeletal toxicity.
Level of Agreement: 92%.
Level of Clinical Applicability: T3-BR.

Diffuse-midline Gliomas

Essential biomarkers

Upfront

DMG1 | For diffuse midline gliomas, H3K27M mutation testing is recommended whenever a biopsy can be performed.
Methods: NGS or PCR; IHC for H3K27M as a screening alternative.
Level of Agreement: 100%.
Level of Clinical Applicability: D1-BR.
DMG2 | For diffuse midline gliomas, H3K27me3 histone methylation assessment is recommended whenever a biopsy can be performed.
Method: IHC.
Level of Agreement: 93%.
Level of Clinical Applicability: D2-BR.
DMG3 | For diffuse midline gliomas, consider testing for *PIK3CA* mutations.
Method: NGS.
Level of Agreement: 85%.
Level of Clinical Applicability: P2-BR.
DMG4 | For diffuse midline gliomas, test for *CDK4*, *CDK6*, and *CCND1/2/3* amplifications.
Method: NGS.
Level of Agreement: 78%.
Level of Clinical Applicability: P2-BR.
DMG5 | For diffuse midline gliomas, test for mutations in the *TP53* gene.
Method: NGS.

(Table 3 continues on next page)

Diffuse-midline Gliomas

(Continued from previous page)

Level of Agreement: 85%.

Level of Clinical Applicability: P1-BR.

DMG6 | For diffuse midline gliomas, consider testing for mutations in the *BRAF* gene, especially *BRAF* V600E and *BRAF* fusions.

Methods: RNA-NGS or FISH for *BRAF* fusions; PCR or NGS for *BRAF* V600E.

Level of Agreement: 86%.

Level of Clinical Applicability: P2-BR.

DMG7 | For pediatric high-grade gliomas and diffuse midline gliomas, consider testing for mutations, amplifications, and truncated variants in the *EGFR* gene.

Method: NGS.

Level of Agreement: 86%.

Level of Clinical Applicability: P2-BR.

DMG8 | For diffuse midline gliomas (DMG), consider testing for mutations in the *IDH1* and *IDH2* genes as a prognostic biomarker and predictor of favorable therapeutic response.

Methods: NGS or PCR.

Level of Agreement: 93%.

Level of Clinical Applicability: P2-BR.

Additional biomarkers

Upfront

DMG9 | For diffuse midline gliomas, especially in children, consider testing for mutations in the *ACVR1* gene.

Method: NGS.

Level of Agreement: 78%.

Level of Clinical Applicability: P3-BR.

DMG10 | For diffuse midline gliomas, testing for deletions or loss of function in the *CDKN2A* and *CDKN2B* genes is recommended.

Method: NGS.

Level of Agreement: 92%.

Level of Clinical Applicability: P3-BR.

DMG11 | For diffuse midline gliomas, consider testing for *PDGFRA* gene amplifications and mutations.

Method: NGS.

Level of Agreement: 85%.

Level of Clinical Applicability: P3-BR.

DMG12 | For diffuse midline gliomas, consider testing for mutations and loss of expression of the *ATRX* gene.

Method: NGS.

Level of Agreement: 78%.

Level of Clinical Applicability: P3-BR.

Therapeutic recommendations

No established targeted therapies; biomarkers primarily support classification, prognosis, and trial eligibility.

Ependymomas

Essential biomarkers

Upfront

EP1 | For spinal ependymomas, *MYCN* gene amplification testing should be performed.

Methods: NGS or FISH.

Level of Agreement: 93%.

Level of Clinical Applicability: D1-BR.

EP2 | For spinal ependymomas, test for mutations or deletions in the *NF2* gene.

Method: NGS.

Level of Agreement: 93%.

Level of Clinical Applicability: D2-BR.

EP3 | For posterior fossa ependymomas, classify into group A (PFA) or group B (PFB) using methylation profiling or immunohistochemistry.

Methods: DNA methylation profiling (preferred); IHC for H3K27me3 as alternative.

Level of Agreement: 86%.

Level of Clinical Applicability: D1-BR.

EP4 | For PFA ependymomas, screen for 1q chromosome gain and 6q chromosome loss.

Methods: FISH or MLPA.

Level of Agreement: 87%.

Level of Clinical Applicability: P1-BR.

EP5 | For supratentorial ependymomas, classification between ZFTA or YAP1 should be performed using a gene fusion panel or methylation profiling.

