Comprehensive Pediatric CNS Tumor Reference (WHO 2021 Classification & Treatment Guide)

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Pediatric Low-Grade Gliomas (Diffuse & Circumscribed)

Pediatric low-grade gliomas (pLGGs) are the most common childhood CNS tumors[1]. They encompass WHO grade I and II gliomas[1]. Unlike adult LGGs (often defined by IDH mutation and 1p/19q codeletion), pediatric LGGs are usually driven by aberrations in the MAPK pathway (e.g. *BRAF* alterations) and rarely involve IDH mutations[2]. In fact, the majority of pLGGs have alterations like *KIAA1549-BRAF* fusions, *BRAF^V600E* mutations, or FGFR1/MYB alterations, distinct from adult patterns[2]. This has opened the door to targeted therapies (e.g. BRAF and MEK inhibitors) which are being evaluated and may supplant traditional chemotherapy for pLGGs[3].

Pediatric-type Diffuse Low-Grade Gliomas

WHO 2021 introduced a new category “pediatric-type diffuse low-grade gliomas,” distinct from adult diffuse gliomas[4]. These tumors are generally diffuse (infiltrative) WHO grade 2 gliomas that occur in children and lack IDH mutations. The main subtypes include: **Diffuse astrocytoma, MYB- or MYBL1-altered; Angiocentric glioma; Polymorphous low-grade neuroepithelial tumor of the young;** and **Diffuse low-grade glioma, MAPK pathway–altered**[5][6]. All have relatively favorable prognoses compared to high-grade gliomas[7]. Key features and diagnostic criteria are:

- **Clinical/Radiologic:** These present often with seizures or focal deficits depending on location (commonly cerebral hemispheres or thalamus). MRI typically shows T2/FLAIR hyperintense, non-enhancing or mildly enhancing infiltrative lesions.
- **Histopathology:** Generally show low-grade astrocytic or mixed astro-glial morphology without anaplasia. Angiocentric glioma is characterized by an angiocentric pattern of monomorphic bipolar cells.
- **Molecular:**
- *Diffuse astrocytoma, MYB- or MYBL1-altered* – defined by gene fusions or amplification involving **MYB** or **MYBL1**[5].
- *Angiocentric glioma* – often has **MYB-QKI** fusion as a molecular hallmark.
- *Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)* – recently characterized, often carries **BRAF^V600E** mutations and shows oligodendroglioma-like appearance with neuronal markers.
- *Diffuse low-grade glioma, MAPK pathway–altered* – a broad category for diffuse gliomas driven by MAPK alterations (e.g. fusions in BRAF, FGFR1-TACC, etc.)[5].
- **Immunohistochemistry (IHC):** Variable glial markers (GFAP often positive). PLNTY often has strong CD34 immunopositivity in tumor cells and in ramified neural elements, a feature it shares with dysembryoplastic neuroepithelial tumor.
- **WHO Grade:** Assigned WHO grade 1 or 2 depending on features, but generally considered low-grade.
- **Treatment:** If feasible, surgical resection (especially for accessible lesions) is first-line and can be curative for small circumscribed tumors. For unresectable or progressive diffuse LGGs, standard first-line therapy has been chemotherapy. **Chemotherapy:** A common regimen is weekly vincristine plus carboplatin for ~18 months (the "Packer regimen"), or in some centers, weekly vinblastine monotherapy for 70 weeks[8]. In Canadian practice, single-agent vinblastine is often used as first-line for pLGG[9]. **Targeted therapy:** If a targetable mutation is present (e.g. *BRAF^V600E* or NF1-related pathway), a targeted inhibitor (such as a MEK inhibitor or BRAF inhibitor) is recommended at recurrence or as second-line[9]. In fact, consensus is to use a MAPK pathway inhibitor (like selumetinib or dabrafenib/trametinib) in second line if a MAPK alteration is identified[10]. **Radiation:** Generally avoided or delayed in young children due to long-term toxicity; reserved for refractory cases or older teens. Overall survival of pLGG is excellent (~85–90% at 10 years) but progression-free survival is lower (~42% at 10 years) due to frequent indolent recurrences[11].

Diffuse Astrocytoma, MYB- or MYBL1-altered

This subtype is a diffuse astrocytoma typically occurring in children and defined by alterations in MYB or MYBL1 genes (often gene fusions or amplifications)[5]. It was newly recognized in WHO 2021.

- **Diagnostic:** Histologically resembles a diffuse astrocytoma (WHO grade 2) with relatively bland, fibrillary astrocytic cells. Key to diagnosis is identifying a MYB or

MYBL1 fusion (e.g. MYB-QKI) or amplification. These tumors often occur in cerebral hemispheres of older children or adolescents.

- **IHC/Molecular:** Often OLIG2 and GFAP positive (astrocytic). The MYB-QKI fusion can be detected by FISH or sequencing; it leads to upregulation of MYB oncogene.
- **Clinical:** Patients may present with seizures or headaches depending on tumor location.
- **Treatment:** Maximal safe resection if feasible. If residual tumor or progression, treat as pLGG (chemotherapy such as carboplatin/vincristine or vinblastine). Prognosis is generally favorable (low-grade behavior).

Angiocentric Glioma

Angiocentric glioma is a rare epilepsy-associated tumor of children/young adults, often centered in the cortical or thalamic region. It is characterized by an angiocentric (vessel-centered) growth pattern of bipolar tumor cells.

- **Diagnostic:** Shows monomorphic bipolar spindle cells arrayed around blood vessels (forming pseudo-rosettes). It is WHO grade 1 or 2. Often causes drug-resistant seizures.
- **Molecular:** A hallmark is the **MYB-QKI** fusion in a significant subset[5].
- **IHC:** Usually GFAP positive and EMA dot staining may be seen (suggesting ependymal differentiation).
- **Treatment:** Surgical resection can be curative and often stops seizures. Excellent prognosis when fully resected. Unresectable cases could be observed or treated with chemotherapy if needed, but surgery is primary.

Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY)

PLNTY is a newly defined tumor (WHO 2021) typically affecting children and adolescents with chronic seizures. It often appears as a cortical/subcortical lesion.

- **Diagnostic:** Histology shows a polymorphous population of cells with both neuronal and glial features and calcifications. It resembles oligodendroglioma in some ways but occurs in young patients without 1p/19q co-deletion.
- **Molecular:** Frequently carries *BRAF^V600E* mutations[5]. Lacks IDH mutation.
- **IHC:** Strong diffuse CD34 positivity is characteristic, and neuronal markers (synaptophysin) can be focally positive, reflecting mixed neuroepithelial nature.
- **Treatment:** Surgical resection is often curative; these tumors are indolent. Seizure outcomes are good after surgery. If residual tumor causes issues, could consider targeted BRAF inhibitor in *BRAF^V600E* cases or standard chemo, but usually not necessary.

Diffuse Low-Grade Glioma, MAPK Pathway–altered

This is an inclusive category for pediatric diffuse gliomas driven by MAPK pathway alterations (aside from the specific MYB, etc. above)[5]. It encompasses tumors that might

have historically been “diffuse astrocytoma NOS” in a child but now recognized to have e.g. BRAF fusion or other kinase fusions.

- **Diagnostic:** Diffuse, infiltrative low-grade glial tumor in a child, lacking defining features of other categories but with a known MAPK genetic driver.
- **Molecular:** Alterations can include *KIAA1549-BRAF* fusion (common in pilocytic but can occur in diffuse), FGFR1 mutations or fusions, NTRK fusions, etc. Essentially, any MAPK pathway activation qualifies (excluding MYB family which is separate category).
- **Treatment:** Similar to other pLGGs – surgery if possible; otherwise observe or treat with chemotherapy. Importantly, if a targetable mutation (e.g. BRAF fusion) is present, targeted therapy (like a MEK inhibitor) is an option and increasingly used as second-line[10].
- **Prognosis:** Generally very good long-term survival.

Circumscribed Low-Grade Astrocytic Tumors

These are WHO grade 1 tumors that are typically well-circumscribed (non-diffuse) and often amenable to surgical cure. They fall under “circumscribed astrocytic gliomas” in WHO classification. Key pediatric examples: **Pilocytic astrocytoma, Subependymal giant cell astrocytoma,** and **Pleomorphic xanthoastrocytoma**. These tumors tend to have specific molecular profiles (e.g. pilocytic has KIAA1549-BRAF fusion in ~70% cases).

Pilocytic Astrocytoma (Grade 1)

Pilocytic astrocytoma (PA) is the quintessential benign pediatric brain tumor (WHO grade 1). It most commonly arises in the cerebellum, but also optic pathway (especially in NF1 patients) and brainstem.

- **Clinical/Radiologic:** Often presents with symptoms of a mass in respective location (e.g. cerebellar PA causes headache, ataxia; optic pathway glioma causes vision loss). MRI typically shows a cystic mass with an enhancing mural nodule in the cerebellum, or a solid hypothalamic/optic chiasm mass.
- **Histopathology:** Biphasic pattern – areas of compact bipolar cells with Rosenthal fibers and areas of loose microcystic change. Generally low cellularity and no atypical mitoses.
- **Molecular:** Approximately 70% have **KIAA1549-BRAF** fusion activating the MAPK pathway[2]. NF1-associated PAs have NF1 gene loss as the driver. Rarely BRAF^V600E in non-cerebellar PAs.
- **IHC:** GFAP positive (astrocytic), and often a characteristic pattern of p16 (CDKN2A) is intact (in contrast to high-grades).
- **Treatment: Surgery** is often curative if complete resection is possible (especially for cerebellar PAs) – 5-year survival ~95%. For tumors in critical locations (optic pathway, brainstem) or subtotally resected tumors, observation is an option if stable. If progression occurs, **chemotherapy** is first-line (particularly in young

children to avoid radiation). Standard regimens include carboplatin/vincristine for 12–18 months[9]. Alternatively weekly vinblastine is used in some centers[10]. **Targeted therapy:** Selumetinib (a MEK inhibitor) has shown efficacy in NF1 optic pathway gliomas and other PAs[3]; it may become standard for progressive cases with MAPK alterations. **Radiation:** Typically avoided in young children; could be considered in older patients or if tumor threatens vision/life and is refractory to chemo, but carries risk of long-term cognitive and vasculopathic effects.

