Pediatric Gliomas: Current Concepts on Diagnosis, Biology, and Clinical Management
Dominik Sturm, Stefan M. Pfister, and David T.W. Jones

ABSTRACT
Gliomas are the most common CNS tumors in children and adolescents, and they show an extremely broad range of clinical behavior. The majority of pediatric gliomas present as benign, slow-growing lesions classified as grade I or II by the WHO classification of CNS tumors. These pediatric low-grade gliomas (LGGs) are fundamentally different from IDH-mutant LGGs occurring in adults, because they rarely undergo malignant transformation and show excellent overall survival under current treatment strategies. However, a significant fraction of gliomas develop over a short period of time and progress rapidly and are therefore classified as WHO grade III or IV high-grade gliomas (HGGs). Despite all therapeutic efforts, they remain largely incurable, with the most aggressive forms being lethal within months. Thus, the intentions of neurosurgeons, pediatric oncologists, and radiotherapists to improve care for pediatric patients with glioma range from increasing quality of life and preventing long-term sequelae in what is often a chronic, but rarely life-threatening disease (LGG), to uncovering effective treatment options to prolong patient survival in an almost universally fatal setting (HGG). The last decade has seen unprecedented progress in understanding the molecular biology underlying pediatric gliomas, fueling hopes to achieve both goals. Large-scale collaborative studies around the globe have cataloged genomic and epigenomic alterations in gliomas across ages, grades, and histologies. These studies have revealed biologic subgroups characterized by distinct molecular, pathologic, and clinical features, with clear relevance for patient management. In this review, we summarize hallmark discoveries that have expanded our knowledge in pediatric LGGs and HGGs, explain their role in tumor biology, and convey our current concepts on how these findings may be translated into novel therapeutic approaches.

LOW-GRADE GLIOMAS
Pediatric low-grade gliomas (LGGs) or glioneuronal tumors (WHO grade I or II) are a highly heterogeneous collection of entities accounting for 25% to 30% of all childhood CNS tumors. They are roughly as common as malignant gliomas and embryonal tumors combined.1,2 The most common single entity is pilocytic astrocytoma (PA; > 15% of tumors in patients age 0 to 19 years3), with ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), and diffuse glioma, each composing a notable minority. Some additional subsets are so rare that they are only now starting to be described.4 Overlapping morphology (eg, variants of DNET, entrapped v neoplastic ganglion cells, and microvascular tumors resembling higher-grade tumors) can pose a diagnostic challenge. Furthermore, the natural proliferative potential of the developing CNS may complicate assessments of malignancy, meaning that slightly increased mitotic indices or Ki-67 immunostaining do not automatically preclude a benign course.

In stark contrast to adult lower-grade gliomas, IDH mutations are almost absent in children, and malignant progression is extremely rare in pediatric LGGs. Outcomes are typically good, with 5-year overall survival of approximately 95% (see Stokland et al).4 Thus, particularly for tumors not amenable to gross resection, LGGs often become a chronic disease, and affected children may experience a protracted reduction in quality of life.5 Although there are some reported prognostic indicators (eg, Stokland et al4), we currently know little about the mechanisms by which these tumors relapse or progress. One exception to this may be BRAF V600E mutant and 9p21 (CDKN2A/B)–deleted tumors (hallmark lesions of pleomorphic xanthoastrocytoma), which likely display an increased propensity for progression and a worse outcome.6
Also in contrast to most adult gliomas, a notable fraction of pediatric LGGs can be linked to a hereditary component. For example, subependymal giant cell astrocytoma is closely associated with germline mutations in TSC1 or TSC2 and occurs in up to 20% of patients with tuberous sclerosis complex. A similar proportion of patients with neurofibromatosis type I (NF1) develop a pilocytic astrocytoma during the first decade of life, typically in the optic pathway. There are also links between a second RASopathy, namely Noonan syndrome, and pilocytic astrocytoma. This syndrome is often a result of germline mutations in PTPN11, which was recently found to be somatically mutated together with BRAF in a subset of PAs.