(Table 3 continues on next page)

Ependymomas
(Continued from previous page)
Methods: RNA-NGS or DNA methylation profiling.
Level of Agreement: 93%.
Level of Clinical Applicability: D1-BR.
Additional biomarkers
Upfront
EP6 | For posterior fossa subependymomas, perform KIT overexpression testing.
Methods: IHC or RNA-NGS.
Level of Agreement: 78%.
Level of Clinical Applicability: P4-BR.
EP7 | For posterior fossa subependymomas, STAT3 pathway activation should be investigated.
Method: IHC.
Level of Agreement: 86%.
Level of Clinical Applicability: P4-BR.
EP8 | For posterior fossa ependymomas, subgroup PFA, consider subclassifying into PFA1 and PFA2 using methylation profiling.
Method: DNA methylation profiling.
Level of Agreement: 78%.
Level of Clinical Applicability: P3-BR.
EP9 | For posterior fossa ependymomas, subgroup PFB, evaluate cytogenetic aberrations, with emphasis on chromosome 13q loss.
Methods: FISH or MLPA.
Level of Agreement: 93%.
Level of Clinical Applicability: P4-BR.
EP10 | For myxopapillary ependymomas, assess *HOXB13* gene overexpression.
Methods: IHC, RNA-NGS or RT-qPCR.
Level of Agreement: 86%.
Level of Clinical Applicability: D4-BR.
Therapeutic recommendations
No established targeted therapies; biomarkers primarily support classification, prognosis, and trial eligibility.

Table 3: **Recommendations for glial tumors.**

detected, due to the risk of paradoxical MAPK pathway activation and subsequent tumor progression.[25] For these patients, tovorafenib may represent an alternative.[26] Alternatively, the use of MEK-inhibitor monotherapy is supported by case reports,[27] small series,[28–30] and at least one phase II study[31] in the context of LGG harboring a MAPK-activating *BRAF* fusion.

Additional targeted therapies were considered relevant in specific molecular contexts, including alectinib for *ALK*-fusion–positive LGGs,[32] mTOR inhibitors for tumors with *TSC1*, *TSC2*, or PI3K-AKT-mTOR pathway alterations,[33] and bevacizumab for progressive optic pathway gliomas unresponsive to standard chemotherapy.[34,35] These agents should be considered in these specific contexts if drug access is feasible.

High-grade gliomas

The H3K27M mutation remains the most important biomarker in pediatric high-grade gliomas (HGGs), as its presence is strongly associated with an unfavorable prognosis,[36] and is particularly important in midline tumors. Differently from adults, *IDH1* and *IDH2* mutations are rare in the pediatric population; however, their assessment is still recommended, especially in adolescents, as *IDH* mutation status has prognostic relevance, with *IDH* wild-type tumors generally associated with poorer outcomes, while *IDH*-mutant tumors may represent potential candidates for targeted therapy with IDH inhibitors such as vorasidenib.[15,37]

The *BRAF* V600E mutation is present in approximately 5–15% of pediatric HGGs and may confer sensitivity to BRAF and MEK inhibitors.[38] *EGFR*, *PDGFRA*, and *MYCN* amplifications or mutations are recurrent in both pediatric and adult HGGs, defining molecular subgroups associated with a worse prognosis.[39] Testing for *ALK*, *ROS1*, *MET*, and *NTRK* gene fusions is particularly relevant in infant hemispheric HGGs, as these alterations may inform targeted treatment strategies. Another biomarker with prognostic significance is *TP53*, mutated in approximately one-third of pediatric HGGs, conferring more aggressive tumor behavior.[39,40]

Within the essential biomarker panel, *MGMT* promoter methylation testing is also recommended, although it is less frequently observed in the pediatric population than in adults. This epigenetic modification reduces MGMT protein expression, a key enzyme involved in the repair of DNA damage induced by alkylating agents such as temozolomide. As a result, tumors harboring *MGMT* promoter methylation are

generally more sensitive to chemotherapy, and this information can be critical for therapeutic decision-making.[41]

