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RESEARCH ARTICLE

microRNAs as Biomarkers and Therapeutic Targets in Pediatric H3K27M-Mutant Diffuse Midline Gliomas

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ABSTRACT: Pediatric diffuse midline gliomas (DMG) with an H3K27M mutation are a highly invasive brain tumor group, and within the CBTRUS subcategory of pediatric high-grade gliomas (pHGGs), they account for approximately 15% of all central nervous system tumors in children and adolescents. These tumors generally have a poor prognosis with 5-year survival rates of less than 20% and limited treatment options. The poor prognosis is due to challenges in early detection, such as vague symptoms and limitations in imaging diagnostic techniques, as well as challenges in treatment options. Due to the location of the tumor, surgical resections are rarely possible, and traditional therapies, including radiation therapy and chemotherapy, are ineffective against DMG, with only palliative care options. This review explores the emerging role of microRNA as a highly promising biomarker in cerebrospinal fluid, through the use of liquid biopsies, a non-invasive tool for diagnosis and monitoring. Moreover, microRNA can be used to regulate oncogene expression through inhibitors such as miRNA sponge or antisense RNA, as well as miRNA mimetics. Continued research into microRNA-based liquid biopsies and targeted therapies may enable advancements for earlier detection and effective, personalized tumor treatment.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, microRNA, H3K27M Diffuse Midline Glioma, Liquid Biopsy.

Introduction

Pediatric high-grade gliomas:

Pediatric high-grade gliomas (pHGGs) are a highly invasive brain tumor group that accounts for approximately 15% of all central nervous system tumors in children and adolescents. These tumors generally have a poor prognosis with 5-year survival rates of less than 20% and limited treatment options.[1,2] Despite advances in clinical technologies and surgical techniques, current diagnostic methods, such as an MRI (magnetic resonance imaging) and surgical biopsies, are still limited. This is due to their invasive nature as well as their ineffectiveness in detecting tumors at a molecular level. Early detection of brain gliomas is critical to improve patient prognosis and overall survival (OS), but these limitations in current diagnostic methods require an alternative. Traditionally, tissue samples through a biopsy or surgical resection were used to identify molecular markers; however, in recent years, new methods have surfaced in which bodily fluids can be used. Known as a "liquid biopsy", this refers to a non-invasive method to analyze the tumor using cerebrospinal fluid (CSF), blood, or urine. This method is becoming increasingly popular, especially for CNS (central nervous system) cancer patients. This may include patients with midline gliomas in the brainstem, in which tissue biopsies carry a high risk of post-surgical morbidity due to their location.[3,4] Circulating microRNA can be used as biomarkers for specific CNS tumors as they are released in these body fluids, allowing detection by liquid biopsies.[5,6] Through the use of liquid biopsies, biomarkers can be detected in the body fluids of glioma patients without requiring invasive procedures, serving as biomarkers for the early detection of the disease.[7] The main objective of early detection is to find substantial cancer or precancerous abnormalities at the earliest possible time, when action might improve survival chances or lessen sickness. Early cancer identification can lessen the severity of the disease and increase survival rates.[8]

While many existing research papers on miRNA in pediatric brain tumors focus on their biological roles in regulation patterns, this paper adopts a separate approach in highlighting the most recent advances for miRNA potential in diagnosis and targeted therapy. This review draws attention to how these small non-coding RNAs are being explored as biomarkers in minimally invasive liquid biopsies. It encompasses novel therapeutic approaches, including antisense RNA, microRNA sponges, and microRNA mimetics.

Moreover, this paper aims to delineate a lesser-known subtype of pediatric high-grade glioma, specifically H3K27M mutant gliomas. This particularly aggressive subtype of diffuse midline gliomas has a poor prognosis, due to their resistance to conventional treatments and their invasive nature to other surrounding tissue. This review emphasizes recent studies investigating the potential of miRNA to offer tumor-specific biomarkers and therapeutic targets for more effective and precise clinical interventions for this devastating subtype of glioma.

Epidemiology:

The 2022 CBTRUS (Central Brain Tumor Registry of the United States) Statistical Report provides comprehensive data on the incidence and prevalence of primary malignant and non-malignant brain and other CNS tumors in children and young adults in the U.S. from 2017 to 2021. The overall incidence for malignant tumors was 3.55 per 100,000, and only

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2.67 for non-malignant tumors. The incidence rate was higher for females (6.35) compared to males (6.11), and higher in non-Hispanics (6.52) compared to Hispanics (5.33). Also, from the data, higher-income countries, especially the U.S. and Canada, have the highest average annual incidence.[9] Figure 1 below shows the countries with the highest incidence of malignant CNS tumors.

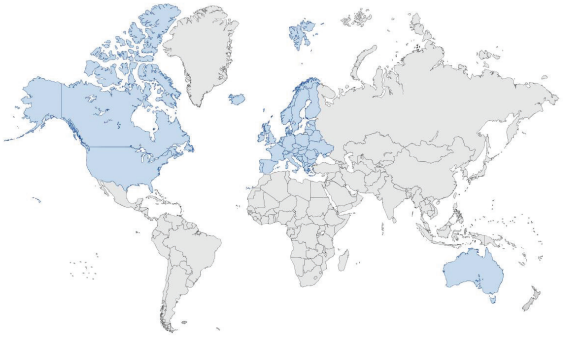

Figure 1: Countries with the highest incidence rates of the most malignant CNS tumors. Overall, the highest incidences of most malignant brain and other CNS tumors have been found in Europe, Canada, the United States, and Australia. The highest childhood brain tumor (CBT) incidences were found in North America and the lowest in Africa.[10,11]

Additionally, previous studies found higher childhood brain tumor incidence in high-income countries (HICs) compared to low-middle income countries (LMICs), with significantly increasing incidence rates with increasing GDP per capita. However, due to varying study and reporting methods, direct comparisons between countries may be challenging. While HICs usually have a wealth of data, including CBT prevalence and management advancements, LMICs have a significant scarcity of data due to limitations in the poor healthcare systems of cancer diagnosis and reporting.[12] Subsequently, low-income regions may lack quality research on pediatric brain tumors, leading to incomplete data. Also, according to the WHO (World Health Organization), only 15-45% of pediatric cancer patients in LMICs receive optimal care that leads to a cure, in comparison to 80% in developed HICs. This may be due to the scarce, unequally distributed number of neurosurgeons, as surgery is usually the primary treatment for CBTs. This means there may be incidence disparities that are a result of misinformation bias rather than genuine differences in risk factor exposure. Further research is required to comprehensively describe CBT epidemiology and explain study findings.[11]

Types of pHGGs:

Pediatric high-grade gliomas are the primary brain tumor group that has caused fatalities during childhood.[13] The 2021 WHO Classification (fifth version) recognizes the subtypes of pediatric-type diffuse gliomas, both high-grade and low-grade. The pediatric-type diffuse high-grade gliomas (expected to be aggressive) are subdivided into four different categories: diffuse midline glioma H3K27-altered, diffuse hemispheric glioma H3 G34-mutant, diffuse pediatric-type high-grade glioma H3-wildtype and IDH-wildtype, and finally the infant-type hemispheric glioma.[14, 15] These subcategories are novel, excluding the first type, diffuse midline glioma H3K27-altered, which has been revised and renamed in the latest WHO classification of CNS tumors.[16] "Diffuse midline glioma (DMG)" replaced the previous "diffuse intrinsic pontine glioma (DIPG)" to highlight the fact that these lesions are not solely centered in the pons, but may also originate in other midline structures. These structures include the thalami, gangliocapsular region, cerebrum, spinal cord, and various others.[17]

In this review, we will be focusing on the diffuse midline glioma H3K27-altered.

Diffuse midline glioma (DMG), previously known as diffuse intrinsic pontine gliomas (DIPG) is a rare, high-grade malignant brain stem tumor, that commonly occurs between ages of 5 and 10 years.[17, 18] They account for around 75% of brain stem tumors in children and current prognosis for DMGs remain poor, with a median survival rate of less than one year post-diagnosis.[9,18] The delicate location of DMGs as well as their highly aggressive nature, tending to infiltrate any surrounding brain tissue, eliminates surgical removal as a treatment option. [17,19] Additionally, DMGs seem to be inherently resistant to conventional therapy treatments for other types of brain tumors, including chemotherapy and radiation therapy.[19, 20] Contrasting with adult gliomas, DMGs are uniquely dependent on the H3K27M mutation for their initiation and maintenance.[21]

Clinical Presentation and Diagnosis:

A heterozygous point mutation of the histone H3, H3K27M mutation, is a genetic biomarker in patients with suspected DIPG who have supporting clinical and radiographic findings.[22, 23] Nearly 80% of DMGs have lysine-to-methionine substitutions at position H3K27 encoding H3.3 (H3F3A), and H3.1 (HIST1H3B), collectively referred to as the H3K27M mutation.[20, 24, 25] In 2016, the World Health Organization (WHO) classified all gliomas harboring the H3K27M mutant as "Diffuse Midline Glioma H3K27M-mutant". Figure 2 shows a diagram of this H3K27M mutation.

