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MOLECULAR SUBTYPING OF PEDIATRIC MEDULLOBLASTOMA: CLINICAL, PROGNOSTIC, AND THERAPEUTIC IMPLICATIONS

Begali Sayitov[1],
Sabirov Djakhongir [2],
Iskandarov Kamol [1],
Tashmatov Suhkrob[3]
Abdugafforov Azamjon[1],
[1] National Children's Medical Center, Department of Oncology and Hematology — Pediatric Onco-hematologist.
[2]National Children's Medical Center, Deputy Director for Science, Education and International Relations.
[3]National Children's Medical Center, Department of Phatology.

Abstract: Medulloblastoma (MB) is the most common malignant pediatric brain tumor and is now recognized as a molecularly stratified spectrum comprising four principal subgroups: WNT, SHH, Group 3, and Group 4. Implementation of genomic and epigenomic profiling and the incorporation of subgrouping into the 2021 WHO CNS5 classification have clarified substantial heterogeneity in tumor biology, prognosis, metastatic behavior, and therapeutic response. However, translating molecular understanding into durable, less toxic therapies remains challenging, particularly for biologically aggressive disease such as metastatic Group 3 and TP53-mutant SHH tumors. This review summarizes molecular classification and diagnostic algorithms (including DNA methylation profiling), subgroup biology, prognostic implications, current standard-of-care treatment by subgroup, and emerging therapeutic directions including pathway inhibition, epigenetic therapies, drug repurposing, immunotherapy, and novel delivery approaches. Persistent barriers—especially blood–brain barrier (BBB) constraints and global inequities in access to molecular diagnostics and advanced radiotherapy—must be addressed to ensure that precision neuro-oncology improves outcomes and quality of life for children with medulloblastoma worldwide.

Keywords: Medulloblastoma; molecular subtyping; DNA methylation profiling; WNT; SHH; Group 3; Group 4; risk stratification; targeted therapy; immunotherapy; pediatric neuro-oncology; global health disparities..

Introduction

Medulloblastoma accounts for a substantial fraction of pediatric malignant CNS tumors and remains a major cause of childhood cancer-related morbidity and mortality. Long-term survival has improved with modern multimodality treatment, yet many survivors experience significant late effects including neurocognitive impairment, endocrine dysfunction, hearing loss, and psychosocial morbidity. These outcomes have shifted the definition of therapeutic success toward achieving cure while minimizing developmental and neurological toxicity. [1–3] Molecular profiling has transformed MB from a histologically defined tumor into a biologically stratified disease characterized by four reproducible subgroups—WNT, SHH, Group 3, and Group 4—with subgroup-specific drivers, cells of origin, metastatic tendencies, and outcomes. These concepts are embedded in WHO CNS5, supporting biologically informed risk stratification and molecularly stratified clinical trial design. [2,4,5] This review synthesizes contemporary evidence on molecular classification, subgroup biology, prognosis, and treatment

implications, and discusses emerging targeted and immunotherapeutic strategies alongside major implementation barriers, including BBB drug delivery limitations and global inequities in access to molecular diagnostics and modern radiotherapy. [2,3,6]

Materials and Methods

A literature review was conducted of publications from 2015 to 2025 focusing on the molecular subtyping of pediatric medulloblastoma and its clinical, prognostic, and therapeutic implications. Data Sources: Searches were performed in PubMed/MEDLINE and Scopus using keywords including *medulloblastoma, pediatric brain tumor, molecular subtyping, DNA methylation profiling, WNT, SHH, Group 3, Group 4, risk stratification, precision medicine, targeted therapy, immunotherapy,* and *global health disparities*. Additional sources included WHO publications, FDA and EMA regulatory documents, and the WHO CNS5 (2021) classification. Eligibility: Included studies were peer-reviewed articles published between 2015 and 2025 that addressed pediatric medulloblastoma with molecular subgroup context, diagnostics, prognosis, or treatment. Adult-only studies, case reports, and non-subgrouped analyses were excluded.
Study Selection and Synthesis: Approximately 150 records were screened, and 25–30 key publications with quantitative outcomes, subgroup-specific data, and relevance to clinical implementation were selected. Due to heterogeneity, results were synthesized using a narrative IMRAD framework.
Ethics: No ethical approval was required as only published data were analyzed.