- **Prognosis:** Excellent overall survival. Recurrences can often be managed with further therapy. Transformation to higher grade is very rare.

Subependymal Giant Cell Astrocytoma (SEGA)

SEGA is a benign tumor (WHO grade 1) almost exclusively seen in the setting of **Tuberous Sclerosis Complex (TSC)**. It typically arises in the lateral ventricle near the foramen of Monro, often causing hydrocephalus.

- **Clinical:** Usually presents in children or adolescents with TSC, often when tumor enlargement causes obstructive hydrocephalus (headache, increased intracranial pressure). TSC stigmata like seizures, skin lesions, etc., are present.
- **Histology:** As the name suggests, contains large epithelioid "giant" astrocytes with abundant cytoplasm and often multinucleation. They can calcify. Despite alarming histology, behavior is benign.
- **Molecular:** Caused by loss of **TSC1 or TSC2** genes (TSC patients carry germline mutation, and SEGA is a result of biallelic inactivation). This leads to mTOR pathway activation.
- **IHC:** Positive for GFAP and often S100; can also express neuronal markers like synaptophysin (reflecting mixed glioneuronal features).
- **Treatment:** Traditionally, surgical resection was standard if the SEGA was causing hydrocephalus. However, **mTOR inhibitors** (like everolimus) have become a cornerstone therapy, often leading to significant tumor shrinkage in TSC patients[12]. Everolimus is often the first-line treatment now, potentially obviating need for surgery in many cases.
- **Prognosis:** Excellent; tumors generally stop growing in adulthood. Management is aimed at preventing hydrocephalus and treating before vision/cognitive issues occur.

Pleomorphic Xanthoastrocytoma (PXA)

PXA is an unusual astrocytoma (typically WHO grade 2) often occurring in children and young adults, usually superficially in the cerebral hemispheres (temporal lobe is common). Many patients have seizures.

- **Histology:** As the name "pleomorphic xanthoastrocytoma" suggests, it has pleomorphic, lipid-laden astrocytes (xanthomatous cells) and often dense lymphocytic infiltrates. Despite cytologic atypia, mitotic activity is low in grade 2 PXA. Anaplastic PXA (WHO 3) is defined by brisk mitoses (≥5/10 HPF).

- **Molecular:** Frequently carries the **BRAF^V600E** mutation (50–60% of cases). IDH-wildtype. No 1p/19q co-deletion.
- **IHC:** GFAP positive. Often strong CD34 immunostaining in tumor and adjacent brain, similar to gangliogliomas.
- **Treatment:** Complete surgical resection is the primary treatment and can be curative for grade 2 PXA. If resected, often no further therapy is needed aside from monitoring. If incompletely resected or if anaplastic features, adjuvant therapy is considered. **Chemotherapy:** Because of BRAF^V600E, targeted therapy (dabrafenib ± trametinib) is a potential option for recurrence or unresectable tumors. Traditional chemo (temozolomide or vincristine/carboplatin) has been used but efficacy data is limited due to rarity. **Radiation:** could be used for anaplastic PXA or recurrence, but often avoided in young patients.
- **Prognosis:** Good for grade 2 PXAs (5-year survival ~90%); worse if anaplastic or incomplete resection. Transformation to glioblastoma can occur in some cases.

Neuronal and Mixed Neuronal-Glial Tumors

This group includes tumors that have mixed glial and neuronal differentiation, common in pediatric/young patients, often presenting with seizures. Many are WHO grade 1. Key examples: **Ganglioglioma** and **Dysembryoplastic Neuroepithelial Tumor (DNET)**. WHO 2021 also lists newly recognized entities like **Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)**, **Myxoid glioneuronal tumor**, and **Multinodular and vacuolating neuronal tumor (MVNT)**[13][14].

Ganglioglioma

Ganglioglioma (GG) is a common mixed neuronal-glial tumor (WHO grade 1) typically seen in children and young adults, often presenting with seizures. It most often occurs in the temporal lobe.

- **Histology:** By definition, it contains both neoplastic ganglion cells (neuronal component) and neoplastic glial cells (usually astrocytic). Often there is a dysplastic architecture. Calcifications can be present. If significant mitoses or anaplasia in glial component, it could be designated anaplastic ganglioglioma (WHO 3).
- **Molecular:** ~20–50% have *BRAF^V600E* mutations. No IDH mutation. Occasionally FGFR1 mutations or duplication. CDKN2A deletion can be seen in anaplastic cases.
- **IHC:** Neuronal markers (synaptophysin, NeuN) highlight the ganglion cells; GFAP highlights the glial component. CD34 often positive in tumor and surrounding cortex (similar to PXA).
- **Clinical:** Often longstanding seizures; imaging shows a cystic and solid cortical mass, often with calcifications and variable enhancement.
- **Treatment:** Surgical resection is usually curative for low-grade ganglioglioma and often also controls epilepsy. If completely resected, 10-year survival >90%. If

incompletely resected or progressive, options include re-operation or adjuvant therapy. **Chemotherapy:** not standard but regimens for pLGG (carboplatin/vincristine) have been used in unresectable cases. **Targeted therapy:** *BRAF^V600E* mutated cases might respond to BRAF ± MEK inhibitors if needed. Radiation is reserved for rare malignant transformations or refractory cases.

- **Prognosis:** Excellent for grade 1; anaplastic gangliogliomas have a less favorable outcome (but still better than diffuse high-grade gliomas).

Dysembryoplastic Neuroepithelial Tumor (DNET)

DNET is a benign glioneuronal tumor (WHO grade 1) classically associated with childhood epilepsy. It typically occurs in the cortex (often temporal lobe) and is often superficial.

- **Histology:** The classic form shows specific glioneuronal elements with columnar arrangement of oligodendroglia-like cells floating in mucinous pools, with interspersed "floating" neurons. It has a specific architecture reflecting a developmental lesion. It is usually low cellularity.
- **Molecular:** Typically no recurrent single driver mutation (usually *BRAF* is wildtype in classic DNET). Some DNET-like tumors may have FGFR1 mutations or BRAF alterations, but classic DNET is genetically quiet. It is thought to be a malformative tumor.
- **IHC:** Neuronal markers highlight the scattered neurons; glial component is GFAP positive.
- **Clinical:** Presents with longstanding, drug-resistant focal seizures in a child or adolescent. MRI often shows a cortical lesion with multinodular bright T2 signal and little to no enhancement (sometimes called a "bubbly" cortex lesion).
- **Treatment:** Surgical removal typically cures the epilepsy and is curative for the tumor. These do not usually recur if completely excised. Adjuvant therapy is not needed for classic DNET.
- **Prognosis:** Excellent (essentially benign).

Diffuse Glioneuronal Tumor with Oligodendroglioma-like Features and Nuclear Clusters (DGONC)

DGONC is a provisional new entity (WHO 2021) seen in children. It was previously colloquially called "CNS neuroepithelial tumor with oligodendroglioma-like features and nuclear clusters" (also known by an acronym "CNS NET-O" or "HGNET-O").

- **Histology:** It shows diffuse infiltration with cells that resemble oligodendroglioma (round nuclei, clear cytoplasm) and characteristic "nuclear clusters" (clusters of cells without intervening cytoplasm). It lacks the 1p/19q codeletion of true oligodendrogliomas and occurs in children.
- **Molecular:** Frequently associated with **MN1** gene alterations (e.g. MN1-BEND2 fusion) – in fact it is sometimes referred to as MN1-altered glioneuronal tumor[15].

- **IHC:** Mixed neuronal-glial; can have some synaptophysin positivity and GFAP for glial cells. Often CD34 positive.
- **Behavior:** Considered an intermediate-grade neoplasm (not clearly grade 1, often behaves as grade 2–3).
- **Treatment:** Due to rarity, there is no standard established. Surgery followed by observation or adjuvant therapy if residual. Some have indolent course, others can progress.
- **Prognosis:** Not fully defined; likely variable.

Other Rare Low-Grade Neuronal Tumors

- **Myxoid Glioneuronal Tumor:** A newly characterized tumor (WHO 2021) often in septum pellucidum or periventricular region. It has a myxoid matrix and both glial and neuronal features. It often carries an **PDGFRA** mutation or FGFR1 alteration. Behavior is indolent (likely grade 1–2).
- **Multinodular and Vacuolating Neuronal Tumor (MVNT):** A peculiar lesion usually found incidentally in adults (sometimes in adolescents). Appears as multiple nodules in subcortical white matter with prominent vacuolation. It's probably a hamartomatous lesion; often just observed. WHO 2021 lists it, but it's often not surgically removed unless needed.
- **Rosette-forming Glioneuronal Tumor (RGNT):** Occurs in the fourth ventricle region (often cerebellar vermis) of young adults. Has both glial and neuronal rosettes. Typically grade 1. Treated with surgery; good prognosis.
- **Central Neurocytoma:** Predominantly in young adults (ventricular tumor of neuronal cells). Rare in children but can occur in older adolescents. Typically WHO 2, treated with surgery ± radiation.

Pediatric High-Grade Gliomas

Pediatric high-grade gliomas (pHGG) include various aggressive astrocytic tumors (WHO grade 3 and 4) arising in children. They behave aggressively and, unlike adult glioblastomas, have distinct biology (often lack IDH mutation, and many have pediatric-specific mutations like H3 histone mutations)[2]. Historically, pediatric HGG outcomes have been poor, making them the leading cause of cancer-related mortality in children[16]. WHO 2021 created a category "pediatric-type diffuse high-grade gliomas" separate from adult types[17]. Major entities are: **Diffuse midline glioma, H3 K27-altered; Diffuse hemispheric glioma, H3 G34-mutant; Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype;** and **Infant-type hemispheric glioma**[18][19]. Additionally, some high-grade astrocytomas with unique features (like *piloid* features) are recognized. Common clinical presentation for pHGG is subacute neurologic decline (raised intracranial pressure, focal deficits, seizures depending on location).

Diagnostic criteria: High-grade gliomas are defined histologically by high cellularity, mitotic activity, microvascular proliferation and/or necrosis (which would classify it as

WHO grade 4 glioblastoma). In children, molecular features are crucial: e.g. presence of H3K27M (now H3 K27-altered) defines a specific diffuse midline glioma entity[20].