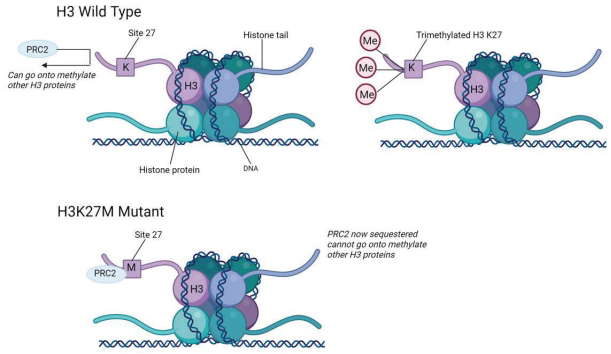

Figure 2: The histone tail of H3K27 can be subject to an H3K27M mutation where lysine (K) is replaced by methionine (M). The mutation causes a loss in H3K27me3 (trimethylation, a repressive mark) and an increase in H3K27 acetylation (an activating mark).[26] Trimethylation is crucial for the silencing of specific gene expressions, which may include tumor suppressors and oncogenes.

This has resulted in research focused on the development of pharmacological inhibitors designed to regulate these epigenetic mechanisms.[20] The loss of the trimethylation by the PRC2

complex is mainly due to the inhibition of the EZH2 (histone methyltransferase enhancer of zeste homolog 2), which is the catalytic subunit of PRC2 (polycomb repressive complex 2).[20,27]

Studies have identified a key functional consequence of the H3K27M mutation, which is mutant protein sequestration of the PRC2 methyltransferase, resulting in functional inactivation of PRC2.[21,28,29] Thus, this leads to a global reduction of H3K27 trimethylation (H3K27me3), which leads to an extensive transcriptional reprogramming of mutant cells and promotes a stem cell-like therapy-resistant phenotype.[21] While the mutation decreases methylation, it also increases acetylation (K27ac) which is necessary for the transcriptional activation of bro- mo- and extraterminal domain (BET) through Poll II (RNA Polymerase II).[21,30] Highly selective BET bromodomain inhibitors, such as JQ1 and I-BET, suppress gene transcription by blocking binding between bromodomain proteins (BRD) and acetylated histones, representing a promising therapeutic strategy for treating DMG.

Signs and Symptoms:

A challenge associated with diagnosis for pHGGs is the nonspecific nature of the presenting symptoms, shown in Figure 3 below.

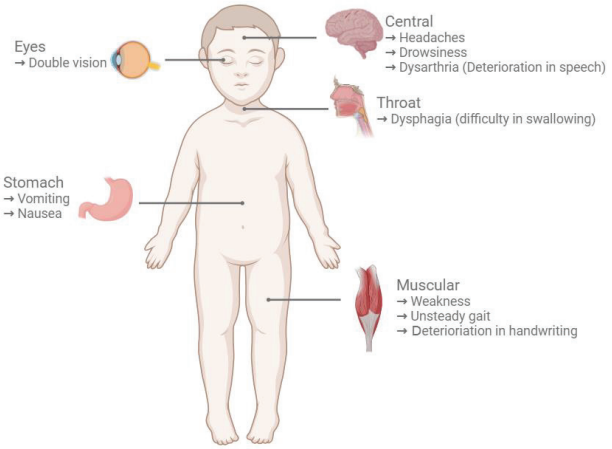

Figure 3: Common presenting symptoms may include headaches, weakness, double vision, drowsiness, and vomiting, which are often attributed to other etiologies and lead to a further delay in diagnosis.[31] For infants and very young children, the onset of symptoms is often delayed due to the elasticity and expandability of their skulls, which allow brain tumors to grow significantly without increased intracranial pressure.[32]

Diagnosis:

The most common imaging methods for pHGG diagnosis include magnetic resonance imaging (MRI) and computed tomography, which is the diagnostic standard. These imaging methods help to identify the location of the brain tumor and guide further interventions such as surgical resection and radiation field planning.[32] According to the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group, there are several differences in the recommended imaging protocol, compared to adult gliomas, for pediatric diffuse high-grade gliomas.[33] Imaging of the different types of pHGGs (excluding infant-type hemispheric glioma) is shown in Figures 4-6 below.

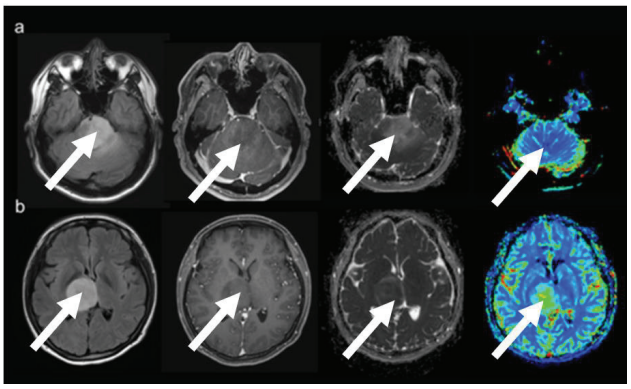

Figure 4: Images of two different patients with diffuse midline glioma, H3 K27-altered. a) 28-year-old male and b) 30-year-old female showing the tumors crossing the midline (image reproduced from Park *et al.*, 2023).[34]

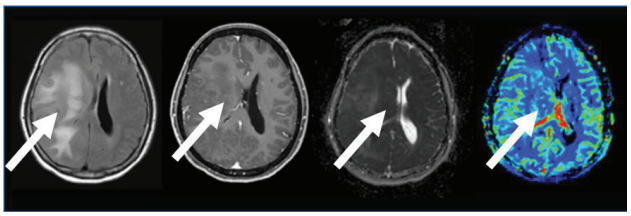

Figure 5: Image of a 54-year-old female with diffuse hemispheric glioma, H3 G34-mutant (image reproduced from Park *et al.*, 2023).[34]

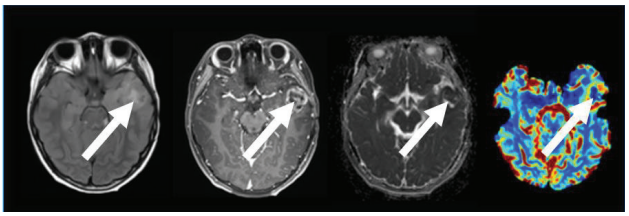

Figure 6: Image of an 8-year-old boy with diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype (image reproduced from Park *et al.*, 2023).[34]

However, there are a few challenges regarding imaging techniques for the diagnosis of pHGGs. Firstly, there are limitations in specificity for tumor characterization. Although the primary features may be identified, there may be an overlap with other brain tumors, which can lead to delayed diagnosis. Also, conventional MRI cannot accurately assess the full extent of tumor infiltration, which can impact surgical planning. Furthermore, the lack of information at a molecular level limits options for personalized treatment approaches.[35]

Current Management (Investigation and treatment):

Standard of care treatment for HGG (high-grade glioma) in children is not as clearly established as it is in adults. The most common treatment modalities for pediatric patients with high-grade gliomas are surgical resection, radiation therapy, occasionally chemotherapy, and targeted therapies. Below will cover these four treatments in detail.