Molecular Classification of Medulloblastoma

WHO CNS5 formally integrates molecular subgrouping into MB diagnosis and recognizes WNT-activated, SHH-activated (TP53-wildtype and TP53-mutant), Group 3, and Group 4 entities. This shift supports improved prognostic precision and more rational trial enrollment, particularly for de-escalation in favorable-risk disease and intensified or experimental approaches in biologically high-risk subsets. [5]

Core molecular subgroups

WNT-activated MB (~10%) is typically CTNNB1-driven and has low metastatic frequency and excellent outcomes; it is the leading candidate for treatment de-escalation protocols.[2,4] SHH-activated MB (~25–30%) spans infancy to adulthood; TP53 mutation status is a major risk modifier, with TP53-mutant SHH representing a biologically high-risk entity. [2,4,5] Group 3 MB is frequently metastatic, often MYC-driven, and carries the poorest prognosis; it remains a priority for escalation and novel trials. [2,4] Group 4 MB is the most common subgroup (~35–40%) and shows heterogeneous biology and intermediate prognosis; risk refinement increasingly relies on methylation and copy-number subclassification. [2,4,7]

DNA methylation profiling and modern diagnostic algorithms

Genome-wide DNA methylation profiling has become a reference standard for pediatric CNS tumor classification and is particularly valuable for MB subgrouping and subtype refinement. Compared with limited immunohistochemistry panels or single-gene approaches, methylation profiling provides stable tumor “fingerprints,” improves diagnostic accuracy in ambiguous cases, and enables integrated copy-number calls (e.g., MYC/MYCN amplification, i(17q)) relevant to risk stratification. [7–9] Many centers apply a tiered approach: histology and immunohistochemistry for rapid screening (e.g., β-catenin, YAP1, GAB1, p53), targeted

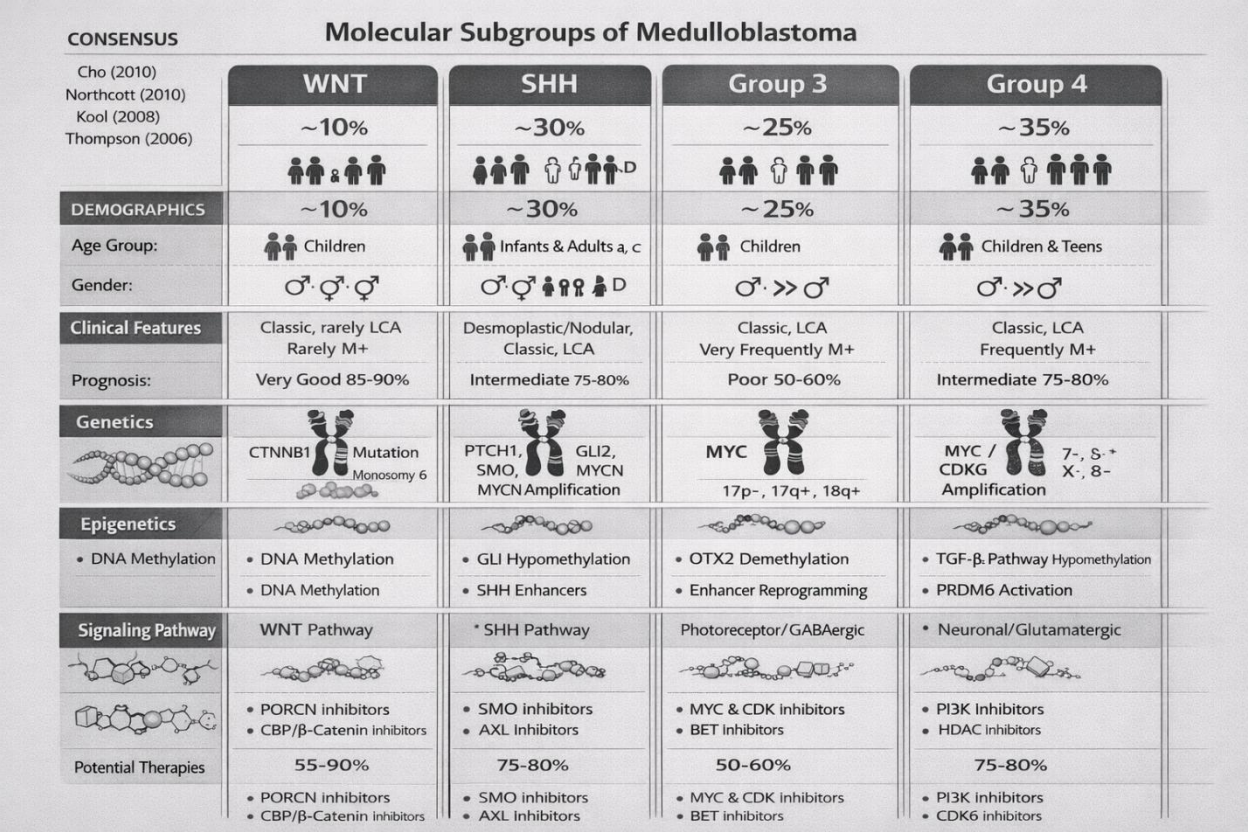
sequencing for key alterations (CTNNB1, TP53), and methylation profiling for definitive classification and risk refinement. [5,8,9]