An additional panel of biomarkers was also recommended, if access is feasible. Tyrosine kinase receptor activation analysis in the context of *MET*, *ERBB2* (*HER2*), *EGFR*, or *PDGFRA* amplification or mutation may indicate a more aggressive tumor phenotype. The presence of multiple concurrent alterations within this pathway can confer resistance to monotherapy, thereby potentially justifying a combined targeted therapeutic approach[42]; however, evidence supporting this strategy in the pediatric population remains limited. The detection of mutations or deletions in components of the PI3K–AKT–mTOR pathway, including *PIK3CA*, *PIK3R1*, and *PTEN*, could indicate a possible benefit from mTOR inhibitors.[43] In addition, alterations in *CDKN2A* and *CDKN2B*, as well as mutations in *ATRX* and *DAXX*, are associated with a worse prognosis.[39]

Therapeutic recommendations were also formulated for pediatric HGGs. Targeted therapies may be considered for tumors harboring *BRAF* V600E mutations (e.g., dabrafenib and trametinib), *NTRK* fusions (e.g., larotrectinib or entrectinib), or alterations in *MET* (e.g., volitinib), *ALK* (e.g., alectinib), or *FGFR* (e.g., *FGFR1-4* inhibitor–erdafitinib or MEK inhibitors–trametinib, selumetinib or mirdametinib) genes. Selection among different MEK inhibitors should consider local regulatory approvals as well as access to these agents. Given the dismal prognosis of these tumors, targeted approaches may even be considered upfront when drug access is feasible, either through clinical trials or compassionate-use programs. Since evidence in pediatrics is still limited, additional data are needed to better define the prevalence of these alterations in the pediatric population and to clarify the magnitude of benefit associated with biomarker testing and targeted therapy in this setting. Evidence supporting combined targeted therapies based on multiple actionable biomarkers in pediatric HGGs remains very limited and such approaches should be pursued only with extreme caution and preferably within clinical trials.

Diffuse-midline gliomas

Recommendations regarding biomarker testing in diffuse midline gliomas (DMGs) were limited to clinical scenarios in which a biopsy can be safely performed. Given the current absence of established targeted therapeutic strategies for this tumor type, the direct clinical applicability of extensive molecular panels remains low. In this context, broader biomarker testing is justified selectively and primarily intended to support diagnostic refinement, prognostic stratification, and eligibility for clinical trials, as well as to enable research on future therapeutic development.

The H3K27M histone alteration is a defining feature of DMG. This somatic missense mutation occurs in genes encoding one of the two histone H3 isoforms: *H3F3A* (H3.3) or *HIST1H3B/C* (H3.1) and is detected in up to 80% of pediatric and 60% of adult DMGs.[44] The mutation results in a mutant form of histone H3 that profoundly alters chromatin regulation and epigenetic programming. Inclusion of this biomarker in the essential panel is consistent with the 2021 WHO Classification of CNS Tumors, which defines "diffuse midline glioma, H3K27-altered" as a distinct entity. The presence of this alteration is associated with an aggressive clinical course and poor prognosis.[45]

In addition to direct mutation testing, assessment of H3K27me3 histone methylation by immunohistochemistry was also recommended. Loss of H3K27me3 is a downstream epigenetic consequence of the H3K27M mutation and serves as a useful surrogate marker,[46] particularly in settings where molecular sequencing is unavailable or where histopathological features are ambiguous.

Following a similar rationale to that applied in other HGGs, the investigation of *PIK3CA* mutations, *TP53* alterations, *BRAF* V600E mutations and *BRAF* fusions, *EGFR* alterations, *IDH1/IDH2* mutations, *CDKN2A* and *CDKN2B* deletions, *PDGFRA* amplifications and mutations, as well as *ATRX* mutations or loss of expression, was considered important. In addition, assessment of *CDK4*, *CDK6*, and *CCND1/2/3* amplifications may further refine molecular characterization.[39]

Ependymomas

No specific targeted therapeutic recommendations were made for ependymomas, however biomarker testing was considered essential for accurate tumor classification according to the 2021 WHO CNS criteria, including the distinction between posterior fossa group A (PFA) and group B (PFB) infratentorial ependymomas, as well as the identification of ZFTA- and YAP1 fusion–positive supratentorial tumors. Within this essential biomarker framework, additional cytogenetic profiling was specifically recommended for PFA ependymomas, including assessment of chromosome 1q gain and 6q loss. These alterations have been consistently associated with adverse clinical outcomes, define high- and ultra–high-risk subsets, and provide prognostic information.[47] In spinal ependymomas, MYCN amplification and NF2 mutations were also regarded as clinically relevant, contributing to diagnostic refinement and prognostic assessment.[47,48]