Surgical Resection:

For pHGG patients, surgical resection is often the initial treatment strategy. Gross total resection (GTR) is attempted when feasible, with studies by Hatoum *et al.* showing that GTR is associated with improved prognosis compared to subtotal resection or biopsy, especially in patients with hemi-

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spheric and infratentorial tumors.[36] This is typically followed by adjuvant radiotherapy, with exceptions made for infants and younger children due to neuro-developmental toxicity concerns.[37] However, tumor resection has some important limitations. These tumors are highly infiltrative and therefore invade the surrounding brain tissue beyond the tumor margins visible on neuroimaging. Hence, even with a successful GTR, microscopic disease is present beyond the surgical margins, and surgery alone is not considered curative.[38] Surgical resection is not feasible for most diffuse midline gliomas due to their extremely delicate location, carrying a high risk of post-surgical morbidity.[3] Their highly aggressive nature also means the tumor tends to infiltrate surrounding brain tissue, and is thus not amenable to surgical treatment.[4, 24]

Radiation Therapy:

Radiation therapy (RT) is a standard method against pHGG and generally the only modality, apart from surgical resection, to provide symptom relief and a delay in tumor progression.[39] It has become the mainstay of therapeutic strategies for children above 3 years of age, as younger children are more susceptible to harmful side effects, and they are often treated with chemotherapy alone. For older children, the standard of care therapy has become maximal surgical resection if possible, followed by focal radiotherapy with a margin around the tumor bed, and has remained unchanged for decades.[40] However, this therapy is essentially palliative, and although it can temporarily reduce the symptoms and slow tumor growth, it does not offer a cure against pHGG.[41] Also, as with most therapy methods, the cancer cells often acquire resistance mechanisms that stimulate regrowth after treatment or permit survival, limiting radiation therapy efficacy.[39]

In 2024, Williamson *et al.* conducted a study including a total of 498 pHGG patients to evaluate the impact of radiation therapy on outcomes using the National Cancer Database (NCDB). They found there were no benefits to early RT timing when RT is initiated within 90 days of diagnosis or a higher RT dose in their dataset.[42]

Chemotherapy:

Chemotherapy was first introduced as a therapeutic method against pHGGs in the 1970s. Several anti-tumor agents have shown effectiveness in various malignancies; however, they have not proven effective in treating pediatric brain tumors. This is due to the presence of the blood–brain barrier (BBB), which plays an important role in maintaining suboptimal concentrations of anti-cancer drugs in the CNS. Ongoing research focuses on adjusting the BBB to reach clinically effective drug levels in the CNS. However, scientists still have limited knowledge of the interaction of exogenous chemical agents with the BBB. Hence, they are unable to provide a comprehensive explanation for the ineffectiveness of established anti-cancer drugs in pediatric brain tumors.[43] Also, despite many past clinical trials, DIPG has mainly never been shown to respond to chemotherapy.[40]

However, chemotherapy causes potentially significant adverse effects such as post-treatment pancytopenia, encephalopathy, ataxia, and motor weakness, among many other undesirable effects.[44]

Additionally, palliative chemotherapy is given to patients when cancers have metastasized, and general therapeutic methods are not working to reduce the high symptom burden and their impaired quality of life (QoL). Palliative interventions can address symptoms including seizures, headaches, depression, and treatment-induced toxicity. Caregivers and families report disproportionately high supportive care needs, differing from other systemic cancers.[43]

Targeted Therapy:

With increasing numbers of pediatric cancer survivors, the long-term complications, such as relapse of cancers at a later stage or during adulthood, of standard therapies, including radiation and chemotherapy, are becoming increasingly apparent. Therefore, in recent years, efforts have been directed toward the use of precision medicine in developing new and innovative treatments.[46]

For pHGGs, targeted therapies are able to be used to target specific oncoproteins that are overexpressed in the tumor to reduce their effects.

Below is Table 1, showing different ongoing, completed, and terminated clinical trials based on specific molecular targets, assessing various drugs for pediatric brain tumors.

Table 1: Table of various clinical trials. Many of these clinical trials are in Phase I or II with unpublished results, indicating they are still in the preliminary stages of estimating the safety of the drug for pediatric patients. Pediatric patients behave differently regarding drug use because many of these young patients cannot tolerate the toxicity at the dose that would work for adults, because their organs are still immature. At this stage of assessing the safety of the drugs, the balance between the toxicity levels and clinical benefit for patients must be considered.

Drug on trial, NCT #	Phase	Cohort	Trial Objective	Results
Gemcitabine, NCT02992015	1	Pediatric DIPG	Determine the presence of gemcitabine in childhood DIPG tissue after systemic treatment with the drug and quantify the intertumoral gemcitabine concentration.	All patients experienced a reduction of tumor-related symptoms. Gemcitabine up to 200mg/m^2/once weekly, added to radiotherapy, is safe and well tolerated in pediatric DIPG.
Pomalidomide, NCT03257631	2	pediatric recurrent or progressive primary brain tumors in 1 of 4 primary brain tumor types: HGG, medulloblastoma. ependymoma and DIPG	Assess efficacy, safety, and tolerability of pomalidomide	Treatment with POM monotherapy did not meet the primary measure of success in any cohort. Future studies are needed to evaluate if POM would show efficacy in tumors with specific molecular signatures or in combination with other anti-cancer agents.
Dordaviprone (ONC201), NCT05580562	3	H3 K27M-mutant diffuse glioma and have completed standard frontline radiotherapy	Assess overall survival with ONC201 treatment following frontline radiotherapy	Estimated study completion: 2026-08
Nivolumab, NCT02960230	1/2	pediatric DIPG or other midline gliomas with H3.3K27M	Assess safety and immune activity of a synthetic peptide vaccine specific for the H3.3K27M epitope given in combination with poly-ICLC and the H3.3K27M epitope given in combination with poly-ICLC and the PD-1 inhibitor, nivolumab.	Administration of the H3.3K27M-specific vaccine was well tolerated. Patients with H3.3K27M-specific CD-8 + immunological responses demonstrated prolonged OS compared with non-responders. However, the outcome of the vaccine used requires/relies on a strong immune response to demonstrate proper therapeutic benefit.
Lorlatinib + BABYPOG/HIT-SKK, NCT06333899	1	pHGG with ALK or ROS1 fusion	Response of loratinib - target genes ALK, TRK receptors	Estimated study completion: 2035-06
ACT001, NCT06838676	2	DIPG and H3K27-altered HGG	Investigate the safety and efficacy of ACT001	Estimated study completion: 2035-07

Berubicin, NCT06838676	1	progressive, refractory, or recurrent pHGG who have completed at least 1 standard line of therapy	Examine safety, tolerability, and PK of Berubicin and estimate its MTD and/or RP2D	No results published
BXQ-350, NCT04771897	1	pediatric DIPG or DMG	Evaluate the safety of BXQ-350 and determine MTD	BXQ-350 was well-tolerated; MTD was not established. Safety profile warranted the investigation of combination studies at the highest dose tested (3.2 mg/kg)
Atovaquone, NCT06624371	1	pHGG/DMG/DIPG	Assess the safety and tolerability of atovaquone in combination with RT	Estimated study completion: 2027-10
GDC-0084, NCT03696355	1	pediatric DIPG or other diffuse midline H3K27M-mutant gliomas	Examine the safety, tolerability, and pharmacokinetics of GDC-0084 and estimate MTD	MTD of 27mg/m^2 has been reported
NEO100, NCT06357377	1	pediatric diffuse HGG	Safety, dosing, and delivery of NEO100	Estimated study completion: 2025-10
rHSC-DIPGVax in combination with BALSTILIMAB and ZALIFRELIMAB, NCT04943848	1	DIPG and DMG	Evaluate the safety and tolerability of rHSC-DIPGVax in combination with BALSTILIMAB and ZALIFRELIMAB.	Estimated study completion: 2025-12
Selinexor, NCT05099003	1/2	pediatric DIPG or pHGG with H3K27M mutation	Test safety, side effects, and the best dose of selinexor given in combination with RT	Estimated study completion: 2027
Abemaciclib, NCT02644460	1	Pediatric relapsed or refractory, or progressive DIPG	Evaluate doses of abemaciclib	The pediatric MTD of abemaciclib was 130 mg/m^2/dose administered orally twice daily on a 28-day cycle. Abemaciclib was well-tolerated with mainly hematologic toxicity. PK and PD will be used to further inform if 130 mg/m^2/dose is the pediatric recommended phase 2 dose.
Indoximod, NCT04049669	2	age 3 to 21 years who have progressive brain cancer (glioblastoma, medulloblastoma, or ependymoma) or DIPG	Test indoximod-based combination chemo-radio-rimmunotherapy for treatment	Estimated study completion: 2027-10
Vorinostat and Temsirolimus, NCT02420613	1	pediatric DIPG	Studies the side effects and best dose of temsirolimus when given together with vorinostat, with or without RT	No results published