Molecular Subgroup Biology

WNT tumors show canonical WNT/β-catenin pathway activation, relatively stable genomes, and limited dissemination. Their biology and microenvironmental features may facilitate treatment sensitivity, supporting de-escalation research. [2,4] SHH tumors are defined by alterations in PTCH1/SMO/SUFU/GLI signaling and arise from granule neuron progenitor lineages. TP53-mutant SHH tumors show genomic instability and poor outcomes, supporting intensified/experimental strategies; TP53-wildtype SHH is more heterogeneous and remains the primary subgroup for pathway-targeted therapy development. [2,4,5] Group 3 tumors commonly show MYC-driven programs, stem-like transcriptional states, and high rates of metastasis, consistent with aggressive behavior and resistance. [2,4] Group 4 tumors are characterized by epigenetic and chromosomal alterations rather than a single dominant signaling pathway; molecular subclassification is increasingly important for refined risk assignment. [4,7]

Prognostic Implications of Molecular Subtypes

Molecular subgroup is a major determinant of survival and is increasingly integrated with age, metastatic stage, and residual disease to guide risk-adapted therapy. [2,4,10] WNT shows the best outcomes and is central to de-escalation strategies. Group 3 has the worst outcomes, especially in metastatic disease and MYC-driven biology. SHH prognosis is strongly modified by TP53 status. Group 4 is intermediate but heterogeneous and increasingly stratified by methylation/copy-number features. [2,4,10]



Comparison of the various subgroups of medulloblastoma including their affiliations with previously published papers on medulloblastoma molecular subgrouping

Metastatic disease and residual tumor in the molecular era

Metastatic dissemination at diagnosis remains one of the strongest adverse prognostic variables, and it continues to define high-risk disease in most schemas. However, metastatic frequency and prognostic impact differ by subgroup. Group 3 commonly presents metastatic and is highly vulnerable to dissemination-associated failure. Group 4 shows meaningful metastatic rates but heterogeneous outcomes that depend on additional molecular features. In SHH, metastasis interacts with TP53 status and age-related biology. WNT metastasis is uncommon and outcomes remain favorable in most contemporary series, though metastatic WNT is typically treated as high risk in protocols. [2,4,10] Residual tumor remains relevant but is increasingly interpreted in context: modern practice emphasizes “maximal safe resection” and neurological preservation, recognizing that small residual burden may be acceptable when balanced against morbidity and when adjuvant therapy is effective. [10,11]

Current Standard of Care by Molecular Subgroup

Modern management integrates surgery, risk-adapted CSI (when age-appropriate), and multi-agent chemotherapy, with subgroup-informed de-escalation for WNT and selective intensification signals for high-risk Group 3. [2,10–12] Surgical goals include diagnostic confirmation with adequate tissue for molecular profiling and maximal safe resection while limiting neurological morbidity. Management of hydrocephalus and structured perioperative care pathways are critical components of outcomes and are best delivered in specialized centers. [10,11] CSI remains a cornerstone for most children ≥3–4 years. Standard-risk regimens commonly use reduced-dose CSI (historically ~23.4 Gy) with conformal boost to posterior fossa or tumor bed and adjuvant chemotherapy. Efforts to reduce CSI dose/volume are most developed