Now seen as a canonical single-pathway disease, essentially 100% of PAs harbor an alteration in the MAPK axis, most commonly KIAA1549:BRAF fusion. A variety of additional alterations in this pathway have been identified in other LGG histologies, including additional BRAF fusions and mutations; RAI fusions; mutations, fusions, or kinase domain duplications of FGFR1; and fusions of the NTRK gene family. The link between individual alterations and particular histologies is not 100% clear, as summarized in Figure 1. Although BRAF fusions are almost exclusive to PA, BRAF V600E mutation, for example, is seen in some PAs as well as a substantial fraction of ganglioglioma and pleomorphic xanthoastrocytoma. One notable exception with BRAF fusions is the recently described diffuse leptomeningeal glioneuronal tumor (also known as disseminated oligodendroglial-like leptomeningeal neoplasm), which often shows a KIAA1549:BRAF fusion together with isolated 1p or combined 1p/19q deletion. FGFR1 alterations also occur across histologies but with an apparent enrichment in DNETs.

Thus, MAPK alterations underlie many low-grade glial/glioneuronal entities. MAPK-related oncogene-induced senescence is also likely one reason for their relatively benign behavior. However, additional signaling programs are altered in some subsets. A role for amplification and/or rearrangement of MYB/MYBL1, for example, has been identified in a proportion of LGGs, particularly with a diffuse astrocytic or angiocentric morphology. Although the ultimate downstream consequences are not yet fully clear, it is thought that the most common fusion event (MYB:QKI) acts through a triple mechanism of MYB truncation, increased expression through enhancer hijacking, and loss of QKI tumor suppressor function.

The mainstay of current LGG therapy is surgical excision, which may be curative where total resection is possible. In areas where subtotal (or no) resection is possible, however, the chances of progression or relapse are substantial. Here, chemotherapy with either a vincristine plus carboplatin or vinblastine monotherapy regimen is usually given. Of note is that temozolomide, the treatment of choice for adult diffuse gliomas, is no better than standard therapy for pediatric LGG. Although current chemotherapies are associated with good overall survival, long-term treatment (especially over several rounds) is often associated with significant morbidity. A more tailored approach is therefore needed to improve quality of life.

To address issues such as translation of biologic knowledge into planning of future LGG trials, a group of scientists and clinicians recently established a consensus-finding group. Their recommendations noted that functional outcomes, not just survival, should be considered as key end points; that molecular analysis through resection or biopsy should be performed before adjuvant therapy, and that a combined histologic and molecular...
stratification should be routinely implemented to facilitate assignment to novel therapeutic studies. It is hoped that a targeted approach may deliver improvements in tumor control and in functional measures with fewer adverse effects, focusing on quality of survival rather than absolute rates. A success story in LGG is the use of mTOR inhibitors for treating subependymal giant cell astrocytoma, a safe and effective treatment which is now approved.30 On the basis of growing knowledge of activated signaling pathways in other LGGs, several early-phase clinical trials looking at MAPK-targeted therapy have recently been completed or are currently in progress.

Initial results with MEK inhibitors (MEKi), which should block pathway activity regardless of the precise upstream alteration, seem to be promising. Both selumetinib and trametinib have completed phase II trials, and plans for phase III trials are in advanced stages. Initial evidence suggests a particularly strong signal in NF1-associated tumors, which would be in keeping with recent results in NF1-associated plexiform neurofibroma.34

Studies with drugs targeting the V600E-mutant form of BRAF have also shown positive results, with at least disease stabilization seen in almost all patients in a dabrafenib study.32 Care must be taken, however, when considering treatment with these type I BRAF V600E–specific inhibitors, because some (such as sorafenib)33 can show paradoxical stimulation of tumor growth in the context of the more common KIAA1549:BRAF fusion.34 The next round of early-phase trials includes both type II RAF inhibitors, which should overcome this activation, and BRAF inhibitor/MEKi combinations (ClinicalTrials.gov identifier: NCT02124772), whereas both FGFR1 and NTRK kinases represent additional possible targets. Thus, although they have a ways to go before they become standard of care, there is reason for optimism about the impact that personalized medicine may have on the survival and especially the quality of life of children with LGG.