Among the promising trials, Dordaviprone (ONC201) is in Phase III clinical trials for newly diagnosed patients with H3 K27M-mutant diffuse glioma and has passed safety evaluations. It is being administered to adult and pediatric patients to assess overall survival (OS) compared to conventional therapy. ONC201, an orally administered small molecule drug, antagonizes the overexpressed dopamine receptor D2 (DRD2) in some tumors and activates ClpP to disrupt energy production, reducing tumor growth. This international trial aims to improve OS following radiotherapy and support regulatory approval globally if effective. This international clinical trial will determine whether ONC201 can improve OS following radiotherapy. If proven effective treatment for this brain glioma type, it intends to support regulatory approval in multiple countries.[47]

Results and Discussion

Liquid biopsy:

In recent years, liquid biopsies have emerged as a potential non-invasive tool for the detection of cancerous tumors in the brain. This is of great clinical need as currently, glioma diagnosis relies on biopsy of tumor tissue and thus, surgical intervention. Studies have shown that gene information for tumors can be detected from the patients' blood, and since then has become the standard liquid biopsy specimen for various types of tumors. However, CSF can circulate in the ventricles and cisterns of the spinal cord and carry tumor metabolites and exfoliated tumor cells, making CSF the ideal sample for CNS tumor liquid biopsies.[48] CSF is mostly collected through lumbar puncture or surgery around the brain area. Currently, liquid biopsy techniques include Enzyme-linked Immunosorbent Assay (ELISA), Polymerase Chain Reaction (PCR), and Next-Generation Sequencing (NGS) for the detection of potential CSF biomarkers.[49] Furthermore, the development of liquid biopsies may be most beneficial for DMG patients, as DMG is resistant to standard cancer therapies, and surgical intervention is not yet accepted.[24] The ability to diagnose patients and assess their response to therapy treatments in a non-invasive manner would become an important clinical advancement in the management of this patient population. Liquid biopsies have been found to confirm diagnosis, identify the presence of the histone H3K27M mutation, and assess response to therapy for pediatric DMG patients.[50] However, despite this, many studies showcase differences in the collection and storage process, making it difficult to make comparisons, particularly as many studies use small patient cohorts.

microRNA:

MicroRNAs (miRNAs) are a type of small, single-stranded non-coding RNA with a length of 19-25 nucleotides, which can be released and detected in biological fluids such as plasma or CSF.[5,6] Recent studies have demonstrated that miRNAs play an important role in posttranscriptional gene regulation.[51] Their main function is to regulate gene expression through silencing or contributing to the degradation of messenger RNA (mRNA).[52] miRNA, which travel outside the cells and enter bodily fluids, are known as circulating miRNAs. This indicates that circulating miRNA is a potential tumor biomarker as well as an important therapeutic target. Below is Figure 7 showing the process of miRNA biogenesis.

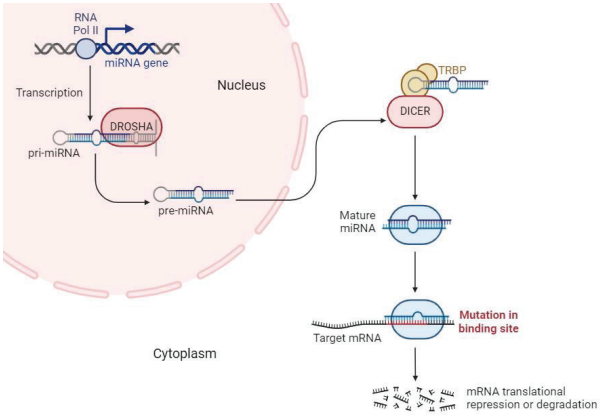

Figure 7: The biogenesis of the miRNA gene begins in the nucleus and finishes in the cytoplasm. First, the RNA Polymerase II enzymes (Pol II) transcribe the miRNA, forming a primary miRNA (pri-miRNA) with one or more hairpin structures.[53] Within the nucleus, the pri-miRNA is then processed by DROSHA, an enzyme that cuts off the redundant tails to then become 70 to 100 nucleotide pre-miRNAs. Furthermore, DICER, another enzyme, dices the pre-miRNA to double-stranded RNA in the cytoplasm, which makes a complementary sequence with the miRNA strand.[54] The now mature miRNA latches onto the mRNA (messenger RNA), and translational repression or degradation can now occur.[52]

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Why is microRNA promising?:

In recent years, microRNAs have emerged as a highly promising class of potential non-invasive biomarkers for early diagnosis and treatment monitoring of brain gliomas, including pHGGs, to indicate tumor presence and progression. Scientists have found that not only is miRNA abundant in tissues, but traces of circulating miRNAs exist in biological fluids.[55,56] Circulating miRNAs are promising biomarkers with beneficial clinical information regarding diagnosis, prognosis, and response to treatment. They originated from difficulties in the diagnosis and monitoring of gliomas without invasive biopsies, as they can be achieved through liquid biopsy analysis, which may replace traditional invasive brain biopsies for diagnosis. This allows for repeatable biopsies for monitoring the progression of the tumor. According to a study by Kopkova *et al.*, these miRNA biomarkers in CSF seem to be a stable and resistant source in even extreme conditions. This allows their possible use to support imaging for CNS tumor diagnosis and monitoring treatment instead of invasive surgical procedures.[56]

Although blood or urine are the most common liquid biopsies for other tumors, due to the BBB, many systemic biomarkers cannot be used for brain gliomas. However, miRNAs have been detected in CSF. CSF is a bodily fluid that is in direct contact with the entire extracellular environment of the CNS, making it an ideal source of CNS disease diagnostic markers, including brain tumors, shown in Figure 8 below.[56,57]

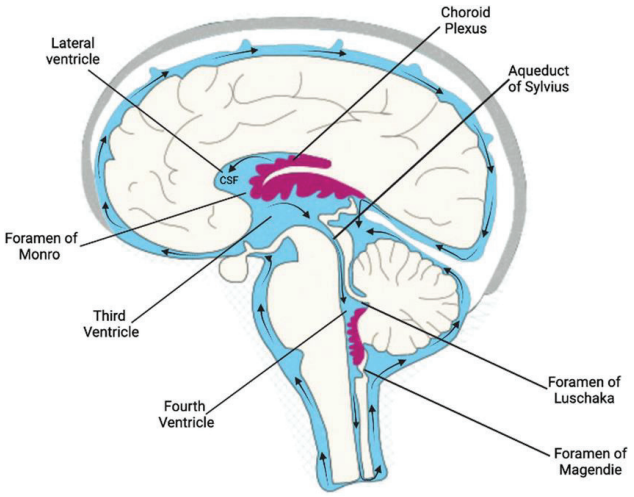

Figure 8: Throughout its circulation pathway, the cerebrospinal fluid is in direct contact with the entire extracellular environment of the central nervous system.[56] Thus, for brain tumors, including DMG, circulating microRNA is released in the CSF and can be extracted for diagnostic testing.

Shi *et al.* compared *miR-21* levels in CSF, blood serum, and exosomes from recurrent glioma patients. While the blood serum-derived exosomal *miR-21* levels did not differ from the control group, the miRNA levels in the CSF significantly increased in the glioma patients, reflecting tumor presence and spinal/ventricle metastasis. Thus, authors suggest that this miRNA may serve as a potential diagnostic and prognostic biomarker for brain gliomas.[58]

A study by Kopkova *et al.* identified specific miRNA signatures for a range of brain tumor types through performing miRNA profiling. qRT-PCR (Quantitative Reverse Transcription Polymerase Chain Reaction) was then used to validate 9 of the candidate miRNAs, successfully resulting in various combination patterns of *miR-30e*, *miR-140*, *miR-10a*, and *miR-21-3p*.[56]

Through the use of the NanoString nCounter assay, a hybridization-based technology enabling direct measurement of the miRNAs, Drusco *et al.* conducted research that suggests that CSF levels of *miR-125b*, *miR-223*, *miR-451*, *miR-711*, and *miR-935* might be efficient diagnostic biomarkers for various CNS malignancies. These include glioblastoma, medulloblastoma, lung metastasis, breast metastasis, and primary CNS lymphoma.[59]

However, microRNA biomarkers in CSF have some limitations. This includes the small sample sizes in current studies, and must be tested on a larger scale to be able to be given out to the public. Moreover, although recent studies have shown the presence of circulating miRNAs in CSF, researchers are facing difficulties in detecting the miRNAs in CSF due to technological difficulties and a lack of standardization. Another important consideration is the biological specificity, as miRNAs are not always tumor-specific, and other processes can alter miRNA expression profiles, which raises concern regarding the accuracy of results and diagnosis.

microRNAs can be used as potential therapeutic targets through specific inhibitors (miRNA sponge and antisense siRNA) or mimetics (increase beneficial miRNA through synthetic oligonucleotides), as shown in Figure 9 below.