Predisposition: Unlike adult GBM (where prior radiation or germline conditions are rare causes), a notable fraction of pHGGs occur in children with predispositions like Neurofibromatosis type 1, Li-Fraumeni syndrome (germline TP53), or Constitutional MMR deficiency (Lynch syndrome variant)[21]. For example, NF1 patients can develop high-grade astrocytomas, and biallelic mismatch repair mutation carriers often develop childhood glioblastomas[21].

Treatment: Multidisciplinary management is needed. Standard approach (if trial unavailable) is maximal safe resection, followed by focal radiation therapy and adjuvant chemotherapy[22]. The Children's Oncology Group trial **ACNS0423** established a chemo-radiation approach often used as a guideline[23]. Typically: - **Surgery:** Aim for maximal resection of tumor when location permits (except intrinsic brainstem lesions like DIPG where resection is not feasible). Even partial debulking is thought to help symptoms and possibly survival[22]. - **Radiation:** Conventional focal radiation ~54–60 Gy in 1.8–2 Gy fractions to the tumor bed is standard for children ≥3 years[24]. For example, a dose of 54 Gy in 30 fractions is typical for supratentorial HGG[25]. Brainstem gliomas (DIPG) typically get 54 Gy to the pons[26]. Children <3 are often spared radiation initially due to severe long-term effects; chemo is used to delay radiation. - **Chemotherapy:** Pediatric HGG chemotherapy often mirrors adult regimens (e.g. **temozolomide (TMZ)** given daily during RT and for 6–12 cycles after). However, clinical trials have explored adding agents like **lomustine** or **vincristine**. COG ACNS0423 evaluated TMZ-based chemoradiation; earlier CCG trials (e.g. CCG-945) used adjuvant CCNU/VCR/Prednisone without clear survival benefit[22]. Recent trends include incorporating targeted therapy if a driver is known (e.g. BRAF^V600E mutant HGG treated with BRAF/MEK inhibitors on trial). - **Clinical Trials:** Enrollment is strongly encouraged, given poor outcomes. Trials targeting histone mutations or using immunotherapy (checkpoint inhibitors, oncolytic viruses) are ongoing.

Prognosis: Generally poor. The 5-year survival for pediatric glioblastoma remains under 20% in most series. One subset with better outcome are infants with certain gene fusions (see below) and perhaps those amenable to total resection, but overall, outcomes lag behind other pediatric tumors.

Below are specific entities:

Pediatric-type Diffuse High-Grade Gliomas

Diffuse Midline Glioma, H3 K27-altered (DIPG)

Diffuse midline glioma, H3 K27-altered is defined by a characteristic **H3 K27M mutation** in one of the histone H3 genes (typically *H3F3A* or *HIST1H3B*) or alternative mechanisms that disrupt H3K27 trimethylation[20]. This entity most classically presents as the intrinsic pontine glioma (DIPG) in children, but can also occur in other midline structures (thalamus, spinal cord).

- **Location/Clinical:** Often in the pons (DIPG), affecting children around 5–10 years old. Presents with brainstem signs: cranial nerve palsies, long tract signs, ataxia. DIPG is diagnosed radiologically (expansile T2 hyperintense pontine lesion) since biopsy is often not done (though now sometimes done for trials). Thalamic or spinal cord H3 K27M gliomas cause corresponding focal deficits.
- **Histology:** High-grade infiltrative astrocytoma. May show indistinct histologic features (could appear as anaplastic astrocytoma or GBM); the defining feature is the molecular alteration. *WHO grade is 4* by definition due to its behavior, even if histology is moderate[27][28].
- **Molecular: H3 K27M** mutation leads to global reduction of H3K27 trimethylation (loss of H3K27me3 on IHC). WHO 2021 uses "H3 K27-altered" to allow for non-mutational mechanisms (e.g. overexpression of EZHIP in some midline tumors) that have same effect[20][29]. Often co-occurs with TP53 mutations and ACVR1 mutations (the latter especially in DIPG). ATRX loss is common in thalamic cases.
- **IHC:** Loss of H3K27me3 staining in tumor nuclei is a diagnostic surrogate marker[30]. GFAP typically positive (glial).
- **Treatment: Radiation therapy** is the mainstay for DIPG – 54 Gy in 30 fractions to the pons provides transient palliation[26]. It improves symptoms and possibly short-term survival but is not curative. No chemotherapy has proven effective for DIPG; numerous trials (EGFR inhibitors, ACVR1 inhibitors, checkpoint inhibitors, ONC201 etc.) are ongoing. Standard chemotherapy (TMZ or others) has not clearly extended survival. For non-pontine midline gliomas (thalamic/spinal), maximal resection might be attempted if feasible (rarely possible in thalamus), followed by chemoradiation as per other HGG.
- **Prognosis:** Dismal in DIPG – median survival ~9–12 months. 2-year survival <10%. Non-pontine midline H3K27M gliomas also fare poorly, though a subset (spinal cord) may live longer if lower-grade histology.
- **Note:** Because of the uniformly poor outcome, DIPG is often handled as a distinct entity. **Focal RT** is considered the standard of care[31]. In the Canadian consensus, DIPG recommendation is just focal RT, acknowledging lack of effective chemo[31]. Clinical trials (like PNOC or BIOMEDE) are exploring targeted agents.

Diffuse Hemispheric Glioma, H3 G34-mutant

This is another specific molecular entity: pediatric high-grade gliomas in the cerebral hemispheres with an **H3F3A G34R/V** mutation (glycine-to-arginine/valine at position 34 of H3.3).

- **Epidemiology:** Occur in older children and adolescents, typically in the cerebral cortex. Often present with seizures (due to cortical location).
- **Histology:** High-grade astrocytic tumor (often grade 4 glioblastoma morphology). Can have large bizarre nuclei and multinucleated cells; often significant necrosis and microvascular proliferation.

- **Molecular:** Defined by **H3.3 G34** mutation. These tumors frequently have co-mutations in TP53 and ATRX (somewhat resembling the profile of adult IDH-wildtype GBM except for the H3 mutation). They do *not* have IDH mutations (mutually exclusive).
- **IHC:** No specific immunohistochemical surrogate for G34R/V is widely used clinically (unlike K27M). ATRX loss and p53 positivity are common.
- **Treatment:** Similar approach as other HGG – surgical resection if possible, followed by focal radiation (typically ~60 Gy) and adjuvant chemotherapy (e.g. TMZ). No tailored therapy yet for H3G34.
- **Prognosis:** Poor, though possibly slightly better than DIPG. These are aggressive tumors with median survival on the order of 1–3 years in reports.

Diffuse Pediatric High-Grade Glioma, H3/IDH-wildtype

This category covers pediatric diffuse high-grade gliomas that lack both H3 mutations and IDH1/2 mutations[17]. Essentially it is a diagnosis of exclusion for pediatric GBM-like tumors that don't fit the other molecularly-defined groups (and are not the infant type, see below). These would have been called "GBM, IDH-wildtype" in an older scheme, but in a child under 18 they fall here if no H3 mutation.

- **Examples:** A GBM in a 10-year-old that is H3 wildtype, IDH wildtype. Some of these may have other alterations like EGFR amplification, TERT promoter mutation, etc., but those are more common in adults. Others may have novel pediatric drivers (e.g. *MET* fusions).
- **Histology:** High-grade (WHO 4) features: necrosis and/or microvascular proliferation, or at least anaplastic astrocytoma features with high mitotic count.
- **Molecular:** By definition IDH-wt, H3-wt. They might have PTEN loss, CDKN2A/B deletions, or other genetic changes. If they have EGFR amp or TERT promoter mut, biologically they are like adult GBM, but those changes are less frequent in young children.
- **Treatment:** Maximal surgery + RT + TMZ (following adult GBM paradigm) is generally used if child's age permits. Clinical trials are strongly considered.
- **Prognosis:** Very poor (median survival ~1 year or less if true GBM). Some younger children in this category might actually have better outcomes if they carry unusual fusions (e.g. NTRK) – those might be reclassified as infant-type or other emerging subgroups as understanding improves.

Infant-Type Hemispheric Glioma

This is a newly recognized subset of high-grade gliomas occurring in infants (typically <1–3 years old) that have characteristic gene fusions and surprisingly better outcomes than usual HGG. WHO 2021 lists "Infant-type hemispheric glioma" as a distinct entity[32].

- **Molecular:** Common gene fusions in these tumors include **ETV6-NTRK3**, **ALK/ROS1 fusions**, and MET fusions. These are receptor tyrosine kinase fusions that drive the tumor.
- **Clinical:** Present in infants with large hemispheric masses; often very large at diagnosis. Despite being high-grade histologically, some infants respond dramatically to targeted therapy.
- **Treatment:** Aside from surgery and conventional chemo, importantly **targeted inhibitors** (like TRK inhibitors for NTRK fusions, ALK inhibitors, etc.) have shown striking efficacy in case reports. For example, use of larotrectinib (TRK inhibitor) has led to tumor regression allowing avoidance of intense chemo/radiation during infancy.
- **Prognosis:** With modern targeted approaches, some of these infants do very well, achieving long-term remission, in contrast to historically poor outcomes. Thus, identifying the fusion is critical.

High-Grade Astrocytoma with Piloid Features

Another new entity in WHO 2021, this refers to an astrocytoma that morphologically has features of pilocytic astrocytoma (like biphasic architecture, Rosenthal fibers) but behaves in a high-grade manner and has genetic alterations more akin to high-grade tumors.

- **Molecular:** Often has *BRAF* alterations or TP53 mutations. Some may arise from a PA that underwent malignant transformation.
- **Significance:** It highlights that even tumors that look somewhat like pilocytic can in rare cases be aggressive; however, this is an uncommon diagnosis. Treatment would follow HGG guidelines.

Note: Other uncommon pediatric high-grade tumors include anaplastic pleomorphic xanthoastrocytoma and anaplastic ganglioglioma, but those are variants of the low-grade entities described earlier when they show high-grade features.