**HIGH-GRADE GLIOMAS**

Pediatric high-grade glioma (HGG) essentially includes anaplastic astrocytoma (WHO grade III) and glioblastoma multiforme (GBM; WHO grade IV), both malignant, diffuse, infiltrating astrocytic tumors.2 Gliomatosis cerebri, a highly infiltrative HGG manifestation affecting multiple brain regions, is thought to represent a phenotypic extreme rather than a distinct entity.36 Diffuse intrinsic pontine glioma (DIPG), a diagnosis frequently established by a combination of clinical symptoms (rapidly developing brain stem dysfunction and/or cerebrospinal fluid obstruction) and radiologic criteria (large, expansile brain stem mass occupying more than two thirds of the pons), shows a uniformly aggressive behavior, even when displaying lower-grade histology.37 This is partly reflected in the updated WHO 2016 criteria, whereby diffuse midline gliomas with K27M histone mutations (including most DIPGs) are classed as WHO grade IV, regardless of histology.32

The morphology and neuropathologic characteristics of anaplastic astrocytoma (ie, foci of increased cell density, nuclear atypia, and mitotic activity) and glioblastoma (additional microvascular proliferation and/or necrosis) usually correspond with a poorly defined tumor mass on magnetic resonance imaging. Analysis of adult glioma has shown that most IDH-wild-type grade III astrocytomas have a dismal prognosis, which mimics that of GBM,38 and the prognostic/biologic relevance of histologically distinguishing between grade III and grade IV in children is also not clear.

Pediatric HGGs may manifest across all ages and anatomic CNS compartments and are among the most common malignant CNS tumors in children. The reported age-adjusted incidence of 0.26 per 100,000 population is likely an underestimate, because DIPGs with low-grade histology or without histologic assessment are not assigned as HGG in epidemiologic registries, and poorly differentiated HGG variants previously may have been diagnosed as primitive neuroectodermal tumors39 or tumors with mixed ependymal, glial, or glioneuronal features. Improved profiling through methods such as DNA methylation analysis may help with the latter issue.

Phenotypically indistinguishable from the adult disease, early molecular profiling studies suggested a different biology underlying childhood HGG.40-45 International next-generation sequencing efforts shortly thereafter discovered somatic histone mutations as a hallmark of HGG in children and young adults, namely K27M and G34R/V mutations in H3.3- and H3.1-coding genes.35,45 Subsequently, numerous reports have investigated the impact of these mutations on the epigenome,46-51 and associations with other molecular,52-56 pathologic,56-59 or clinical49,60-63 features, highlighting a pivotal role in gliomagenesis. The resulting insights have formed our current concept of molecular HGG subgroups: that distinct cell-of-origin populations of the developing CNS, susceptible to specific oncogenic hits, give rise to biologically and clinically distinct groups of tumors that are likely to respond to different therapies. An overview of key alterations by location is summarized in Figure 2, and an example visualization of distinct subclasses of both LGGs and HGGs is provided in Figure 3.