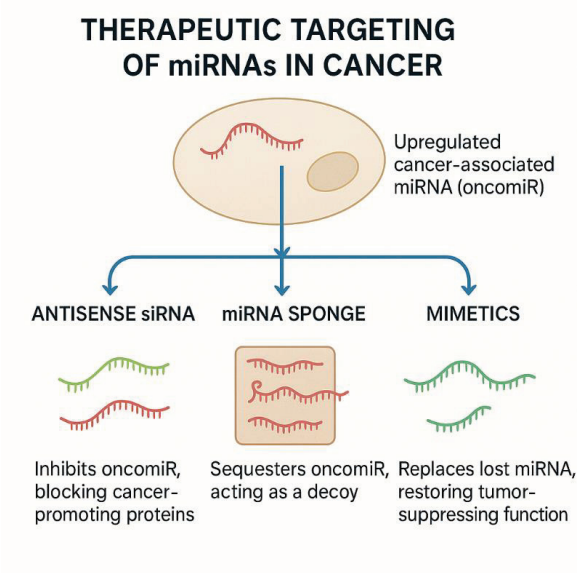

Figure 9: The three main types of miRNA therapeutic targeting strategies include the use of miRNA sponges, antisense siRNA, and miRNA mimetics. These approaches aim to rebalance gene regulation by targeting and blocking oncogenic miRNAs or restoring beneficial miRNAs that suppress the tumor in order to slow tumor growth.

Currently, there are many available delivery vectors of miRNA for the regulation of gene expression to allow access to these therapeutic targets. The two main areas of delivery vectors are viral and non-viral. Viral vectors, for example, lentiviruses, offer high transfection efficiency, whereas non-viral vectors, including lipid and polymer nanoparticles, may have lower transfection efficiency. However, non-viral vectors are

generally safer than viral vectors and are less immunogenic. These methods are outlined in Figure 10 below.

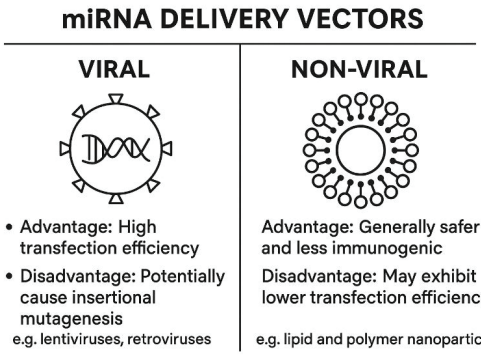

Figure 10: miRNA delivery vectors transport the miRNA into their target cells to allow for regulation of gene expression. Viral vectors generally achieve high transfection efficiency, while non-viral vectors tend to have improved safety profiles for the patient.

Despite advances in delivery techniques, transport of miRNA-based therapies in an effective manner across the BBB continues to be a challenge, with both viral and non-viral vectors causing a trade-off between efficacy and safety for the patient.

miRNA Sponge:

When a miRNA is too active and is causing cancer cells to proliferate, miRNA sponges are used to trap the miRNA. A current example is *miR-10b*. It is typically upregulated in high-grade gliomas as well as other cancers and commonly targets CDKN2A, a crucial cell-cycle regulator responsible for halting cell division when abnormalities are detected. By suppressing CDKN2A, *miR-10b* weakens checkpoint controls, allowing cancer cells to continue dividing. By using this miRNA "anti-*miR-10b* sponge", it acts as a decoy and blocks the oncogenic miRNA, allowing the tumor-suppressing genes to function again, and the tumor growth slows down, and the cancer stops spreading. However, currently, challenges include the delivery of the drug to the brain across the BBB.[60, 61]

Antisense and siRNA:

Antisense RNA and siRNA act as gene silencers to stop cancer-promoting proteins from being made. Antisense RNA, or antisense oligonucleotides, bind to a specific mRNA and block the mRNA from being read by ribosomes, to prevent harmful protein production. For instance, antisense RNA can be synthetically created against *miR-10b*, stopping it from silencing tumor suppressor genes. siRNA (small interfering RNA) binds to a matching mRNA sequence and causes mRNA degradation (permanently silences an overactive oncogene).[60]

A clinical trial for autologous cell immunotherapy (IGV-001) with IGF-2R antisense oligonucleotide (NCT04485949) is currently undergoing assessment of progression-free survival and overall survival in newly diagnosed glioblastoma patients. It has already passed Phase 1 of the trial, demonstrating that IGV-001 is safe in patients with astrocytoma and glioblastoma, and is currently in Phase 2.[62]

miRNA Mimetics:

On the other hand, mimetics can be used as lab replacements for beneficial miRNA that the body is missing. miRNA mimics are synthetic oligonucleotides that can replace the tumor-suppressing function of miRNAs. miRNA *let-7* is a tumor suppressor that is downregulated in certain gliomas. When *let-7* levels are significantly reduced or lost, its inhibitory influence on multiple oncogenes is removed, and these cancer cells proliferate, tilting the balance towards aggressive tumor growth and survival. Scientists inject *let-7* mimics into tumors, which allows replacement of the lost tumor-suppressing miRNAs, and subsequently slows tumor growth, and makes the cancer less aggressive.[60]

Therefore, through these therapeutic strategies of restoring miRNA *let-7* levels or inhibiting *miR-10b*, normal regulation of oncogenes and cell-cycle checkpoints may be able to be restored. Future research can focus on developing specific inhibitors (via miRNA sponge or antisense siRNA) or mimetics (increase miRNA via synthetic oligonucleotides) that modulate these miRNAs for clinical benefit.

Currently, miRNA mimetics have shown signs of success in other conditions such as pleural mesothelioma. In a study by van Zandwijk *et al.* in 2017, they investigated a drug loaded with miR-16-based mimic miRNA to target the unsuppressed tumor growth in adults with a confirmed diagnosis of malignant pleural mesothelioma. The results of suppressing the tumor were successful, and the maximum tolerated dosage amounts were found.

For brain-related tumors, future research of miRNA-based medicine should target the improvement of delivery systems to cross the BBB, minimize off-target effects to avoid unintended gene silencing, and the development of personalized miRNA therapies based on individual tumor profiles (therapeutic potential: exploiting RNA sponges could be a precision oncology strategy, provided we validate their safety, specificity, and efficacy in clinical models).

Conclusion

This review highlights the highly promising potential of microRNAs as both biomarkers for diagnosis and therapeutic targets for pediatric H3K27M-mutant diffuse midline gliomas. Within the 2022 CBTRUS Statistical Report Subcategory Pediatric High-Grade Glioma, they account for approximately 15% of all pediatric CNS tumors, and have an extremely poor prognosis worldwide, with overall survival of 5-year survival rates less than 20%.[2,13,17] This is due to the poor early detection methods and limited treatment options. Early detection is a crucial aspect to improve the overall survival of particularly aggressive cancers like DMG; however, currently it is limited by the vagueness of the presenting symptoms, leading to further diagnosis delay and the unreliability of detection through imaging techniques.[31] In specific tumor characterization, there may be limitations in distinguishing between various brain gliomas, as the extent of the tumor infiltration is often not accurately displayed.[35] The current treatment options are also extremely limited, as DMG has been found to be resistant and ineffec-

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tive against traditional therapies, including chemotherapy and radiotherapy, possibly because of the challenges regarding the blood-brain barrier.[40,43] The tumor's delicate location and highly aggressive nature, infiltrating surrounding brain tissue, also eliminates surgical resection as an option.[4,24] Targeted therapies are the most promising option, as they are able to target specific overexpressed oncoproteins. Among the promising trials, Dordaviprone (ONC201) is a drug currently in Phase III and has so far had successful results for H3 K27M-mutant diffuse glioma patients. It is now assessing overall survival compared to conventional therapies.[47] Although ONC201 is showing promise, many of the clinical trials for targeted therapies are in the early stages, still estimating the safety of the drug, and have limited results.