Treatment Considerations and Protocols: In practice, pediatric HGG patients (excluding DIPG) often follow protocols like ACNS0423 which used radiation with concurrent TMZ and adjuvant TMZ/lomustine[33]. The **Canadian consensus** indicates using "chemotherapy/radiation per ACNS0423" for pediatric HGG[23]. For children <3, a common strategy is high-dose chemotherapy regimens to delay radiation (e.g. the Baby POG/Head Start protocols using multiple chemo agents with stem cell rescue). Incorporation of molecular targeted therapy is on the horizon for cases with identifiable targets[34][35]. Unfortunately, recurrence is common in pHGG and salvage options are limited (clinical trials or re-irradiation for focal recurrences might be attempted). Palliative care is an important facet of management given outcomes.

Ependymal Tumors

Ependymomas are glial tumors arising from ependymal lining cells of the ventricular system or central canal. They can occur anywhere in CNS, but in children, common

locations are the **posterior fossa** (fourth ventricle) and **supratentorial** (cerebral ventricular region). Spinal cord ependymomas are more common in adults (except NF2 teens). Pediatric ependymomas are usually WHO grade 2 or 3 and tend to recur locally. The 2021 WHO classification revolutionized ependymoma classification by incorporating site and molecular profile: ependymomas are now classified by **anatomic site and molecular subgroup**[36][37]:

- **Supratentorial ependymoma** – subdivided into **ZFTA fusion-positive** (ZFTA is same as C11orf95 fusion, historically called RELA-fusion ependymoma) and **YAP1 fusion-positive**[38].
- **Posterior fossa ependymoma** – subdivided into **Group PFA** and **Group PFB** based on methylation profiling[39].
- **Spinal ependymoma** – includes **MYCN-amplified** subtype versus others[40].
- Classic histologic variants (cellular, clear cell, papillary) are no longer separate entities, just patterns[41][42]. WHO grades: subependymoma (grade 1), myxopapillary (now grade 2)[43], other ependymomas can be grade 2 or 3.

Diagnostic features: Ependymomas show characteristic perivascular pseudorosettes (tumor cells arranged around blood vessels with an intervening zone of processes) and sometimes true ependymal rosettes. They may calcify. Anaplastic ependymoma (grade 3) shows increased cell density, mitoses, and microvascular proliferation, but grading reproducibility is an issue[44][45]. WHO now does *not* mandate a grade in the integrated diagnosis of molecularly-defined ependymomas, but histologically one can still assign grade 2 vs 3 if desired[46].

Clinical: Posterior fossa ependymomas (typically PFA) often present in young children (<5 years) with signs of raised intracranial pressure (headache, vomiting, ataxia). Supratentorial ependymomas present with seizures or focal deficits depending on location. Drop metastases can occur (via CSF spread), though less common than in medulloblastoma.

Treatment: The cornerstone is **maximal surgical resection**. Ependymomas are relatively radioresistant, so a gross total resection greatly improves outcome. Post-operative **radiation therapy** is standard for patients >12–18 months old: - For localized ependymoma, **focal irradiation** to the tumor bed is recommended (craniospinal irradiation is not routinely done unless there is confirmed CSF dissemination, which is rare at diagnosis). Dose typically **54–59.4 Gy** to the resection cavity region[24]. Photon or proton conformal therapy can be used to spare normal tissue. - Children <3 years: often initial approach is surgery + **chemotherapy** to delay radiation until the child is older. Chemotherapy (e.g. regimens with vincristine, carboplatin, etoposide, cyclophosphamide – like the COG ACNS1221 or earlier Baby Brain protocols) can cause temporary responses, allowing some delay of RT. - **Chemotherapy:** Unlike medulloblastoma, chemo is less effective in ependymoma. Its role is mainly in infants or in recurrence. Ependymomas generally do not have a standard chemo that improves cure rate after surgery+RT; trials have not shown clear benefit of adjuvant chemo in older children. However, in recurrence,

a regimen like TMZ or a platinum-based chemo might be tried. - **Targeted therapy:** No established targeted agents yet, but research ongoing (some supratentorial RELA-fused ependymomas overexpress certain pathways that could be targeted, and MEK inhibitors were tried in trials for recurrent ependymoma with limited success[47]). - **NCCN Guidelines** emphasize maximal resection and radiation; chemotherapy is optional or trial-based in older kids. European protocols often avoid delaying radiation beyond 12–15 months of age because local control is critical.

Outcome: Prognosis is intermediate. 5-year survival is ~50–70% for localized ependymoma with gross total resection and radiation. PFA type (infant posterior fossa) has worse prognosis than PFB (which often occurs in slightly older children)[48]. Molecular grouping correlates: PFA ependymomas often recur (even after seemingly good resection) and have poorer outcome, whereas PFB has better outcomes in some studies. Supratentorial YAP1-fused ependymomas (often in young children) may have favorable outcomes, whereas ZFTA(C11orf95)-fusion ependymomas are more aggressive.

Now specifics by subtype:

Supratentorial Ependymoma (ZFTA fusion-positive & YAP1 fusion-positive)

Supratentorial ependymomas (ST-EPN) arise in the cerebral hemispheres (often cortical or deep, sometimes large). Two major molecular subtypes: - **ZFTA fusion–positive:** formerly known as RELA-fusion ependymoma (C11orf95-RELA fusion first described). ZFTA (C11orf95) is a gene that fuses with RELA or other partners. This subtype is the most common supratentorial ependymoma in children[49]. Tends to present in kids around 5–10 years. It's usually WHO grade 3 histologically. These are aggressive. - **YAP1 fusion–positive:** less common, seen in younger patients sometimes. YAP1-MAMLD1 is a fusion example. May have a different clinical behavior (somewhat better, possibly corresponding to what was "balanced" genomic subtype).

Diagnosis: Histologically, ST ependymomas look similar to other ependymomas (pseudorosettes etc.). The fusion is identified by molecular testing.

Treatment: Surgical resection is often challenging due to location, but goal is GTR. After surgery, focal RT to ~59.4 Gy to residual cavity is recommended[24]. For ZFTA-fused, some trials consider chemotherapy (e.g. using pediatric HGG-type regimens) but unclear benefit. According to Canadian consensus, for localized ependymoma (which includes supratentorial), the recommended therapy is surgery followed by focal radiation only[50]. No chemotherapy was included in consensus standard outside trials[50].

Outcome: ZFTA-fusion ependymomas have high relapse rates and ~5-year survival around 50%. YAP1-fusion ependymomas possibly have better outcomes (data limited due to rarity). Surveillance imaging for relapse (especially local) is done frequently in first 2–3 years post-treatment.

Posterior Fossa Ependymoma (Group PFA & PFB)

Posterior fossa ependymomas (PF-EPN) arise in the 4th ventricle region. WHO 2021 separates: - **Group PFA:** Posterior fossa ependymoma group A – typically infants and young children. These have a distinct epigenetic profile (often with high EZHIP protein expression causing epigenetic dysregulation)[51]. More aggressive. - **Group PFB:** Group B – tends to occur in older children or adolescents, with a different methylation profile and generally better prognosis.

Diagnosis: PF ependymomas often show moderate-to-densely cellular tumors with ependymal pseudorosettes. Sometimes PFA tumors can appear less differentiated. There is no easy immunohistochemical test for PFA vs PFB, though PFA often shows loss of H3K27me3 similar to K27M gliomas due to EZHIP overexpression, but that's not specific enough clinically.

Treatment: Aggressive surgical resection is critical. Because these sit in the 4th ventricle, involvement of brainstem structures can limit resection. Post-op, all patients (if >12–18 months) should get **focal radiation** to the tumor bed (typically 54–59.4 Gy)[24]. If child is too young (<1), some will attempt chemo for a period and later do RT. No CSI unless disseminated. Chemotherapy after radiation has not definitively shown benefit, but some protocols give adjuvant chemo (e.g. PDECT regimen) especially if residual disease, though it's not standard. European trial results (e.g. SIOP Ependymoma II) are pending to clarify chemo benefit.

Outcome: PFA ependymomas have high risk of recurrence; 5-year PFS may be only ~40%. PFB ependymomas can have 5-year PFS ~75% in some series. Recurrences are typically local (around the resection site). Salvage therapy might include re-resection, re-irradiation, or experimental therapies.

Spinal Ependymoma (incl. MYCN-amplified subtype)

Spinal cord ependymomas in children are rare (except in NF2 patients). They include: - **Conventional spinal ependymoma** (usually WHO grade 2) – often intramedullary in cervical or thoracic cord. - **Myxopapillary ependymoma** – occurs in filum terminale (see below), traditionally grade 1 but now upgraded to grade 2[43]. - **Spinal ependymoma, MYCN-amplified** – a very aggressive subtype recently recognized in children/adolescents, often cervical, with MYCN gene amplification[52]. This behaves like a high-grade malignancy.

Clinical: Back pain, motor/sensory signs depending on level. MRI shows an intramedullary enhancing cord lesion (for myxopapillary, a filum mass often with drop mets).

Treatment: Surgery is first-line. For fully resected grade 2 spinal ependymoma, observation can be considered. For subtotally resected or any high-grade features, **radiation** to involved spinal levels (typically ~50–54 Gy) is recommended. The MYCN-amplified subtype likely merits post-op radiation and maybe chemo similar to HGG due to

its aggressive nature. Myxopapillary ependymomas (even though now grade 2) are often cured by resection, but if residual or if CSF seeding, radiation or CSI might be used.

Outcome: Conventional spinal ependymomas have good prognosis, especially if resected (many are cured). MYCN-amplified ones have poor outcomes (tend to recur early and disseminate). NF2-associated ependymomas (often multiple) can be an ongoing issue but are usually manageable individually.

Myxopapillary Ependymoma

A variant typically occurring in the **filum terminale** of the spinal cord (lumbar region). It is characterized by cuboidal tumor cells in papillary arrangements in a myxoid background with blood vessels.

- **WHO grade:** Now considered grade 2 (was grade 1) because they can recur or drop metastasize[43].
- **Clinical:** Presents in young adults (20s) more commonly, with low back pain or sciatica. Rare in young children but can occur in adolescence.
- **Treatment:** Surgical removal (often curative). If completely resected and no drop mets, observation. If residual tumor or disseminated along CSF, consider radiation to residual or CSI in dissemination.
- **Prognosis:** Very good if resected; long-term control is high, but lifelong follow-up is needed.

Subependymoma

A benign, slow-growing ependymal tumor (WHO grade 1) usually in adults (4th or lateral ventricle). Rare in children. When present, usually incidental or causes obstruction symptoms.