for WNT tumors in carefully selected settings. [10–12] Proton CSI reduces integral dose to normal tissues and is increasingly adopted to mitigate acute and late toxicities. Outcomes data continue to mature, but consensus supports proton CSI when available and appropriately implemented. [12,13] Standard-risk therapy commonly includes vincristine during radiotherapy followed by cisplatin-based multi-agent chemotherapy (protocol-dependent). Subgroup-informed approaches are increasingly emphasized: WNT de-escalation in trials; SHH risk modification by TP53; high-risk Group 3 selective radiosensitization benefits (carboplatin during radiotherapy in ACNS0332); and Group 4 risk assignment refined by molecular features. [10,12,14]

Emerging and Targeted Therapies

Emerging therapies aim to exploit subgroup dependencies while addressing late toxicity and BBB constraints. [2,10] Together, these therapeutic strategies illustrate a paradigm shift in medulloblastoma management—from uniform cytotoxic therapy toward molecularly guided, subgroup-specific treatment that seeks to maximize efficacy while minimizing long-term toxicity. The integration of targeted inhibition, epigenetic modulation, and drug repurposing with innovative delivery technologies is expected to play a central role in future precision-medicine–based treatment algorithms.

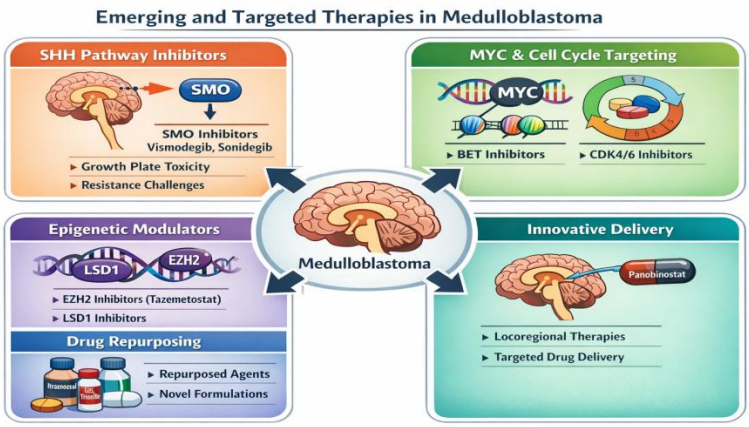


Figure 1. Emerging and Targeted Therapies in Medulloblastoma.

This figure summarizes key molecularly driven therapeutic strategies currently under development for pediatric medulloblastoma, aligned with subgroup-specific biological dependencies and translational challenges.

SHH Pathway Inhibitors

The Sonic Hedgehog (SHH) subgroup of medulloblastoma is characterized by constitutive activation of the SHH signaling cascade, most commonly through aberrant Smoothened (SMO) signaling and upstream pathway dysregulation. Targeted SMO inhibitors, including vismodegib and sonidegib, have demonstrated clinical activity in molecularly selected relapsed SHH medulloblastoma, confirming oncogenic pathway dependence and validating SHH as a therapeutic target [1,2,15].However, their use in pediatric populations is constrained by significant skeletal toxicity, most notably premature growth-plate fusion, which can result in permanent growth impairment and has led to restrictions on use in skeletally immature patients [16]. In addition, acquired resistance through SMO mutations or downstream pathway reactivation frequently limits the durability of response [15]. These challenges have driven the development of next-generation SHH pathway inhibitors and biomarker-guided combination strategies aimed at improving both efficacy and safety [2,3].

MYC and Cell-Cycle Targeting

Group 3 medulloblastoma is driven by MYC amplification or overexpression, which confers aggressive biological behavior, early dissemination, and poor prognosis [1,4,6]. Because MYC is not directly druggable, therapeutic strategies have focused on indirect MYC suppression, particularly through BET bromodomain inhibition, which downregulates MYC transcription and disrupts oncogenic transcriptional programs [18,19]. Preclinical and translational studies support the biological rationale for BET inhibition in MYC-driven medulloblastoma [2,18]. In parallel, cell-cycle vulnerabilities have emerged as a targetable dependency in MYC-driven tumors. CDK4/6 inhibitors, including palbociclib, have demonstrated clinical feasibility in pediatric CNS tumors in early-phase trials, supporting the viability of cell-cycle blockade in this setting [17]. These approaches represent promising precision-based strategies for high-risk Group 3 medulloblastoma, particularly in combination-based regimens [2,10,19].