Therefore, an alternative for both early detection and treatment is required. microRNA biomarkers from a liquid biopsy offer significant promise for both. It is a non-invasive method of treatment, only requiring body fluid that has traces of the tumor information. The minimally invasive nature of a liquid biopsy ensures the process can be repeated to track the molecular changes in the tumor through analyzing the circulating microRNAs in the CSF. microRNA has also been found to be a stable source in cerebrospinal fluid, which is easily accessible through the lumbar puncture.[56] This accessibility allows miRNA analysis using CSF to be practical for clinical monitoring protocol integration. The CSF can be analyzed at a molecular level as it bathes the entire central nervous system, and due to this direct contact, early detection and detection of minimal residual disease becomes feasible.[56,57] It will help identify a relapse of the brain tumor before any symptoms emerge. Other body fluids, such as serum and urine, are also being explored but are less promising as they are not in direct contact with the CNS and may contain lower concentrations of the tumor-specific microRNA. MicroRNA also has significant potential as a therapeutic target by regulating gene expression of the oncoproteins post-transcriptionally through inhibitors such as miRNA sponge or antisense RNA and siRNA, as well as miRNA mimetics, which can act as lab replacements for the beneficial tumor-suppressing miRNA that the body is missing.[41,61] However, successful clinical translation will depend on the effectiveness of delivery techniques of the miRNA across the BBB and improvements in minimizing off-target effects. Antisense oligonucleotides are particularly promising, with a clinical trial (NCT04485949) in Phase II, undergoing assessment for progression-free survival and overall survival in glioblastoma patients (also classified as a high-grade glioma).[62]

However, the limitation of this review is the current lack of extensive clinical studies for the use of microRNA as biomarkers or therapeutic targets. With clinical and technological advancements from the growing interest in microRNAs, further exploration of miRNA-based approaches may lead to discoveries for improving the overall survival of pediatric DMG patients. Looking into the future, I believe DMG research will become increasingly focused on non-invasive methods, including liquid biopsies using cerebrospinal fluid, due to its direct contact with the brain. This will allow for earlier detection and diagnosis through biomarkers like microRNA, which offer viable solutions to address the challenges regarding early detection as well as targeted treatment, in a less invasive manner.

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References

1. Ostrom, Q. T., Cioffi, G., Gittleman, H., Patil, N., Waite, K., Kruchko, C., & Barnholtz-Sloan, J. S. (2019). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. *Neuro-Oncology, 21*(Supplement_5), v1–v100. https://doi.org/10.1093/neuonc/noz150
2. Szychot, E., Giraud, G., Hargrave, D., van Vuurden, D., Grill, J., Biassoni, V., Massimino, M., von Bueren, A. O., Kebudi, R., Gilda-Costa, M. J., van Zanten, S. V., Bailey, S., Karremann, M., Bolle, S., Ajithkumar, T., Krause, M., Lassen-Ramshad, Y., Janssens, G., Morana, G., … Kramm, C. M. (2025). European standard clinical practice recommendations for pediatric high-grade gliomas. *EJC Pediatric Oncology, 5*, 100210. https://doi.org/10.1016/j.ejcped.2024.100210
3. Bounajem, M. T., Karsy, M., & Jensen, R. L. (2020). *Liquid biopsies for the diagnosis and surveillance of primary pediatric central nervous system tumors: A review for practicing neurosurgeons*. https://doi.org/10.3171/2019.9.FOCUS19712
4. Greuter, L., Frank, N., Guzman, R., & Soleman, J. (2022). The Clinical Applications of Liquid Biopsies in Pediatric Brain Tumors: A Systematic Literature Review. *Cancers, 14*(11), Article 11. https://doi.org/10.3390/cancers14112683
5. Petrescu, G. E. D., Sabo, A. A., Torsin, L. I., Calin, G. A., & Dragomir, M. P. (2019). MicroRNA-based theranostics for brain cancer: Basic principles. *Journal of Experimental & Clinical Cancer Research, 38*(1), 231. https://doi.org/10.1186/s13046-019-1180-5
6. Preethi, K. A., Selvakumar, S. C., Ross, K., Jayaraman, S., Tusubira, D., & Sekar, D. (2022). Liquid biopsy: Exosomal microRNAs as novel diagnostic and prognostic biomarkers in cancer. *Molecular Cancer, 21*(1), 54. https://doi.org/10.1186/s12943-022-01525-9
7. Malhotra, S., Miras, M. C. M., Pappolla, A., Montalban, X., & Comabella, M. (2023). Liquid Biopsy in Neurological Diseases. *Cells, 12*(14), Article 14. https://doi.org/10.3390/cells12141911
8. Prasanth, B. K., Alkhowaiter, S., Sawarkar, G., Dharshini, B. D., & R. Baskaran, A. (2023). Unlocking Early Cancer Detection: Exploring Biomarkers, Circulating DNA, and Innovative Technological Approaches. *Cureus, 15*(12), e51090. https://doi.org/10.7759/cureus.51090
9. Ostrom, Q. T., Price, M., Ryan, K., Edelson, J., Neff, C., Cioffi, G., Waite, K. A., Kruchko, C., & Barnholtz-Sloan, J. S. (2022). CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018. *Neuro-Oncology, 24*(Suppl 3), iii1. https://doi.org/10.1093/neuonc/noac161
10. Leece, R., Xu, J., Ostrom, Q. T., Chen, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (2017). Global incidence of malignant brain and other central nervous system tumors by histology, 2003–2007. *Neuro-Oncology, 19*(11), 1553. https://doi.org/10.1093/neuonc/nox091
11. Raja, N., Hayes, L., Basta, N., & McNally, R. J. Q. (2021). International trends in the incidence of brain tumors in children and young

adults and their association with indicators of economic development. *Cancer Epidemiology, 74*, 102006. https://doi.org/10.1016/j.canep.2021.102006