- **Histology:** Very low cellularity, microcystic, with clusters of ependymal nuclei on a fibrillary background.
- **Treatment:** Often observation if small/incidental. If causing hydrocephalus, surgical removal fixes it.
- **Prognosis:** Excellent; essentially never transforms.

Summary of Therapy: The **NCCN pediatric CNS tumor guidelines** emphasize that for ependymomas, maximal safe resection and involved-field radiation are standards[53][54]. The Canadian consensus specifically: “Localized Ependymoma – Focal radiation” (after surgery)[50]. No chemotherapy is listed as standard, reflecting its limited impact[50].

Choroid Plexus Tumors

Choroid plexus tumors originate from the choroid plexus epithelium in the ventricles. They are most common in young children. Two main types: - **Choroid Plexus Papilloma (CPP)** – WHO grade 1 (benign). - **Choroid Plexus Carcinoma (CPC)** – WHO grade 3 (malignant).

There is also an intermediate atypical papilloma (grade 2) if increased mitoses but not frank carcinoma.

Clinical: Present with hydrocephalus signs due to CSF overproduction or blockage. Often tumors in lateral ventricle (in infants) or 4th ventricle (older kids).

Diagnosis: Papillomas have papillary structures with a single layer of uniform cuboidal epithelial cells. Carcinomas show frank malignancy: cellular atypia, mitoses, brain invasion.

Molecular: Some CPCs are associated with germline TP53 mutations (Li-Fraumeni syndrome)[55], which dramatically increases CPC risk in infancy. Otherwise, not many signature mutations known, though recent data shows RB pathway involvement in some.

Treatment: - **Papilloma (CPP):** Surgical resection is usually curative. Hydrocephalus may resolve after resection. No adjuvant therapy needed for CPP. - **Carcinoma (CPC):** Treatment is aggressive. **Surgery:** Attempt gross total resection. **Chemotherapy:** Given high propensity for spread, intensive chemo regimens are used, often similar to infant brain tumor protocols (e.g. alternating courses of etoposide, vincristine, cyclophosphamide, cisplatin as used in COG protocols). **Radiation:** If child is old enough (≥3 years), craniospinal irradiation might be considered due to metastatic tendency, followed by focal boost. However, because CPC often occurs in infants, high-dose chemo with stem cell transplant has been tried to avoid CSI. - For instance, the **COG trial ACNS0721** explored high-dose methotrexate-based chemo for CPC. Some European protocols include CSI for CPC in older kids. - **Prognosis:** CPP – excellent (near 100% survival if resected). CPC – guarded; 5-year survival maybe ~40-50% with aggressive therapy. Outcome improves with complete resection and when treated at experienced centers. TP53 germline CPC has particularly poor outcome due to inherent resistance.

Note on predisposition: Choroid plexus carcinoma is a hallmark of Li-Fraumeni syndrome in children (germline TP53)[55], so any CPC, especially bilateral or in an infant, warrants genetic evaluation.

Embryonal Tumors

Embryonal tumors are a group of highly malignant (WHO grade 4) tumors thought to arise from primitive progenitor cells. They are generally composed of densely packed small round blue cells. Historically all called “PNET”, they are now separated by specific molecular types. Key pediatric embryonal tumors include: - **Medulloblastoma** – the most common malignant brain tumor in children, arising in cerebellum. - **Atypical Teratoid/Rhabdoid Tumor (ATRT)** – occurs in infants, defined by loss of INI1 protein (SMARCB1 mutation). - **Embryonal Tumor with Multilayered Rosettes (ETMR)** – rare infant tumor, usually with C19MC alteration. - **Other newly defined entities: CNS neuroblastoma, FOXR2-activated** and **CNS tumor with BCOR internal tandem duplication** (these cover tumors that were previously CNS-PNET, now recognized by molecular drivers)[56]. - **Pineoblastoma** – an embryonal tumor of the pineal (covered in

pineal section). - (Historical note: older terms like CNS PNET, e.g. “ependymoblastoma” or “medulloepithelioma”, have been retired or folded into ETMR).

Medulloblastoma

Medulloblastoma is a malignant embryonal tumor of the **cerebellum** (posterior fossa). It is a leading cause of cancer mortality in children but also one of the most treatable CNS tumors with combined modality therapy. Medulloblastomas are all WHO grade 4 by definition[27], reflecting their aggressive nature but also highly therapy-responsive in many cases (especially certain subgroups)[27].

Epidemiology: Primarily a pediatric tumor (peak incidence at age 3–9). It accounts for ~20% of pediatric brain tumors. Slight male predominance. Rare in adults.

Location: Arises in the cerebellum – midline (vermis) in younger children (often causing truncal ataxia) or cerebellar hemisphere in teens. Often extends into 4th ventricle. CSF dissemination at diagnosis is seen in ~30% cases (drop metastases to spinal cord or nodules in subarachnoid space).

Molecular Classification: A landmark development is the classification into **4 major molecular subgroups**[57]: 1. **WNT-activated** – (~10% of cases). Typically older children (average ~10 years). Often arise from cerebellar peduncle region. Very good prognosis (5-year OS >90% with therapy)[57][58]. Characterized by CTNNB1 (β-catenin) mutations and often monosomy 6[59]. **Nuclear β-catenin IHC positive** in most (a diagnostic clue). Hardly ever metastatic at diagnosis[58]. 2. **SHH-activated** – (~30%). Can occur bimodally: infants and adolescents. Sonic Hedgehog pathway activated (mutations in PTCH1, SMO, SUFU, or amplifications like GLI2, MYCN). Prognosis intermediate, but varies: infants without TP53 mutation do well; older children with TP53 mutant SHH medullo (often associated with Li-Fraumeni) do poorly[60][61]. **Gorlin syndrome (PTCH1 germline)** predisposes to SHH medulloblastoma[60]. - SHH subgroup can be **SHH TP53-wildtype** (average prognosis) or **SHH TP53-mutant** (very poor, tends to be in 10–17 years old, often Li-Fraumeni)[60]. 3. **Group 3** – (~25%). Non-WNT, non-SHH, historically “classic” or “c-MYC driven”. Often infants or young children, frequently metastatic at diagnosis, often large cell/anaplastic histology. MYC amplification is common in Group 3, and it portends a very poor prognosis (5-year OS can be ~50% or less)[57]. Male predominance. 4. **Group 4** – (~35%). The most common subgroup. Characterized by certain structural variations (e.g. isochromosome 17q). No single dominant pathway like WNT/SHH. Intermediate prognosis. Often presents age ~7, more males. Frequently metastatic but outcome is a bit better than Group 3. Group 4 can have MYCN or CDK6 amplifications in some cases.

These molecular subgroups have **prognostic and potential treatment implications**[62]. They are now integrated into risk stratification along with clinical factors[63]. For example, WNT is “low risk” (excellent prognosis), standard therapy might be de-escalated; Group 3 high MYC is “very high risk” potentially needing intensification.

Histological Variants: - Classic (small round blue cells, Homer Wright rosettes common). - Desmoplastic/Nodular (with pale islands) – often SHH-subgroup infants. - Large cell/Anaplastic – aggressive histology, common in Group 3 and SHH TP53-mutant.

Diagnostic Workup: MRI of brain and spine pre-op (to assess metastasis)[64], and CSF cytology (lumbar puncture) after surgery (≥10–14 days post-op)[65]. Staging uses Chang criteria (M0 = localized, M1 = CSF microscopic, M2/M3 gross nodules, M4 extraneural). Molecular testing (by either IHC, sequencing or DNA methylation) is now standard to assign subgroup.

Standard Risk vs High Risk: Clinically, medulloblastoma patients are stratified: - **Standard/average risk:** Age ≥3, <1.5 cm^2 residual tumor post-op, and M0 (no metastasis). No high-risk molecular features. - **High risk:** Presence of metastatic disease (M1–M3), or large residual, or younger than 3 (though <3 usually separate infant category). TP53-mutant SHH is considered very high risk by some (in trials they separated it).

Treatment: Multimodal: - **Surgery:** Maximal safe resection is critical. Aim to remove as much as possible, often achieving >90% removal in many cases[66]. This relieves hydrocephalus and provides tissue for dx. Sometimes a CSF shunt or ETV is needed for hydrocephalus[67]. - **Radiation:** This is key for patients >3. **Craniospinal Irradiation (CSI)** is given to eradicate microscopic CSF disease. Standard-risk kids get **23.4 Gy CSI** (lower dose) and high-risk get **36.0 Gy CSI**[68][69]. All receive a **boost** to the posterior fossa or tumor bed (~54 Gy total)[68]. (Often 23.4 Gy CSI + 30.6 Gy boost = 54 Gy for average risk; 36 Gy CSI + ~18 Gy boost to ~54 Gy for high risk)[68]. Radiation is not used for infants <3 due to neurotoxicity[70]. - **Chemotherapy:** Combined with radiation and post-RT. The **"Packer regimen"** is classic for average risk: weekly vincristine during RT, then 6 cycles of CCNU (lomustine), cisplatin, vincristine[71]. High-risk protocols (COG ACNS0332) added **carboplatin** during RT and used higher CSI dose[72]. Infant protocols avoid RT and use intensive chemo ± autologous stem cell transplant (e.g. COG P9934, or Head Start III which includes high-dose methotrexate, etc.). In the Canadian consensus, recommendations were: - Average-risk (>3 years, non-metastatic): CSI 23.4 Gy + boost, with concurrent vincristine, then **adjuvant cisplatin, CCNU, vincristine** as per COG ACNS0331[71]. - High-risk (metastatic or residual): CSI 36 Gy + boost, with concurrent vincristine (±carboplatin) and intensive adjuvant chemo as per ACNS0332 Regimen A[72]. - Infants (<3): intensive chemotherapy (like CCG 99703 regimen) often with intrathecal chemo if high-risk features[73]. Some use high-dose chemo with stem cell rescue (Head Start or other) to avoid radiation[70]. - **Molecular-targeted therapy:** Not yet standard, but smoothened (SMO) inhibitors (vismodegib) were tried in SHH-subgroup trials (with limited success in upfront setting). Ongoing studies will incorporate subgroup stratification (e.g. de-escalating WNT: possibly omitting chemo or reducing CSI; escalating therapy for Group3). - **Supportive:** Endocrine follow-up (growth hormone, thyroid, etc.) since CSI causes hormonal deficits[74]. Neurocognitive rehab for learning issues.