The majority of pediatric diffuse midline gliomas arising in the brain stem (ie, DIPG; > 90%),64 thalamus (approximately 50%),65 and spinal cord (approximately 60%)66 harbor mutations at position 27 (K27M) in genes coding for histone variants (H3F3A, approximately three fourths; HIST1H3A/C, approximately one fourth, and other rare variations).61 The K27M-mutant histone 3 protein inhibits polycomb repressive complex 2 (PRC2) activity via sequestration of its catalytic subunit EZH2,46 resulting in globally decreased H3 K27 trimethylation (H3 K27me3).60 Emerging patterns suggest further biologic diversity within K27M-mutated tumors: H3.3 mutations are found across midline structures (co-occurring with FGFR1 and/or NF1 mutations in some thalamic gliomas65), typically affect children age 7 to 10 years and are associated with very poor outcome.61 In contrast, H3.1 mutations are largely restricted to DIPG with earlier onset (age 4 to 6 years), have been associated with distinct clinicopathologic and radiologic features and a slightly better prognosis, and frequently co-occur with ACVR1 mutations.52-55,61 Initially thought to be pathognomonic for high-grade astrocytic tumors,50,66 the spectrum of CNS tumors with H3 K27M mutations has recently been expanded to include rare examples of lower-grade midline gliomas and posterior fossa ependymomas, in which their prognostic impact is yet to be defined.

Up to one third of hemispheric pediatric HGGs carry mutations at position 34 (G34R/V) in H3F3A.46,47,49,52 Although the exact consequences of H3.3 G34 mutations are not yet understood, associations with mutations in ATRX and subtelomeric hypomethylation may indicate a role for telomerase-independent telomere maintenance mechanisms (ie, alternative lengthening of telomeres) in this subset of
An estimated 5% to 10% of pediatric HGGs harbor BRAF V600E mutations. These tumors are predominantly cortical, share histologic and epigenetic characteristics with pleomorphic xanthoastrocytoma (PXA), and frequently harbor homozygous CDKN2A/B deletions.6 The slightly better clinical outcome of patients with these tumors may explain some of the long-term survivors seen in HGG clinical trials.71 More importantly, targeted therapy for this molecularly defined group of patients72-74 is currently being tested in clinical trials (ClinicalTrials.gov identifiers: NCT01677741 and NCT01748149). Of note, BRAF V600E mutations are also commonly encountered in epithelioid GBM, which can display histologic features similar to those of PXA but typically with a worse prognosis.75,76 The association between these two entities both clinically and biologically (eg, whether epithelioid GBM may represent a malignant transformation of PXA) is worthy of additional investigation.

A small number of pediatric HGGs are thought to result from cancer predisposition syndromes. Some GBMs arise in patients with constitutional mismatch repair deficiency (caused by homozygous mutations in mismatch repair genes PMS2, MLH1, MSH2, and MSH6), and exhibit a greatly increased mutational burden. Recent reports of responses of such tumors to immune checkpoint inhibition, likely through presenting a high load of T-cell activating neoantigens, have implications for constitutional mismatch repair deficiency–associated GBM and other HGGs with an acquired hypermutator phenotype.77

Only a small number of HGGs in older adolescents display hotspot mutations in IDH1/2 genes, thereby representing the lower age spectrum of adult gliomas (reviewed in Sturm et al64). From the remaining heterogeneous fraction of H3/IDH-wild-type pediatric HGGs (approximately 50%), more subgroups are beginning to emerge. For example, amplifications of MYCN, often co-amplified with ID2, may drive a subset of DIPGs and supratentorial tumors with variable glial or primitive neuroectodermal tumor–like morphology.39,54 Other subgroups are enriched for amplifications or mutations in receptor tyrosine kinase genes such as PDGFRA or EGFR.39,65,69 Initial evidence points toward possible prognostic differences in these subsets.69 Other recently detected alterations include fusions involving MET70 and NTRK1-3 genes, the latter being enriched in infant HGGs and pointing to some overlap with LGG biology in this age group.92
Although core drivers may be both spatially and temporally stable, additional modifying alterations in subpopulations can also play important roles (see Nikbakht et al83).