The additional biomarker panel comprises predominantly markers with prognostic or diagnostic relevance that may further refine risk stratification in posterior fossa ependymomas, myxopapillary ependymomas, and subependymomas. In posterior fossa subependymomas, KIT overexpression and activation of the STAT3 signaling pathway have been associated with a more aggressive biological phenotype and poorer clinical outcomes; however, these features do not define

formal molecular subgroups and currently have no established therapeutic implications. Although the general principle that KIT overexpression may confer sensitivity to tyrosine kinase inhibitors has been described in other malignancies,[49] this remains a hypothesis in subependymomas and should be regarded as exploratory. In myxopapillary ependymomas, HOXB13 overexpression has been proposed as a potential diagnostic biomarker.[50]

In PFA ependymomas, DNA methylation profiling enables further subclassification into PFA1 and PFA2, a distinction that currently has primarily prognostic value. PFA1 tumors are more likely to recur, and the time to recurrence is often shorter compared with PFA2 tumors.[51] This stratification is prognostic and does not yet change routine clinical management. In PFB ependymomas, evaluation of cytogenetic aberrations, particularly chromosome 13q loss, may help identify patients with a worse prognosis even within this generally favorable subgroup, although this marker is not yet routinely implemented in clinical practice.[52]

Medulloblastomas

Concerning medulloblastomas (Table 4), the essential molecular evaluation included molecular subgrouping as recommended by the 2021 WHO CNS classification, stratifying tumors into four principal subgroups: WNT, SHH, Group 3, and Group 4. Additional essential analyses comprised *TP53* mutation testing within the SHH subgroup and assessment of *MYC* and *MYCN* amplification in Groups 3 and 4, given their well-established role in risk stratification.[53] In cases where somatic *TP53* mutations are identified, evaluation for Li-Fraumeni syndrome is recommended. Similarly, the identification of wild-type *CTNNB1* in WNT medulloblastomas should prompt assessment for *APC* mutations, as germline *APC* alterations may indicate familial adenomatous polyposis–associated syndromes.[54]

For Group 4 medulloblastomas, cytogenetic analysis was classified as an additional biomarker to detect chromosome 11 loss and chromosome 17 gain, alterations associated with a more favorable prognosis.[55] These markers refine prognostic stratification within Group 4 but currently do not modify standard therapeutic management, supporting their designation as additional rather than essential biomarkers.

Therapeutic recommendations were also addressed, primarily within the context of risk-adapted management. For WNT subgroup medulloblastomas, inclusion of patients in clinical trials evaluating radiotherapy dose de-escalation was recommended, reflecting the favorable prognosis and high radiosensitivity of this subgroup. A multicenter Brazilian trial coordinated by SOBOPE, registered on *Plataforma Brasil* under the title "*Protocolo para tratamento do meduloblastoma de acordo com estratificação molecular de risco*", is currently evaluating radiotherapy dose de-escalation in this setting. In contrast, SHH subgroup tumors harboring *TP53* mutations and medulloblastomas with MYC amplification, particularly those in Group 3, should be treated as high-risk disease due to their aggressive clinical behavior and poor outcomes.[53]

For relapsed SHH medulloblastomas, the use of SMO inhibitors (such as vismodegib or sonidegib) may be considered in carefully selected cases, including adolescents aged ≥12 years harboring actionable alterations in the SHH pathway, specifically SMO or PTCH1 mutations. In this context, pathway inhibition may offer clinical benefits. However, given the limited pediatric data, potential skeletal toxicity in younger children, and restricted access in many settings, the use of SMO inhibitors should be considered preferably within clinical trials, compassionate use programs, or ethically approved off-label use, where available.[56]

Discussion

The global burden of cancer is a worldwide major concern. Projections point to its continuous growth, disproportionately affecting lower-resource settings.[57] While precision oncology has shown meaningful benefits in selected scenarios, the overall costs required for its implementation, including molecular testing, targeted therapy, and monitoring for adverse effects, remain significant challenges. There are few studies specifically addressing these economic considerations. The Zero Childhood Cancer Precision Medicine Program from Australia estimated multiomic and pre-clinical average costs, in a low-cost scenario, at $9122 Australian dollars per patient.[58] As a general trend, costs may decrease over time and with higher sample volumes. Although challenging, it is important to recognize that giving children and adolescents the opportunity to treat their cancer with new and more effective strategies represents a long-term investment. According to Atun et al.,[59] approximately 11 million children and adolescents will die from cancer from 2020 to 2050. Importantly, a net return of $3 for every $1 invested is expected for pediatric cancer care. Although the cost of targeted therapy is high, there is an urgent need for studies addressing the total costs of a child with cancer treated with suboptimal regimens, which frequently lead to additional financial burdens associated with treatment-related morbidity, late effects, and long-term social and functional impairment.