Prognosis: - Average-risk medulloblastoma has ~75–85% 5-year survival with current therapy[75]. WNT-subgroup is ~95% survival (some consider it "cured" in most cases)[57].

- High-risk (metastatic) historically ~50–60% 5-year survival. Group 3 with MYC amplification is <50%. - Infants without RT: outcomes vary by biology; some cured with chemo alone, but many relapse. - Late effects are significant (neurocognitive decline, endocrinopathies, risk of strokes from RT, secondary malignancies, hearing loss from cisplatin, etc.).

Predisposition: - **Gorlin syndrome** (PTCH1 mutation) predisposes to SHH medulloblastoma[76][77]. - **Turcot syndrome type 2** (APC gene in FAP) predisposes to medulloblastoma (often WNT subtype)[59]. - **Li-Fraumeni** (TP53) – predisposes to SHH medulloblastomas in childhood; these patients (SHH+TP53 mutant) have particularly poor outcomes[61]. - **BRCA2/Fanconi anemia** biallelic mutations can also lead to medulloblastoma[78]. - **PALB2, GPR161, etc.:** recent research shows several other germline mutations in a proportion of medulloblastomas[78].

Atypical Teratoid/Rhabdoid Tumor (ATRT)

ATRT is a highly malignant embryonal tumor usually occurring in **infants and young toddlers**. It can arise anywhere in CNS (posterior fossa is common, also supratentorial). ATRT is characterized by **inactivation of the SMARCB1 (INI1) gene** (or rarely SMARCA4)[79]. This genetic hallmark distinguishes it.

- **Histology:** As the name suggests, it is "atypical" and heterogeneous (teratoid – mixed elements, rhabdoid – cells with eccentric nuclei and eosinophilic cytoplasm). Typically one sees rhabdoid cells (resembling rhabdomyoblasts) and a mix of primitive neuroepithelial and epithelial-looking areas. Can resemble medulloblastoma or PNET but with rhabdoid cells.
- **Molecular:** Loss of **SMARCB1 (INI1)** on chromosome 22q is seen in ~95%[79]. The remaining ~5% have loss of SMARCA4 (BRG1) instead. SMARCB1 is a tumor suppressor part of SWI/SNF chromatin remodeling complex. It can be germline mutated in **Rhabdoid Tumor Predisposition Syndrome** (some ATRT patients have a congenital mutation)[80].
- **IHC: INI1 protein is absent** in tumor nuclei (diagnostic)[80]. This is a critical diagnostic test (INI1-negative by IHC, whereas other embryonal tumors retain INI1). Other markers: epithelial membrane antigen (EMA) often positive, GFAP in some cells, neuronal markers in some – reflecting mixed lineage.
- **Classification:** There are molecular subgroups of ATRT (TYR, SHH, and MYC groups) identified by DNA methylation, which may have prognostic differences, but treatment is not yet subgroup-specific.
- **Clinical:** Rapidly growing tumor in infants; often presents with signs of increased ICP. Can disseminate via CSF early.
- **Treatment:** Due to patient age (usually <3), therapy avoids upfront radiation.
- **Surgery:** Attempt maximal resection; often difficult if large or invasive.
- **Chemotherapy:** Very intensive regimens are used. Common approach is **high-dose chemotherapy with stem cell rescue**. For example, the European Rhabdoid Tumor

Protocol and COG protocol ACNS0333 use multi-agent induction (vincristine, cisplatin, cyclophosphamide, etoposide, high-dose methotrexate in some) followed by high-dose thiotepa or carboplatin-based chemo with autologous stem cell transplant[81].

- **Intrathecal chemo:** Sometimes given (e.g. methotrexate, cytarabine) due to high risk of leptomeningeal spread[82].
- **Radiation:** Often **avoided or delayed** until child is older because infants suffer severe side effects. If tumor persists or recurs and child >3, focal RT (or even CSI if disseminated) might be done. Some centers do focal RT in children as young as 1 if needed (proton therapy can be considered).
- The Canadian consensus: ATRT therapy is "chemo per 99703 (infant brain tumor regimen) +/– maintenance chemo, avoid/delay RT"[83].
- **Prognosis:** ATRT is among the poorest of pediatric brain tumors. Median survival ~12–18 months in many series. Some improvement seen with aggressive regimens: 2-year survival up to ~30–40% in recent reports with high-dose chemo. Long-term survivors exist (especially if complete remission achieved and possibly with some radiation or focal therapy).
- **Predisposition:** ~30% of ATRT patients have a germline SMARCB1 mutation (Rhabdoid predisposition syndrome)[80], which also causes rhabdoid tumors in kidney or soft tissue. These families need genetic counseling and screening of siblings.

Embryonal Tumor with Multilayered Rosettes (ETMR)

ETMR is a rare, highly aggressive embryonal tumor typically in infants. It was defined in WHO 2016/2021 as combining entities like "ependymoblastoma" and "medulloepithelioma". A hallmark is **C19MC locus alteration** (a microRNA cluster amplification) on chromosome 19.

- **Histology:** Small round blue cell tumor with ependymoblastic rosettes (true multilayered rosettes reminiscent of embryonic neural tube). Also areas of neuroepithelial tube-like structures. It may have divergent differentiation.
- **Molecular:** ~90% have **C19MC amplification** (fusion of TTYH1 with C19MC region). If C19MC amp is absent, some still classify as ETMR if they have classic histology and LIN28A expression. **LIN28A** IHC is strongly positive in most ETMR and is a useful diagnostic marker[84].
- **IHC:** LIN28A positive (helps distinguish from medullo). INI1 is retained (helps vs ATRT).
- **Location:** Often supratentorial (cerebrum) in infants, but can be anywhere including brainstem.
- **Treatment:** No standardized regimen due to rarity, but generally maximal surgery and intensive chemo similar to other infant malignancies. Some have attempted

approaches like those for ATRT or using the Head Start protocol. Radiation is usually not feasible due to infant age. Outcome is extremely poor.

- **Prognosis:** Median survival <12 months in many cases. Very few long-term survivors reported.

CNS Neuroblastoma, FOXR2-activated

This is a new entity encompassing some tumors that were previously "CNS embryonal tumor NOS" which have a specific genetic driver: activation of FOXR2 (often by gene fusion).

- **Clinical/Pathology:** Occur in children, often cerebral hemispheres. Histology resembles other small round cell tumors (neuroblastoma-like or CIC-rearranged tumor-like) – small blue cells, maybe some neuropil-like areas.
- **Molecular: FOXR2** overexpression (via fusion with another gene, or other enhancer hijacking) is the defining feature (detected by DNA methylation profiling typically).
- **Treatment:** Given embryonal nature, would be treated like a high-risk PNET: surgery, craniospinal RT (if age allows), intensive chemo. But exact protocols aren't established (some might follow medullo or ETMR-like regimens).
- **Prognosis:** Not well-defined yet; likely poor if high-grade.

CNS Tumor with BCOR Internal Tandem Duplication

Another new molecularly-defined tumor (previously some "CNS PNET" fell here). Characterized by an **internal tandem duplication in the BCOR gene**.

- **Clinical:** Typically seen in young children, often supratentorial.
- **Histology:** High-grade round cell tumor, can have some faint resemblance to embryonal tumor or sarcoma.
- **Molecular:** BCOR ITD is identified via sequencing or methylation profile.
- **Treatment/Prognosis:** Also not well established. Analogous tumors outside CNS (e.g. clear cell sarcoma of kidney with BCOR) are aggressive. In CNS, limited cases but prognosis appears poor without intensive therapy. Likely treat with surgery + intensive chemo ± RT.

Other Rare Embryonal Tumors

- **CNS WHO 2021** lists **"CIC-rearranged sarcoma"** and **"intracranial sarcoma, DICER1-mutant"** which, while labeled sarcomas, can histologically resemble embryonal tumors and occur in children (discussed under mesenchymal section).
- **Medulloepithelioma:** A very rare primitive neuroepithelial tumor (previously separate, now usually considered under ETMR if multilayered rosettes). Arises in young kids, e.g. in the cerebrum or even retina (embryonal tumor of ciliary body).
- **Pituitary Blastoma:** An extremely rare embryonal tumor of the pituitary in infants, associated with DICER1 syndrome (see pituitary section).

Therapy Note: Historically, all non-medulloblastoma embryonal tumors in CNS were treated with "PNET protocols" similar to high-risk medulloblastoma (CSI + chemo). Outcomes for these (old CNS PNET category) were generally worse than medulloblastoma. With new molecular classification, tailored approaches may emerge (for example, ATRT now has dedicated protocols, ETMR might in future, etc.). However, whenever possible, aggressive multimodal therapy is used. The **Canadian consensus** suggests: - For **ATRT**: chemo-intensive approach, delay radiation[83]. - For **pineoblastoma**: often treated like high-risk medulloblastoma with CSI (see pineal tumors). - For **others** (FOXR2, BCOR): no specific mention, likely handled case-by-case.

Germ Cell Tumors (GCTs)

Intracranial germ cell tumors typically occur in children and adolescents, usually in the midline (pineal and suprasellar regions). They are analogous to gonadal germ cell tumors, with similar histologic subtypes. GCTs are most common in **East Asia** (higher incidence in Japan/Korea) but also occur in Western populations[85]. They constitute about 3–5% of pediatric CNS tumors in the West[86], and up to 8–10% in East Asia. Median age ~10–12 years; more common in males, especially pineal tumors (10:1 male/female for pineal germinoma)[85].

Types of CNS GCT: - **Germinoma** (also called pure germinoma or dysgerminoma/seminoma equivalent) – by far the most common (60–70% of intracranial GCTs)[87]. - **Non-germinomatous germ cell tumors (NGGCT):** includes - **Teratoma** (mature or immature; mature teratoma is benign), - **Yolk sac tumor (endodermal sinus tumor)**, - **Choriocarcinoma**, - **Embryonal carcinoma**, - **Mixed GCT** (with components of the above). - Also a special entity: **Teratoma with malignant transformation** (rare).