In contrast to MEKi for LGG, the heterogeneity of HGG means that any single drug is unlikely to work for a large proportion of patients. Molecularly informed trials will therefore require global collaboration to conduct adequately powered studies. Initiatives such as international DIPG registries will help improve characterization of these tumors and facilitate trial planning.84,85 Individual examples of bench-to-bedside translation also indicate that studying acquired resistance mechanisms will be another challenge.70 Expanding the repertoire of patient-derived preclinical models will help when testing epigenetic modifier therapies for HGG,86,87 some of which are now entering clinical trials (ClinicalTrials.gov identifier: NCT02717455).

Although hurdles such as drug delivery across the blood-brain barrier (especially in DIPGs) remain to be overcome, recent progress in understanding these tumors means that enthusiasm within the research community is greater than ever.

CONCLUSION

Here we have provided an overview of current concepts on diagnosis, biology, and clinical management for the extremely heterogeneous group of pediatric gliomas. For more detail on some of these aspects, we direct the reader to additional recent reviews, a selection of which is provided in Table 1. Although our knowledge of the biology of pediatric gliomas has expanded enormously in recent years, significant challenges remain in translating these insights into clinical practice. For example, the true intertumoral heterogeneity of this group is far wider than anticipated and also broader than what is captured by current diagnostic practice. Definition of combined histo-molecular subgroups of glioma for prognostication and stratification onto (targeted) treatment trials will therefore be of key importance—something which hopefully will be addressed through initiatives such as the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT) group.88 In particular, precise prognostic markers and subgroups for BRAF V600E–mutated tumors would be of substantial value, because tumors with this readily druggable target show something which hopefully will be addressed through initiatives such as the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT) group.88 In particular, precise prognostic markers and subgroups for BRAF V600E–mutated tumors would be of substantial value, because tumors with this readily druggable target show

Fig 3. Molecular subgroups of pediatric low-grade gliomas (LGGs) and high-grade gliomas (HGGs) by DNA methylation patterns. T-distributed stochastic neighbor embedding (TSNE) analysis of selected groups of pediatric gliomas by genome-wide DNA methylation patterns (Illumina Infinium BeadChip Array; 5,000 most variable CpG probes by standard deviation). Patients (n = 10 per class) were selected to emphasize group differences. Each circle represents one sample. Subgroup associations are represented by colors as indicated. Original data from the German Cancer Research Center in Heidelberg were partly published in Sturm et al.39 DMG K27, diffuse midline glioma with H3 K27 mutations; DNT, dysembryoplastic neuroepithelial tumor; GG, gliomatous xanthoastrocytoma; SEGA, subependymal giant cell astrocytoma. (*): These groups in particular can contain patients with either typical HGG or more primitive neuroectodermal tumor–like morphology.

Such translational progress is urgently needed, because current treatment strategies generally bring minimal benefit. The standard therapy in diffuse midline (and therefore unresectable) gliomas is radiotherapy (and best supportive care), temporarily improving quality of life but barely increasing survival.78,79 Most patients die within 1 year after diagnosis. For supratentorial/ hemispheric HGG, maximal surgical resection is followed by radiotherapy (for patients older than age 4 years) and concomitant/ adjuvant chemotherapy. On the basis of positive adult data with temozolomide80 and its decreased toxicity compared with other regimens,81 radiochemotherapy with temozolomide is widely considered as the therapeutic backbone. However, evidence for efficacy of the latter is currently unclear.

Future clinical trials will need to recognize the diversity of these tumors as opposed to an all-comers approach. This will require upfront molecular characterization of tumor tissue, including for DIPGs. When performed in a safe, standardized setting, stereotactic biopsy of DIPGs allows identification of actionable alterations as part of molecularly informed studies (eg, Fontebasso et al82 and Worst et al83). Furthermore, increased efforts are required to ascertain tumor material at relapse (or at autopsy), which would give important information about disease progression.

jco.org

© 2017 by American Society of Clinical Oncology

Downloaded from ascopubs.org by 5.170.29.247 on July 11, 2017 from 005.170.029.247
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.
and possible therapeutic vulnerabilities. The importance of understanding signaling networks and feedback loops within the MAPK pathway, for example, is seen from the paradoxical activation by first-generation RAF inhibitors. Such data may also help identify mechanisms of treatment resistance and suggest rational combinations to overcome them.