Epigenetic Modulators

Epigenetic dysregulation is a defining feature of Group 3 and Group 4 medulloblastomas, involving abnormal chromatin remodeling, histone modification, and transcriptional control [1,2,7]. In this context, EZH2 inhibition, including the clinically available agent tazemetostat, has shown strong preclinical efficacy by reversing oncogenic repression programs and suppressing tumor growth in medulloblastoma models [20]. Similarly, LSD1 inhibition disrupts transcriptional programs critical for medulloblastoma maintenance and has demonstrated subgroup-relevant anti-tumor activity in preclinical studies [21]. However, systemic delivery is constrained by the blood–brain barrier, limiting effective tumor exposure. Consequently, innovative strategies such as locoregional delivery of panobinostat (MTX110) are being developed to enhance intratumoral drug levels while minimizing systemic toxicity [22].

Drug Repurposing

Several non-oncologic drugs with established safety profiles, including itraconazole, arsenic trioxide, and niclosamide, are being repurposed for medulloblastoma due to their anti-tumor and pathway-modulating activity and accelerated translational potential [2,23,24]. These agents have demonstrated inhibition of SHH signaling, MYC-associated pathways, or mitochondrial and transcriptional dependencies in preclinical medulloblastoma models [23,24]. However, their clinical application remains limited by suboptimal CNS penetration and uncertain pediatric pharmacokinetics, which complicate dose optimization and therapeutic consistency [2,23]. Contemporary translational strategies therefore emphasize novel formulations, optimized drug-delivery technologies, and biomarker-guided patient selection to improve the likelihood of meaningful clinical benefit [24].

Immunotherapy in Medulloblastoma

Medulloblastoma is generally considered an immunologically “cold” tumor, characterized by low immune cell infiltration and limited neoantigen expression, which restricts the effectiveness of endogenous antitumor immune responses [25–27]. Consequently, single-agent immune checkpoint inhibitors have demonstrated minimal clinical activity in unselected pediatric medulloblastoma populations, prompting a shift toward alternative immunotherapeutic strategies [25,27]. Current approaches increasingly emphasize active and engineered immunotherapies, including cellular therapies, tumor vaccines, oncolytic viruses, and rational combination regimens designed to either prime antitumor immunity or overcome local immunosuppression within the tumor microenvironment [25]. Importantly, the immune and stromal landscapes differ substantially across molecular subgroups (WNT, SHH, Group 3, and Group 4), with subgroup-

specific patterns of immune infiltration, macrophage polarization, and stromal composition, making subgroup-aware immunotherapy development essential for effective clinical translation [26,27]. Among these strategies, antigen-directed CAR-T cell therapies have emerged as a leading platform for pediatric CNS tumors, including medulloblastoma [25]. Tumor-associated antigens such as B7-H3 (CD276) and GD2 are highly expressed on medulloblastoma cells with limited normal brain expression, making them attractive targets for selective immune targeting [25–27]. Preclinical models and early-phase clinical studies support the feasibility, biological activity, and safety of CAR-T approaches in CNS tumors, and these platforms are increasingly incorporated into medulloblastoma-focused translational pipelines and clinical trial frameworks [25,27]. Overall, immunotherapy in medulloblastoma is transitioning from non-specific immune modulation toward precision-guided, antigen-specific, and subgroup-tailored immune strategies, with the goal of achieving durable tumor control while minimizing neurotoxicity in pediatric patients [25–27].

Global Disparities in Molecular Diagnosis and Treatment

Despite major advances in molecular classification and precision-based therapy, access to contemporary medulloblastoma diagnostics and treatment remains highly unequal worldwide [1,2,28]. Technologies that now define standard-of-care in high-income countries—including DNA methylation profiling, next-generation sequencing, and advanced radiotherapy platforms such as IMRT and proton craniospinal irradiation (CSI)—are unavailable or inconsistently applied in many low- and middle-income countries (LMICs) [8,12,13,28–30]. This disparity directly limits accurate molecular risk stratification, eligibility for molecularly stratified clinical trials, and the ability to deliver subgroup-adapted therapy, resulting in inferior survival and increased treatment-related morbidity in resource-constrained settings [2,9,28]. Recent global outcome analyses demonstrate that survival gaps between high-resource and low-resource regions persist even for biologically favorable medulloblastoma subtypes, highlighting that health-system capacity has become a dominant determinant of outcome in the molecular era [28].