In this study, we present the first precision medicine consensus developed by the BC-PMPO/SOBOPE. This initiative is part of a broader effort to foster multidisciplinary dialog, identify opportunities to advance molecular diagnostics across the country, and generate evidence-based, resource-adapted recommendations. The primary objective was to prioritize recommendations with the greatest clinical impact, from prognostic

Medulloblastomas
Essential biomarkers
Upfront
MB1 | For medulloblastomas, classify the molecular subgroup as WNT, SHH, Group 3, or Group 4.
Methods: DNA methylation profiling; IHC or targeted molecular panel as alternatives.
Level of Agreement: 93%.
Level of Clinical Applicability: D1-BR.
MB2 | For SHH medulloblastomas, *TP53* gene mutation testing should be performed.
Method: NGS.
Level of Agreement: 86%.
Level of Clinical Applicability: D1-BR.
MB3 | For SHH medulloblastomas, Group 3, and Group 4, *MYC* and *MYC-N* gene amplification testing should be performed.
Methods: FISH, MLPA or NGS.
Level of Agreement: 93%.
Level of Clinical Applicability: D1-BR.
MB4 | For WNT group medulloblastomas, investigation of somatic mutations in the *CTNNB1* gene is recommended.
Method: NGS.
Level of Agreement: 80%.
Level of Clinical Applicability: D2-BR.
MB5 | For medulloblastomas with somatic *TP53* mutations, germline mutations in the same gene should be investigated, considering the possibility of Li-Fraumeni syndrome.
Method: Germline NGS.
Level of Agreement: 80%.
Level of Clinical Applicability: D2-BR.
Additional biomarkers
Upfront
MB6 | For Group 4 medulloblastomas, consider investigating cytogenetic aberrations, especially chromosome 11 loss and chromosome 17 gain.
Methods: FISH or MLPA. CGH array or NGS as alternatives.
Level of Agreement: 93%.
Level of Clinical Applicability: P3-BR.
Therapeutic recommendations
MB7 | For WNT subgroup medulloblastomas, consider including the patient in clinical trials evaluating radiotherapy dose reduction.
Level of Agreement: 84%.
Level of Clinical Applicability: T3-BR.
MB8 | For SHH subgroup medulloblastomas with *TP53* gene mutation, consider treatment as high-risk disease.
Level of Agreement: 78%.
Level of Clinical Applicability: T1-BR.
MB9 | For medulloblastomas with *MYC* amplification, especially in Group 3, consider treatment for high-risk disease.
Level of Agreement: 83%.
Level of Clinical Applicability: T1-BR.
MB10 | For relapsed SHH subgroup medulloblastomas with *SMO* or *PTCH1* mutations, in adolescents over 12 years of age, consider the use of SMO inhibitors, such as vismodegib or sonidegib.
Level of Agreement: 91%.
Level of Clinical Applicability: T3-BR.

Table 4: **Recommendations for medulloblastomas.**

assessment to molecularly adapted treatment intensity and targeted therapy.

A total of 72 recommendations were developed, categorized by level of essentiality, stratified by tumor type, and assigned a grade of clinical applicability. As precision medicine is a rapidly evolving field, there is currently no universally accepted framework for classifying the level of evidence for biomarker testing or targeted therapy recommendations. Existing tools, such as OncoKB or NCCN, are not fully applicable to the Brazilian context. To address this, we used an approach similar to OncoKB evidence-level framework to incorporate regulatory considerations from ANVISA. Given Brazil's continental size and significant socioeconomic diversity, this approach aims to support clinicians in selecting the most relevant tests for their specific practice settings and patient populations.

This consensus also seeks to inform how precision oncology can be operationalized in real-world settings with heterogeneous resources. Low-cost testing strategies, including immunohistochemistry and PCR-based approaches, are described for specific tumor types and

biomarkers. To support rational decision-making under constrained resources, the recommendations are structured into tiered panels, distinguishing a minimum set of essential tests, intended to be broadly implementable and to directly impact diagnosis, risk stratification, or standard treatment decisions, from expanded panels that may be pursued when additional infrastructure, funding, or clinical indication is available. This tiered framework aims to maximize clinical utility and equity while minimizing unnecessary costs and testing burden.