Clinical Presentation: - **Pineal region tumors** (pineal GCT): present with Parinaud's syndrome (upward gaze palsy), hydrocephalus (headache, vomiting). - **Suprasellar GCT**: present with diabetes insipidus, visual field deficits, hormonal deficiencies (hypopituitarism, delayed puberty). - Some patients have synchronous tumors in pineal and suprasellar ("bifocal" GCT) which strongly suggests germinoma[88]. - **Tumor markers:** These are critical for diagnosis. Germinomas can secrete low levels of beta-human chorionic gonadotropin (β-HCG) (usually <100 IU/L)[89]; if β-HCG is modestly elevated, it can still be pure germinoma[89]. Non-germinomatous components: yolk sac tumors secrete alpha-fetoprotein (AFP), choriocarcinoma secretes high β-HCG (often thousands). So serum and CSF **AFP and β-HCG** are measured; elevated AFP or high HCG indicates NGGCT[90]. - **Diagnosis:** If markers are diagnostic (e.g. clear elevation of AFP >10 or HCG >100), one may start treatment without biopsy (especially in midline where biopsy is risky)[91]. Otherwise, surgical biopsy or resection is done. Germinomas are soft, gray, homogenous; teratomas are more heterogeneous with calcifications.

Treatment and Outcome differ markedly between Germinoma and NGGCT:

Germinoma

Germinomas are very radiosensitive and chemo-sensitive, with overall excellent prognosis (survival >90% with proper therapy). The strategy is to use **combination of chemotherapy and radiotherapy** to minimize long-term effects: - **Chemotherapy:** Platinum-based chemo (carboplatin or cisplatin + etoposide, sometimes ifosfamide) is given for 2–4 cycles. - **Radiation:** After chemo, a reduced volume/dose radiation. Standard historically was full dose RT alone: CSI 24 Gy + boost to 45 Gy for germinoma, which cured ~90% but caused late effects. Modern approaches reduce field: - **Whole Ventricular Irradiation (WVI)** ~ 18–24 Gy with a boost to tumor bed (total ~30–36 Gy). This is for localized germinoma (pineal or suprasellar). - If multifocal or disseminated, **CSI** (21–24 Gy) with primary site boost ~boost to 30–36 Gy. - Some protocols use ** focal RT only **to tumor (~40–45 Gy) after chemo in localized cases, but risk of marginal relapse is higher, so WVI is more common now in NA. - In the** ACNS1123 trial **(COG), localized germinoma got chemo (carbo/etoposide) then 18 Gy WVI + 12 Gy boost (30 Gy total)[92]. Disseminated got 24 Gy CSI + boost[93]. -** Surgery: **Typically just biopsy. Resection not needed for germinoma because it responds well to chemoRT and surgery has high morbidity in those locations. -** Outcome:** ~90% event-free survival. Relapses can often be salvaged with additional RT or chemo + stem cell transplant.

Canadian consensus: for **Localized Germinoma**, chemo per ACNS1123 (carboplatin/etop) with **WVI ± boost**[94]; for **Disseminated Germinoma**, same chemo with CSI added[95].

Non-Germinomatous GCT (NGGCT)

These are more aggressive and require intensive therapy. Treatment: - **Chemotherapy:** 4–6 cycles of a intensive regimen. Commonly used is **PEI** (cisplatin, etoposide, ifosfamide) – this is the backbone of the **SIOP CNS GCT96** trial regimen[96]. COG's regimen **ACNS0122** used carboplatin, etoposide, and ifosfamide with cycles alternating with cyclophosphamide/vincristine, followed by high-dose chemo with stem cell rescue. Markers often drop to normal if chemo is effective. - **Second-look surgery:** Often after chemo, if residual tumor on MRI, surgical resection is attempted especially if it's a teratoma component (since mature teratoma doesn't respond to chemo/RT). This is debated, but many centers do resect residual masses. - **Radiation:** Crucial for cure. Because NGGCT have high risk of microscopic spread, **CSI** is typically given: - Localized (no metastasis on imaging/CSF): CSI ~30 Gy, plus primary tumor boost to ~54 Gy. - Metastatic: CSI ~36 Gy, plus boosts to primary and large metastases. - *Some European protocols (SIOP) if markers normalize and complete response achieved, use only focal RT, but North American standard is CSI for all NGGCT due to relapse risk.*[96]. - **Outcome:** NGGCT 5-year survival is ~70% in recent series. It's worse if there is choriocarcinoma or high HCG burden. Relapses often involve spine or CNS dissemination if not handled initially. - **Consensus practice:** Canadian centers use either SIOP or COG regimen; Table shows either **SIOP CNS GCT-96** or **ACNS0122**, with **localized NGGCT**: chemo then tumor bed RT[97], **disseminated NGGCT**: chemo then CSI[98]. - **Follow-up:** Both germinoma and

NGGCT need long-term endocrine and neuropsych follow-up. Hormone replacement is often needed (DI, sex hormones, thyroid, GH) especially for suprasellar tumor survivors.

Special notes: - **Teratomas:** Mature teratoma is treated with surgery alone (curative if totally removed). Immature teratomas might get chemo if malignant elements present. They do not need RT if no malignant component. - **Diagnosis nuance:** Sometimes biopsy of a germ cell tumor shows only germinoma but markers suggest NGGCT (i.e., an unseen yolk sac component). In such cases, treat as NGGCT (higher intensity), because treating as germinoma would under-treat the malignant component. Thus, therapy is guided by **highest malignancy component**. - **Bifocal germinoma:** If DI + pineal mass, often germinoma – these can be treated with cranial irradiation (covering both sites) and chemo, sometimes avoiding CSI since they are only intracranial, not spinal (some treat whole ventricles and both tumor sites).

Sellar Region Tumors

Tumors in the hypothalamic-pituitary region of children include **craniopharyngiomas** and less commonly **pituitary adenomas** (and extremely rare **pituitary blastomas** in infants).

Craniopharyngioma

Craniopharyngiomas (CP) are benign epithelial tumors arising from remnants of Rathke's pouch (embryonic pituitary precursor) in the suprasellar region. They account for ~5–10% of pediatric brain tumors[99]. Two histologic subtypes: - **Adamantinomatous craniopharyngioma (adamantinomatous CP)** – occurs in children; has wet keratin, "machine oil" cysts, calcifications. Driven by **CTNNB1 (β-catenin) mutations** leading to Wnt activation[100]. - **Papillary craniopharyngioma** – occurs in adults; has BRAF V600E mutations[101] (rare in children).

Children almost exclusively get the adamantinomatous type[100].

Clinical: Presents with symptoms of: - Increased intracranial pressure (headache, vomiting) from hydrocephalus. - Visual disturbances (classically bitemporal hemianopsia) from optic chiasm compression[102]. - Endocrine dysfunction (growth failure, diabetes insipidus, pituitary hormone deficits) from pituitary/hypothalamic compression[103]. - Often a mix of these.

Radiology: Typically a mixed solid-cystic suprasellar mass with calcifications (which are very common and a clue). Cyst fluid is often cholesterol-rich (motor oil appearance on aspiration).

Behavior: Benign (WHO grade 1) histologically, but can be locally aggressive due to location near critical structures (visual pathways, hypothalamus)[103]. Tends to adhere to surrounding brain, making complete resection difficult and risky. Local recurrences are common (even years later) if not completely resected or adequately irradiated.

Treatment Approaches: - **Surgery:** Traditional approach has been attempt at gross total resection (often via craniotomy or transsphenoidal if primarily in sella). While complete resection can cure, it carries significant morbidity (hypothalamic obesity, panhypopituitarism, cognitive issues)[104]. Modern strategy often favors a more conservative resection to avoid hypothalamic injury, followed by targeted therapy to residual (radiation or intracystic). - **Radiation:** Very effective in controlling residual craniopharyngioma. **Conformal fractionated radiation (~54 Gy)** is standard for residual tumor or recurrence[105]. Proton therapy is often used to spare normal tissue. In older children and adults, often a subtotal resection followed by radiotherapy yields equivalent tumor control to gross total resection but with fewer complications. - **Intracystic therapies:** Particularly for predominantly cystic tumors, **intracystic interferon-α2b** or **intracystic bleomycin** can be used. The Canadian survey noted that many centers use **intracystic interferon alpha** as first-line in young children with cystic craniopharyngiomas to delay or avoid radical surgery/RT[106][107]. Interferon is instilled via an Ommaya reservoir; it can shrink cysts in ~70% of patients and buy time[108][109]. It is relatively low-toxicity (flu-like side effects)[110]. - In the consensus, 8 of 16 Canadian centers use IFN intracystically for cystic cases[111]. Regimen example: IFN 3 million IU injected M/W/F for 4 weeks as one cycle[112]. - **Chemotherapy:** There are **no effective systemic chemotherapies** for craniopharyngioma[113]. Targeted therapy with BRAF inhibitors is an option for the rare pediatric papillary type (BRAF^V600E) – some adult case reports of BRAF inhibitor causing tumor shrinkage. - **Optimal strategy:** Many advocate limited surgery (like cyst decompression or partial removal to relieve pressure) plus radiation for tumor control, rather than radical resection, to preserve hypothalamic function[104]. Hypothalamic obesity and cognitive impairment are major concerns if the hypothalamus is damaged[114]. - **Endocrine management:** Almost all patients require lifelong hormone replacement (growth hormone, thyroid, adrenal, sex steroids, DDAVP for DI). - **Prognosis:** 5-year survival ~90% (most patients die with disease not from it). However, quality of life can be severely affected by obesity, vision loss, etc. Recurrence is common (up to 50% at 10 years if no radiation). Surveillance MRIs are needed long-term.

Pituitary Adenomas and Pituitary Blastoma

- **Pituitary Adenomas:** Rare in pre-pubertal children, but can occur in adolescence. Most often functional (e.g. Cushing disease from ACTH adenoma, or prolactinoma). They are WHO grade 1 benign neoplasms of pituitary gland. In pediatric patients, **prolactinomas** are actually relatively more common (especially in teenage girls or boys with macroadenomas). Treatment is usually medical for prolactinomas (dopamine agonists like cabergoline). ACTH adenomas causing Cushing's require transsphenoidal surgery. Growth hormone secreting adenomas (acromegaly) are extremely rare in childhood (gigantism).
- Pituitary adenomas can be part of **MEN1 syndrome** (rare in pediatrics).
- **Treatment:** Transsphenoidal surgery for non-prolactinoma adenomas. Medical therapy for prolactinomas. Radiotherapy only if persistent or recurrent unresectable tumors.