12. Wireko, A. A., Patel, H., Mehta, A., Jiffry, R., Adebusoye, F. T., & Miteu, G. D. (2023). Pediatric brain tumors in low- and middle-income countries: Available evidence on recent advancements in management, challenges, and recommendations – editorial. *International Journal of Surgery (London, England), 109*(3), 235–238. https://doi.org/10.1097/JS9
13. Mendez, F. M., Núñez, F. J., Garcia-Fabiani, M. B., Haase, S., Carney, S., Gauss, J. C., Becher, O. J., Lowenstein, P. R., & Castro, M. G. (2020). Epigenetic reprogramming and chromatin accessibility in pediatric diffuse intrinsic pontine gliomas: A neural developmental disease. *Neuro-Oncology, 22*(2), 195–206. https://doi.org/10.1093/neuonc/noz218
14. d'Amati, A., Bargiacchi, L., Rossi, S., Carai, A., Bertero, L., Barresi, V., Errico, M. E., Buccoliero, A. M., Asioli, S., Marucci, G., Del Baldo, G., Mastronuzzi, A., Miele, E., D'Antonio, F., Schiavello, E., Biassoni, V., Massimino, M., Gessi, M., Antonelli, M., & Gianno, F. (2024). Pediatric CNS tumors and 2021 WHO classification: What do oncologists need from pathologists? *Frontiers in Molecular Neuroscience, 17*. https://doi.org/10.3389/fnmol.2024.1268038
15. Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., Ohgaki, H., Wiestler, O. D., Kleihues, P., & Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. *Acta Neuropathologica, 131*(6), 803–820. https://doi.org/10.1007/s00401-016-1545-1
16. Gianno, F., Giovannoni, I., Cafferata, B., Diomedi-Camassei, F., Minasi, S., Barresi, S., Buttarelli, F. R., Alesi, V., Cardoni, A., Antonelli, M., Puggioni, C., Colafati, G. S., Carai, A., Vinci, M., Mastronuzzi, A., Miele, E., Alaggio, R., Giangaspero, F., & Rossi, S. (2022). Pediatric-type diffuse high-grade gliomas in the 5th CNS WHO Classification. *Pathologica, 114*(6), 422–435. https://doi.org/10.32074/1591-951X-830
17. Di Ruscio, V., Del Baldo, G., Fabozzi, F., Vinci, M., Cacchione, A., de Billy, E., Megaro, G., Carai, A., & Mastronuzzi, A. (2022). Pediatric Diffuse Midline Gliomas: An Unfinished Puzzle. *Diagnostics, 12*(9), Article 9. https://doi.org/10.3390/diagnostics12092064
18. Hoffman, L. M., Veldhuijzen van Zanten, S. E. M., Colditz, N., Baugh, J., Chaney, B., Hoffmann, M., Lane, A., Fuller, C., Miles, L., Hawkins, C., Bartels, U., Bouffet, E., Goldman, S., Leary, S., Foreman, N. K., Packer, R., Warren, K. E., Broniscer, A., Kieran, M. W., … Fouladi, M. (2018). Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 36*(19), 1963–1972. https://doi.org/10.1200/JCO.2017.75.9308
19. Buczkowicz, P., Hoeman, C., Rakopoulos, P., Pajovic, S., Letourneau, L., Dzamba, M., Morrison, A., Lewis, P., Bouffet, E., Bartels, U., Zuccaro, J., Agnihotri, S., Ryall, S., Barszczyk, M., Chornenkyy, Y., Bourgey, M., Bourque, G., Montpetit, A., Cordero, F., … Hawkins, C. (2014). Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nature Genetics, 46*(5), 451–456. https://doi.org/10.1038/ng.2936
20. Hayden, E., Holliday, H., Lehmann, R., Khan, A., Tsoli, M., Rayner, B. S., & Ziegler, D. S. (2021). Therapeutic Targets in Diffuse Midline Gliomas—An Emerging Landscape. *Cancers, 13*(24), Article 24. https://doi.org/10.3390/cancers13246251
21. Watanabe, J., Clutter, M. R., Gullette, M. J., Sasaki, T., Uchida, E., Kaur, S., Mo, Y., Abe, K., Ishi, Y., Takata, N., Natsumeda, M., Gadd, S., Zhang, Z., Becher, O. J., & Hashizume, R. (2024). BET bromodomain inhibition potentiates radiosensitivity in models of H3K27-altered diffuse midline glioma. *The Journal of Clinical Investigation, 134*(13), e174794. https://doi.org/10.1172/JCI174794
22. Lu, V. M., Alvi, M. A., McDonald, K. L., & Daniels, D. J. (2018). *Impact of the H3K27M mutation on survival in pediatric high-grade glioma: A systematic review and meta-analysis*. https://doi.org/10.3171/2018.9.PEDS18419
23. Piunti, A., Hashizume, R., Morgan, M. A., Bartom, E. T., Horbinski, C. M., Marshall, S. A., Rendleman, E. J., Ma, Q., Takahashi, Y., Woodfin, A. R., Misharin, A. V., Abshiru, N. A., Lulla, R. R., Saratsis, A. M., Kelleher, N. L., James, C. D., & Shilatifard, A. (2017). Therapeutic targeting of polycomb and BET bromodomain proteins in diffuse intrinsic pontine gliomas. *Nature Medicine, 23*(4), 493–500. https://doi.org/10.1038/nm.4296
24. Buczkowicz, P., & Hawkins, C. (2015). Pathology, Molecular Genetics, and Epigenetics of Diffuse Intrinsic Pontine Glioma. *Frontiers in Oncology, 5*, 147. https://doi.org/10.3389/fonc.2015.00147
25. Dufour, C., Perbet, R., Leblond, P., Vasseur, R., Stechly, L., Pierache, A., Reyns, N., Touzet, G., Le Rhun, E., Vinchon, M., Maurage, C., Escande, F., & Renaud, F. (2020). Identification of prognostic markers in diffuse midline gliomas H3K27M-mutant. *Brain Pathology, 30*(1), 179–190. https://doi.org/10.1111/bpa.12768
26. Leszczynska, K. B., Jayaprakash, C., Kaminska, B., & Mieczkowski, J. (2021). Emerging Advances in Combinatorial Treatments of Epigenetically Altered Pediatric High-Grade H3K27M Gliomas. *Frontiers in Genetics, 12*. https://doi.org/10.3389/fgene.2021.742561
27. Chammas, P., Mocavini, I., & Di Croce, L. (2020). Engaging chromatin: PRC2 structure meets function. *British Journal of Cancer, 122*(3), 315–328. https://doi.org/10.1038/s41416-019-0615-2
28. Fang, D., Gan, H., Cheng, L., Lee, J.-H., Zhou, H., Sarkaria, J. N., Daniels, D. J., & Zhang, Z. (n.d.). H3.3K27M mutant proteins reprogram the epigenome by sequestering the PRC2 complex to poised enhancers. *eLife, 7*, e36696. https://doi.org/10.7554/eLife.36696
29. Funato, K., Major, T., Lewis, P. W., Allis, C. D., & Tabar, V. (2014). Use of human embryonic stem cells to model pediatric gliomas with H3.3K27M histone mutation. *Science (New York, N.Y.), 346*(6216), 1529–1533. https://doi.org/10.1126/science.1253799
30. Herz, H.-M., Morgan, M., Gao, X., Jackson, J., Rickels, R., Swanson, S. K., Florens, L., Washburn, M. P., Eissenberg, J. C., & Shilatifard, A. (2014). Histone H3 lysine-to-methionine mutants as a paradigm to study chromatin signaling. *Science (New York, N.Y.), 345*(6200), 1065–1070. https://doi.org/10.1126/science.1255104
31. Aggarwal, P., Luo, W., Pehlivan, K. C., Hoang, H., Rajappa, P., Cripe, T. P., Cassady, K. A., Lee, D. A., & Cairo, M. S. (2022). Pediatric versus adult high-grade glioma: Immunotherapeutic and genomic considerations. *Frontiers in Immunology, 13*, 1038096. https://doi.org/10.3389/fimmu.2022.1038096
32. El-Ayadi, M., Ansari, M., Sturm, D., Gielen, G. H., Warmuth-Metz, M., Kramm, C. M., & Bueren, A. O. von. (2017). High-grade glioma in very young children: A rare and particular patient population. *Oncotarget, 8*(38), 64564–64578. https://doi.org/10.18632/oncotarget.18478
33. Fangusaro, J., Witt, O., Hernáiz Driever, P., Bag, A. K., de Blank, P., Kadom, N., Kilburn, L., Lober, R. M., Robison, N. J., Fisher, M. J., Packer, R. J., Young Poussaint, T., Papusha, L., Avula, S., Brandes, A. A., Bouffet, E., Bowers, D., Artemov, A., Chintagumpala, M., … Warren, K. E. (2020). Response assessment in pediatric

DOI: 10.36838/IJHSR811.212

low-grade glioma: Recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet. Oncology, 21*(6), e305–e316. https://doi.org/10.1016/S1470-2045(20)30064-4