The availability of good preclinical in vitro and in vivo models, particularly for LGG, is another translational bottleneck. The development of such models will enable more functional studies such as high-throughput genetic or compound screening for novel drug targets. In addition, these models need to be used in a more sophisticated way when planning preclinical studies to improve their predictive value (eg, comparison with standard-of-care therapy and use of multiple models to better mimic clinical trials).

There is much work still to be done, but recent advances in LGGs and HGGs provide a framework for the road ahead. For some entities, that road is relatively clear (eg, second-generation RAF inhibitors with or without MEKi for V600E-mutant tumors), whereas for others, the path will likely have more twists and turns (eg, K27-mutant DIPGs). Overall, however, our improved understanding provides grounds for optimism that meaningful clinical benefit can be achieved in the not-too-distant future.

**Table 1.** Selected Recent Review Articles Summarizing Our Current Understanding of Pediatric Gliomas (see also references therein)

<table>
<thead>
<tr>
<th>Authors Year Title Journal</th>
<th>Topics Covered</th>
<th>PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins VP, Jones DT, Giannini C 2015 Pilocytic astrocytoma: pathology, molecular mechanisms and markers</td>
<td>Acta Neuropathologica Molecular alterations in pilocytic astrocytoma; diagnosis/histology and therapeutic implications</td>
<td>25792358</td>
</tr>
<tr>
<td>Northcott PA, Pfister SM, Jones DT 2015 Next-generation (epi) genetic drivers of childhood brain tumours and the outlook for targeted therapies</td>
<td>Lancet Oncology Key findings of the next-generation sequencing era and their therapeutic translation</td>
<td>26065614</td>
</tr>
<tr>
<td>Baker SJ, Ellison DW, Gutmann DH 2016 Pediatric gliomas as neurodevelopmental disorders</td>
<td>Glia Cellular and molecular etiologies of LGG and HGG; developmental neurobiology</td>
<td>26638183</td>
</tr>
<tr>
<td>Jones C, Baker SJ 2014 Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma</td>
<td>Nature Reviews Cancer Genetic complexity of pediatric HGG; driver mutations; chromatin regulation; active pathways</td>
<td>25230881</td>
</tr>
<tr>
<td>Vanan MI, Eisenstat DD 2015 DIPG in Children - What can we learn from the past?</td>
<td>Frontiers in Oncology Clinical features and biopsy of DIPG; diagnostic and therapeutic implications; current and future treatment strategies</td>
<td>26557503</td>
</tr>
<tr>
<td>Jones C, Karajannis MA, Jones DT, et al 2017 Pediatric high-grade glioma: Biologically and clinically in need of new thinking</td>
<td>Neuro-oncology Current understanding of pediatric HGG; approaches for innovative clinical management</td>
<td>27282398</td>
</tr>
</tbody>
</table>

Abbreviations: DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; LGG, low-grade glioma.

Disclosures provided by the authors are available with this article at jco.org.
Conception and design: All authors
Financial support: Stefan M. Pfister
Collection and assembly of data: Dominik Sturm, David T.W. Jones

REFERENCES


AUTHOR CONTRIBUTIONS

Data analysis and interpretation: Dominik Sturm, David T.W. Jones
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pediatric Gliomas: Current Concepts on Diagnosis, Biology, and Clinical Management

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Dominik Sturm
Patents, Royalties, Other Intellectual Property: PCT/CA2012/050834
Mutations of histone proteins associated with proliferative disorders

David T.W. Jones
Patents, Royalties, Other Intellectual Property: PCT/CA2012/050834
Mutations of histone proteins associated with proliferative disorders

Stefan M. Pfister
Patents, Royalties, Other Intellectual Property: PCT/CA2012/050834
Mutations of histone proteins associated with proliferative disorders