In addition, as part of an effort to promote equitable access to precision medicine in pediatric cancer in Brazil, BC-PMPO/SOBOPE regularly conducts Molecular Tumor Boards to guide the selection of the most cost-effective tests on a case-by-case basis. The committee also provides guidance on enrollment in trials, compassionate use programs, or ethically supervised off-label use, when appropriate. Additional strategies include the use of referral networks for complex molecular assays, hybrid models combining centralized and distributed testing for next-generation sequencing and DNA methylation profiling, and standardized logistics for sample processing, reporting, and clinically meaningful turnaround times. A similar implementation model has been successfully applied in Brazil, including a nationwide initiative led by our group that enabled centralized NGS-based cancer predisposition testing for approximately 650 children recruited from multiple states, with molecular analyses performed in a reference laboratory.

As scientific knowledge continues to evolve, updates to this consensus will be necessary. A key limitation of the present work is that not all histological subtypes were addressed in this first endeavor. Methodologically, the study is limited by its reliance on an overview of reviews, potential selection bias inherent to expert-curated evidence sources, the absence of formal quality appraisal of individual studies, and the dependence of recommendations on local availability of technologies. While efforts were made to ensure geographic and professional diversity, the expert panel did not include representatives from all regions of the country, which may limit the full appreciation of region-specific constraints and implementation challenges. These limitations should be considered when interpreting and applying the recommendations in different local contexts.

Although these recommendations were developed specifically for Brazil, we expect they can be useful for other LMICs that share similar challenges. We envision future updates to this consensus engaging a wider network of Latin American and Caribbean partners, which would further enhance the generalizability and collaborative value of these recommendations.

Beyond serving as a set of clinical guidelines, this consensus also represents a statement from Brazilian experts on the urgent need to modernize the care of pediatric brain tumor patients. It highlights the clinical utility of molecular testing and targeted therapies to improve outcomes and demonstrates how structured implementation of precision oncology can be achieved in LMICs.

Conclusion

This consensus represents a step toward systematizing and modernizing pediatric brain tumor care in Brazil. It delivers a structured framework for precision medicine in pediatric neuro-oncology, including tiered molecular testing and targeted therapy panels, as well as a level of clinical applicability framework to support clinical decision-making. The recommendations are intended to guide contextual prioritization of molecular testing and targeted therapies, with adaptation according to local access to technologies. In this context, the consensus may also serve as a starting point for clinicians and policymakers to recognize the importance of incorporating precision medicine tools into pediatric neuro-oncology practice. As a next step, this work provides a foundation for periodic updates, expansion to additional biomarkers and clinical scenarios, and the development of an implementation roadmap to support integration into clinical practice, research protocols, and health policy planning.

Contributors

KAFA (Conceptualization; Methodology; Data Curation; Visualization; Writing–Original Draft); JOA (Data Curation; Visualization Writing–Original Draft); MRS (Data Curation); NSS (Data Curation); MRC (Data Curation); JAP (Data Curation); APR (Data Curation; Writing–Review & Editing); AMC (Data Curation; Writing–Review & Editing); BMM (Data Curation; Writing–Review & Editing); FDC (Data Curation; Writing–Review & Editing); FDM (Data Curation; Writing–Review & Editing); GOB (Data Curation; Writing–Review & Editing); GRT (Data Curation; Writing–Review & Editing); IG (Data Curation; Writing–Review & Editing); LJG (Data Curation; Writing–Review & Editing); OKO (Data Curation; Writing–Review & Editing); PVC (Data Curation; Writing–Review & Editing); RC (Data Curation; Writing–Review & Editing); SEF (Data Curation; Writing–Review & Editing); ETV (Conceptualization; Methodology; Data Curation; Writing–Review & Editing; Supervision).

AI use statement

The authors used ChatGPT-5 and Gemini to improve English accuracy and readability and take full responsibility for the final content.

Declaration of interests

ETV reports a consulting or advisory role with Pfizer and Bayer. The other authors declare no competing interests. This research received no specific grant from any funding agency. Publication fees were supported by SOBOPE.

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Appendix A. Supplementary data

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