To address these inequities, several scalable implementation strategies have emerged. These include centralized reference laboratories for molecular profiling, international referral and multidisciplinary tumor board networks, resource-adapted treatment protocols, and the expanding use of telepathology and teleoncology for remote diagnostic and therapeutic guidance [8,29,30]. In parallel, investment in local infrastructure, workforce training, and quality-assurance systems is essential to ensure sustainable implementation of precision neuro-oncology in LMIC settings [29,30].

Equitable access to molecular diagnostics and modern radiotherapy is now recognized as a core priority of the global medulloblastoma community, ensuring that the survival gains achieved through biological stratification and targeted therapy can be realized worldwide rather than being confined to high-resource centers [2,28–30].

Discussion

Molecular subgrouping has fundamentally redefined pediatric medulloblastoma as a biologically stratified disease, enabling more accurate prognostication and rational treatment personalization [1–7]. Among the four principal subgroups, WNT tumors represent the clearest opportunity for treatment de-escalation, given their consistently excellent survival and low relapse risk [1,4,6,10]. In contrast, Group 3 medulloblastoma remains the greatest therapeutic challenge, characterized by MYC-driven biology, high metastatic burden, and resistance to conventional cytotoxic regimens [1,2,4,6].

The SHH subgroup illustrates the importance of within-subgroup molecular stratification, particularly the adverse prognostic impact of TP53 mutations, which supersede the otherwise intermediate-risk biology of SHH tumors [1,2,4,5]. Group 4, the most prevalent but historically least characterized subgroup, increasingly requires finer molecular subclassification for accurate risk assignment and rational clinical trial design [1,4,6,7].

Despite these advances, major translational barriers remain. The blood–brain barrier (BBB) continues to restrict effective delivery of targeted and epigenetic therapies, while adaptive resistance mechanisms frequently limit the durability of single-agent pathway inhibition, particularly when therapies are not guided by biomarkers or rational combination strategies [2,15,18–24]. Consequently, the most realistic near-term progress is expected to arise from biomarker-driven combination regimens, implemented within molecularly stratified, risk-adapted clinical trials, and supported by innovative drug-delivery platforms capable of achieving therapeutically meaningful intratumoral exposure [2,9,10,22–24].

Finally, global inequities in access to molecular diagnostics and modern radiotherapy represent a critical constraint on the real-world impact of precision neuro-oncology [2,8,12,13,28–30]. Without systematic investment in reference testing networks, capacity building, telemedicine-enabled consultation, and international cooperative frameworks, the survival gains achieved through molecular stratification and targeted therapy will remain geographically confined to high-resource settings [28–30]. Achieving equitable implementation is therefore essential—not optional—for realizing the full promise of molecularly guided medulloblastoma therapy worldwide [2,28–30].

Conclusions

Pediatric medulloblastoma comprises a molecularly defined spectrum of diseases, encompassing the WNT, SHH, Group 3, and Group 4 subgroups as formalized in the WHO CNS5 classification [1,4,5]. This biological framework underpins clinically meaningful risk stratification, enabling treatment de-escalation for favorable-risk tumors while guiding therapeutic innovation for high-risk subgroups, particularly Group 3 and biologically adverse SHH disease [1,2,6,10].

Ongoing advances in targeted therapies, epigenetic modulation, immunotherapy, and drug-delivery technologies are expanding the therapeutic landscape beyond conventional cytotoxic approaches [2,15–27]. However, the full clinical impact of these innovations will depend on their integration into molecularly driven, risk-adapted treatment protocols and their equitable global implementation [2,9,10,28–30].

Ensuring universal access to molecular diagnostics, contemporary radiotherapy, and specialized neuro-oncology care is therefore essential if the survival gains achieved through precision medicine are to translate into durable improvements in survival and long-term quality of life for children worldwide [2,8,12,13,28–30].