34. Park, Y. W., Vollmuth, P., Foltyn-Dumitru, M., Sahm, F., Ahn, S. S., Chang, J. H., & Kim, S. H. (2023). The 2021 WHO Classification for Gliomas and Implications on Imaging Diagnosis: Part 2—Summary of Imaging Findings on Pediatric-Type Diffuse High-Grade Gliomas, Pediatric-Type Diffuse Low-Grade Gliomas, and Circumscribed Astrocytic Gliomas. *Journal of Magnetic Resonance Imaging, 58*(3), 690–708. https://doi.org/10.1002/jmri.28740
35. Henssen, D., Meijer, F., Verburg, F. A., & Smits, M. (2023). Challenges and opportunities for advanced neuroimaging of glioblastoma. *British Journal of Radiology, 96*(1141), 20211232. https://doi.org/10.1259/bjr.20211232
36. Hatoum, R., Chen, J.-S., Lavergne, P., Shlobin, N. A., Wang, A., Elkaim, L. M., Dodin, P., Couturier, C. P., Ibrahim, G. M., Fallah, A., Venne, D., Perreault, S., Wang, A. C., Jabado, N., Dudley, R. W. R., & Weil, A. G. (2022). Extent of Tumor Resection and Survival in Pediatric Patients With High-Grade Gliomas: A Systematic Review and Meta-analysis. *JAMA Network Open, 5*(8), e2226551. https://doi.org/10.1001/jamanetworkopen.2022.26551
37. Huynh-Le, M.-P., Walker, A. J., Burger, P. C., Jallo, G. I., Cohen, K. J., Wharam, M. D., & Terezakis, S. A. (2016). Management of pediatric intracranial low-grade gliomas: Long-term follow-up after radiation therapy. *Child's Nervous System, 32*(8), 1425–1430. https://doi.org/10.1007/s00381-016-3100-8
38. Vanan, M. I., & Eisenstat, D. D. (2014). Management of high-grade gliomas in the pediatric patient: Past, present, and future. *Neuro-Oncology Practice, 1*(4), 145–157. https://doi.org/10.1093/nop/npu022
39. Metselaar, D. S., du Chatinier, A., Stuiver, I., Kaspers, G. J. L., & Hulleman, E. (2021). Radiosensitization in Pediatric High-Grade Glioma: Targets, Resistance, and Developments. *Frontiers in Oncology, 11*, 662209. https://doi.org/10.3389/fonc.2021.662209
40. Fangusaro, J. (2012). Pediatric High Grade Glioma: A Review and Update on Tumor Clinical Characteristics and Biology. *Frontiers in Oncology, 2*. https://doi.org/10.3389/fonc.2012.00105
41. Staunton, J., Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia, Children's Cancer Institute, Lowy Cancer Research Centre, UNSW Sydney, Sydney, NSW, Australia, Ziegler, D. S., Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia, Children's Cancer Institute, Lowy Cancer Research Centre, UNSW Sydney, Sydney, NSW, Australia, & School of Clinical Medicine, UNSW Medicine & Health, UNSW Sydney, Sydney, NSW, Australia. (2023). Temozolomide for Pediatric High-Grade Glioma: Time for a Rethink? *Oncology & Haematology, 19*(2), 4. https://doi.org/10.17925/OHR.2023.19.2.4
42. Williamson, C., Williamson, S., Jiang, R., Sudmeier, L., Esiashvili, N., & Eaton, B. R. (2024). The impact of radiation therapy variables on pediatric high-grade glioma outcomes: A National Cancer Database analysis. *Pediatric Blood & Cancer, 71*(1), e30751. https://doi.org/10.1002/pbc.30751
43. Malik, J. R., Podany, A. T., Khan, P., Shaffer, C. L., Siddiqui, J. A., Baranowska-Kortylewicz, J., Le, J., Fletcher, C. V., Ether, S. A., & Avedissian, S. N. (2023). Chemotherapy in pediatric brain tumors and the challenge of the blood–brain barrier. *Cancer Medicine, 12*(23), 21075–21096. https://doi.org/10.1002/cam4.6647
44. Armstrong, C., & Sun, L. R. (2020). Neurological complications of pediatric cancer. *Cancer Metastasis Reviews, 39*(1), 3–23. https://doi.org/10.1007/s10555-020-09847-0
45. Walbert, T., & Stec, N. E. (2023). Chapter 5—Palliative care in brain tumors. In J. M. Miyasaki & B. M. Kluger (Eds.), *Handbook of Clinical Neurology* (Vol. 191, pp. 69–80). Elsevier. https://doi.org/10.1016/B978-0-12-824535-4.00011-2
46. Butler, E., Ludwig, K., Pacenta, H. L., Klesse, L. J., Watt, T. C., & Laetsch, T. W. (2021). Recent progress in the treatment of cancer in children. *CA: A Cancer Journal for Clinicians, 71*(4), 315–332. https://doi.org/10.3322/caac.21665
47. Arrillaga-Romany, I., Lassman, A., McGovern, S. L., Mueller, S., Nabors, B., van den Bent, M., Vogelbaum, M. A., Allen, J. E., Melemed, A. S., Tarapore, R. S., Wen, P. Y., & Cloughesy, T. (2024). ACTION: A randomized phase 3 study of ONC201 (dordaviprone) in patients with newly diagnosed H3 K27M-mutant diffuse glioma. *Neuro-Oncology, 26*(Supplement_2), S173–S181. https://doi.org/10.1093/neuonc/noae031
48. Aili, Y., Maimaitiming, N., Mahemuti, Y., Qin, H., Wang, Y., & Wang, Z. (2020). Liquid biopsy in central nervous system tumors: The potential roles of circulating miRNA and exosomes. *American Journal of Cancer Research, 10*(12), 4134–4150.
49. Xiao, F., Lv, S., Zong, Z., Wu, L., Tang, X., Kuang, W., Zhang, P., Li, X., Fu, J., Xiao, M., Wu, M., Wu, L., Zhu, X., Huang, K., & Guo, H. (2020). Cerebrospinal fluid biomarkers for brain tumor detection: Clinical roles and current progress. *American Journal of Translational Research, 12*(4), 1379–1396.
50. Soffietti, R., Bettegowda, C., Mellinghoff, I. K., Warren, K. E., Ahluwalia, M. S., De Groot, J. F., Galanis, E., Gilbert, M. R., Jaeckle, K. A., Le Rhun, E., Rudà, R., Seoane, J., Thon, N., Umemura, Y., Weller, M., van den Bent, M. J., Vogelbaum, M. A., Chang, S. M., & Wen, P. Y. (2022). Liquid biopsy in gliomas: A RANO review and proposals for clinical applications. *Neuro-Oncology, 24*(6), 855–871. https://doi.org/10.1093/neuonc/noac004
51. Nakamura, K., Sawada, K., Yoshimura, A., Kinose, Y., Nakatsuka, E., & Kimura, T. (2016). Clinical relevance of circulating cell-free microRNAs in ovarian cancer. *Molecular Cancer, 15*(1), 48. https://doi.org/10.1186/s12943-016-0536-0
52. Liu, H., Lei, C., He, Q., Pan, Z., Xiao, D., & Tao, Y. (2018). Nuclear functions of mammalian MicroRNAs in gene regulation, immunity, and cancer. *Molecular Cancer, 17*(1), 64. https://doi.org/10.1186/s12943-018-0765-5
53. Ho, P. T. B., Clark, I. M., & Le, L. T. T. (2022). MicroRNA-Based Diagnosis and Therapy. *International Journal of Molecular Sciences, 23*(13), Article 13. https://doi.org/10.3390/ijms23137167
54. Leitão, A. L., & Enguita, F. J. (2022). A Structural View of miRNA Biogenesis and Function. *Non-Coding RNA, 8*(1), Article 1. https://doi.org/10.3390/ncrna8010010
55. Suárez, B., Solé, C., Márquez, M., Nanetti, F., & Lawrie, C. H. (2022). Circulating MicroRNAs as Cancer Biomarkers in Liquid Biopsies. In U. Schmitz, O. Wolkenhauer, & J. Vera-González (Eds.), *Systems Biology of MicroRNAs in Cancer* (pp. 23–73). Springer International Publishing. https://doi.org/10.1007/978-3-031-08356-3_2
56. Kopkova, A., Sana, J., Fadrus, P., & Slaby, O. (2018). Cerebrospinal fluid microRNAs as diagnostic biomarkers in brain tumors. *Clinical Chemistry and Laboratory Medicine (CCLM), 56*(6), 869–879. https://doi.org/10.1515/cclm-2017-0958
57. Shalaby, T., Achini, F., & Grotzer, M. A. (2016). Targeting cerebrospinal fluid for the discovery of brain cancer biomarkers. *Journal of Cancer Metastasis and Treatment, 2*(0), 176–187. https://doi.org/10.20517/2394-4722.2016.12
58. Shi, R., Wang, P.-Y., Li, X.-Y., Chen, J.-X., Li, Y., Zhang, X.-Z., Zhang, C.-G., Jiang, T., Li, W.-B., Ding, W., & Cheng, S.-J. (2015). Exosomal levels of miRNA-21 from cerebrospinal fluids are associated with poor prognosis and tumor recurrence of glioma patients.

Oncotarget, 6(29), 26971–26981. https://doi.org/10.18632/oncotarget.4699
59. Drusco, A., Bottoni, A., Laganà, A., Acunzo, M., Fassan, M., Cascione, L., Antenucci, A., Kumchala, P., Vicentini, C., Gardiman, M. P., Alder, H., Carosi, M. A., Ammirati, M., Gherardi, S., Luscrì, M., Carapella, C., Zanesi, N., & Croce, C. M. (2015). A differentially expressed set of microRNAs in cerebrospinal fluid (CSF) can diagnose CNS malignancies. *Oncotarget, 6*(25), 20829–20839.
60. Sufianov, A., Begliarzade, S., Ilyasova, T., Liang, Y., & Beylerli, O. (2022). MicroRNAs as prognostic markers and therapeutic targets in gliomas. *Non-Coding RNA Research, 7*(3), 171–177. https://doi.org/10.1016/j.ncrna.2022.07.001
61. Thomson, D. W., & Dinger, M. E. (2016). Endogenous microRNA sponges: Evidence and controversy. *Nature Reviews Genetics, 17*(5), 272–283. https://doi.org/10.1038/nrg.2016.20
62. Lee, I. Y., Hanft, S., Schulder, M., Judy, K. D., Wong, E. T., Elder, J. B., Evans, L. T., Zuccarello, M., Wu, J., Aulakh, S., Agarwal, V., Ramakrishna, R., Gill, B. J., Quiñones-Hinojosa, A., Brennan, C., Zacharia, B. E., Silva Correia, C. E., Diwanji, M., Pennock, G. K., … Boockvar, J. A. (2024). Autologous cell immunotherapy (IGV-001) with IGF-1R antisense oligonucleotide in newly diagnosed glioblastoma patients. *Future Oncology (London, England), 20*(10), 579–591. https://doi.org/10.2217/fon-2023-0702

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