References

1. Northcott PA, Robinson GW, Kratz CP, et al. Medulloblastoma. Nat Rev Dis Primers. 2019;5:11.
2. Kim DT, Uloho-Okundaye M, Frederico SC, et al. Advancing medulloblastoma therapy in pediatrics: integrative molecular classification and emerging treatments. Brain Sci. 2025;15:896.
3. Choi JY, Kim JH, Lee JY, et al. Medulloblastoma: current perspectives and recent advances. Brain Tumor Res Treat. 2023;11:e22.

4. Schwalbe EC, Lindsey JC, Nakjang S, et al. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma. Lancet Oncol. 2017.
5. WHO Classification of Tumours Editorial Board. Central Nervous System Tumours (WHO CNS5). Lyon: IARC; 2021.
6. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era. Acta Neuropathol. 2016;131:821–831.
7. Schwalbe EC, Lindsey JC, Nakjang S, et al. DNA methylation profiling of medulloblastoma: clinical utility and applications. Acta Neuropathol. 2017;134:703–721.
8. Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of CNS tumors in clinical practice. (clinical implementation series). 2018–2020.
9. Thompson EM, Hielscher T, Bouffet E, et al. Current medulloblastoma subgroup-specific clinical trials. Transl Pediatr. 2020;9:157–162.
10. Perek-Polnik M, et al. Risk-adapted therapy in pediatric medulloblastoma: state of the art. Children (Basel). 2023;10:1321.
11. Perreault S, Ramaswamy V, et al. Neurosurgical and perioperative considerations in medulloblastoma care. 2018–2022 (review-level evidence).
12. Padovani L, Habrand JL, et al. Radiotherapy in pediatric medulloblastoma: contemporary approaches including proton therapy. Clin Oncol. 2019.
13. Ho ESQ, Barrett W, Mullaney LM, et al. Proton versus photon craniospinal irradiation in pediatric medulloblastoma: dosimetric and clinical considerations. Acta Oncol. 2017;56:125–134.
14. Leary SES, et al. Carboplatin radiosensitization in high-risk medulloblastoma (COG ACNS0332). JAMA Oncol. 2021.
15. Li Y, et al. SMO inhibitors in SHH-driven medulloblastoma: early-phase clinical experience. 2018–2021.
16. Robinson GW, et al. Growth plate fusions in children exposed to Hedgehog pathway inhibitors. Oncotarget. 2017.
17. Van Mater D, et al. Phase I trial of palbociclib in pediatric patients with progressive brain tumors (PBTC-042). Pediatr Blood Cancer. 2021.
18. Contemporary translational reviews on BET inhibition and MYC-driven medulloblastoma. 2017–2024.
19. Contemporary translational reviews on MYC biology and cell-cycle vulnerabilities in pediatric brain tumors. 2018–2025.
20. Zhang H, et al. EZH2 targeting and tazemetostat activity in medulloblastoma models. Acta Neuropathol Commun. 2019.
21. Lee C, et al. LSD1 as a therapeutic target in medulloblastoma. Nat Commun. 2019.
22. ClinicalTrials.gov. MTX110 (panobinostat) locoregional delivery in recurrent pediatric CNS tumors including medulloblastoma (NCT04315064).
23. Recent reviews on drug repurposing and BBB limitations in pediatric medulloblastoma. 2019–2025.
24. Recent reviews on itraconazole/arsenic trioxide/niclosamide and delivery constraints. 2018–2025.
25. Voskamp MJ, Zethoven M, Denaro N, et al. Immunotherapy in medulloblastoma: current state of research and clinical trials. Cancers (Basel). 2021;13:1950.
26. Bockmayr M, Mohme M, Klauschen F, et al. Subgroup-specific immune and stromal microenvironment in medulloblastoma. OncoImmunology. 2018;7:e1468526.
27. Kurdi M, Ramaswamy V. The immune microenvironment of medulloblastoma. World J Clin Oncol. 2023;14:647–659.

28. Recent LMIC outcome analyses in pediatric medulloblastoma. Neuro-Oncology Adv. 2023–2025.
29. WHO/consensus implementation papers on global equity in CNS tumor diagnostics. 2019–2025.
30. Cooperative group/consensus guidance on access to methylation profiling and referral networks. 2020–2025.