- **Prognosis:** Excellent in terms of tumor control, but hormone deficits can result either from tumor or treatment.

- **Pituitary Blastoma:** An extremely rare embryonal tumor of the pituitary in infants (usually <1 year). It arises in context of **DICER1 syndrome** often (so if diagnosed, test for DICER1 germline). Presents with Cushing syndrome in an infant (due to ACTH production) and a sellar mass.

- **Treatment:** Surgery (often subtotal) plus maybe chemo has been attempted, and occasionally radiation if child is old enough. Some cases have poor outcome, but a few survived with multimodal therapy.
- Because of rarity, it's included here only for completeness. It's essentially the only truly malignant pituitary-region tumor aside from metastases.

Pineal Region Tumors

The pineal gland (epithalamus) is location for various tumor types in children: - **Pineal Parenchymal Tumors:** pineoblastoma, pineal parenchymal tumor of intermediate differentiation (PPTID), pineocytoma. - **Germ cell tumors:** (already covered) – pineal is the most common site for germinoma and NGGCT. - Others: **Papillary tumor of pineal region (PTPR)** – rare, young adults; **Metastatic tumors** (rare in kids).

Pineoblastoma

Pineoblastoma is a primitive embryonal tumor of the pineal gland, considered a type of embryonal tumor (WHO grade 4), sometimes grouped with supratentorial embryonal tumors. It often occurs in infants and young children (under 5, but also up to preteens). It is part of "trilateral retinoblastoma" when associated with germline RB1 mutation (bilateral retinoblastoma + pineoblastoma).

- **Histology:** Small round blue cell tumor, very similar to medulloblastoma or other PNET. Flexner-Wintersteiner rosettes may be present (like retinoblastoma).
- **Molecular:** No specific defining mutation like medullo's WNT/SHH; however, pineoblastomas are strongly associated with **RB1 germline** (in patients with heritable retinoblastoma) and with **DICER1 syndrome** (pineoblastoma can occur in DICER1 patients, who also can get pituitary blastoma and other tumors – collectively "pinealoblastoma, pituitary blastoma and DICER1" have an association known as DICER1 syndrome)[115].
- **Clinical:** Presents with increased ICP (hydrocephalus) and Parinaud's syndrome. Often disseminated at diagnosis (M1 or M2).
- **Treatment:** Aggressive, similar to high-risk medulloblastoma:
- Maximal surgical resection if possible (though pineal region surgery is high risk).
- CSI (typically 36 Gy) + boost to pineal region (~54 Gy) for children >3.
- Multi-agent chemotherapy like medulloblastoma.

- In infants: use intensive chemotherapy with stem cell rescue (Head Start or COG ACNS0334 regimen) because RT is deferred.
- **Outcome:** Historically poor – 5-year survival often <50%. But with modern therapy, some improvement. Trilateral RB (with RB1 mutation) has very poor prognosis (most die within 2 years).
- Because of high risk, some treat like NGGCT if markers are negative. In the Canadian consensus, pineoblastoma wasn't separately listed, but would likely follow medulloblastoma high-risk style therapy (some protocols combine pineoblastoma with high-risk PNET regimens).

Pineal Parenchymal Tumors (PPTs: PPTID & Pineocytoma)

- **Pineocytoma:** A well-differentiated pineal tumor (WHO grade 1) occurring in adults mostly. Rare in children. Composed of mature pinealocytes with neuronal differentiation. Slow growing. Treated with surgery; excellent prognosis.
- **Pineal Parenchymal Tumor of Intermediate Differentiation (PPTID):** WHO grade 2 or 3, intermediate between pineocytoma and pineoblastoma. Occur in young adults and sometimes adolescents. More cellular and atypical than pineocytoma, but not as primitive as pineoblastoma.
- **Treatment:** Often surgery + focal radiation (around 50–54 Gy). Sometimes also chemo. Outcome variable, but generally better than pineoblastoma.
- These are rare in pediatric cases. If encountered, therapy is tailored to grade and behavior.

Papillary Tumor of the Pineal Region (PTPR)

A distinct tumor (WHO grade 2 or 3) thought to arise from specialized ependymal cells of pineal region (the subcommissural organ). Typically in young adulthood (mean ~30), but can happen in older children.

- **Pathology:** Papillary and epithelioid morphology, mucus production. Immuno: cytokeratins, transthyretin often positive.
- **Treatment:** Surgery + radiotherapy. Chemo role unclear. Tends to have chronic recurrence pattern.
- Rare in kids, mentioned for completeness.

Desmoplastic Myxoid Tumor of Pineal Region, SMARCB1-mutant

A newly recognized entity (WHO 2021) in pineal region that is **SMARCB1-mutant**, but unlike ATRT it's a distinct desmoplastic myxoid tumor (also called "pineal region rhabdoid tumor" in literature). Seems to occur in young patients.

- **Path:** Desmoplastic stroma and myxoid change, with some rhabdoid cells. Loss of INI1 by IHC (since SMARCB1 mutated).

- **Behavior:** Unclear, possibly somewhat less aggressive than ATRT (since distinct name given). But likely malignant.
- **Treat:** would likely treat similar to ATRT (SMARCB1 loss triggers ATRT-like therapy).
- This entity demonstrates that not all INI1-negative CNS tumors are classic ATRTs; location and histology matter.

Meningeal and Mesenchymal Tumors

Pediatric Meningiomas

Meningiomas are tumors of the meninges (coverings of brain). They are usually benign (grade 1) in adults. In children, meningiomas are rare but do occur, often in special contexts: - **Neurofibromatosis type 2 (NF2)**: causes multiple meningiomas from teens onward[116]. - History of cranial irradiation: childhood cancer survivors (e.g. leukemia CNS prophylaxis) can get radiation-induced meningiomas a decade later. - Some sporadic meningiomas happen, sometimes atypical or clear-cell variants, even in very young kids.

Features: Meningiomas in children more often have atypical histology and are more often located in unusual places (intraventricular, etc.) and a higher male ratio than in adults.

Pathology: Same as adult types (whorls, psammomas for grade 1; increased mitoses for grade 2 atypical; anaplastic features for grade 3). NF2-related meningiomas often have loss of NF2 gene (merlin)[116].

Treatment: - **Surgery** is primary; many pediatric meningiomas can be cured if totally resected (Simpson I). - **Radiation:** reserved for subtotally resected or higher grade meningiomas. In NF2 patients, often multiple meningiomas – radiosurgery is used for small ones, or watch-and-wait if asymptomatic. - **Medical:** Hydroxyurea was historically tried in unresectable cases; more recently targeted inhibitors (like SMO inhibitors for rare Hedgehog-mutated meningiomas, or bevacizumab) have been used in trials especially for NF2 cases.

Prognosis: Grade I meningiomas – excellent if resected. Atypical (grade II) have recurrence risk ~40% in 5 years; anaplastic (grade III) behave aggressively. Children, especially NF2 cases, often face multiple recurrences or new tumors over time.

Mesenchymal CNS Tumors (Intracranial Sarcomas)

These are rare. They include a variety of non-meningothelial mesenchymal tumors that can arise in the CNS: - **Chordoma:** A malignant bone tumor from clival/notochord remnants, often at skull base or sacrum. Rare in children, but clival chordomas do occur in adolescents. - **Intracranial Mesenchymal Tumor, FET-CREB fusion-positive:** New provisional entity (e.g. intracranial myxoid mesenchymal tumor with EWSR1-FUS-CREB fusion). These are rare low-grade tumors in young patients. - **CIC-rearranged sarcoma:** Highly malignant; originally described in soft tissue as CIC-DUX4 sarcoma, but similar can arise in CNS. Often presents like an embryonal tumor in children. - **Primary intracranial**

sarcoma, DICER1-mutant: Recognized in DICER1 syndrome patients (or sporadic) – e.g. a child with DICER1 mutation can develop an intracranial spindle cell sarcoma. - **Others:** Hemangiopericytoma (now called solitary fibrous tumor) can occur (though usually adult). - **Hemangioblastoma:** a vascular tumor associated with VHL disease, rarely in children unless they have VHL (then teenagers can get cerebellar hemangioblastomas).

Chordoma

- **Origin:** Skull base (clivus) or upper cervical chordomas can present in childhood, though most chordomas are adult.
- **Path:** Physaliferous (bubbly cytoplasm) cells in cords. Locally invasive into bone.
- **Molecular:** Brachyury (T gene) is overexpressed (used as IHC marker).
- **Treatment:** Surgery (often partial due to location) + proton beam radiation (high dose ~74 Gy). No effective chemo.
- **Outcome:** Tends to recur locally; 5-year survival for peds skull-base chordoma ~60-70%. With advanced RT, control improving.

Intracranial Mesenchymal Tumor, FET-CREB fusion-positive

- Likely refers to what used to be "angiocentric myxoid mesenchymal tumor" or similar – a low-grade neoplasm with EWSR1-ATF1 or other fusions.
- Occurs in young patients, often dura-based or intraventricular.
- Treated by resection; can recur but generally indolent.

CIC-rearranged Sarcoma

- Presents like an embryonal brain tumor (sometimes mistaken for AT/RT or ETMR). Often in cerebral hemispheres of children or young adults.
- Extremely aggressive and resistant to therapy; in systemic cases median survival <2 years.
- No established treatment; typically try surgery, chemo (sarcoma or PNET-like regimens), and radiation.

Primary Intracranial Sarcoma, DICER1-mutant

- DICER1 syndrome patients can develop these (e.g. pineal region or supratentorial).
- Pathologically can be a spindle cell sarcoma or anaplastic primitive tumor.
- Treated with surgery, chemo, RT akin to other high-grade sarcomas.
- Outcome variable; some long-term survivors if localized.

Hemangioblastoma

- Not truly a sarcoma, but a vascular neoplasm (WHO grade 1). Occurs mostly in VHL disease (mutated VHL gene). Can appear in teens with VHL (usually retinal hemangioblastomas first, then CNS).
- Location: cerebellum (most common), brainstem, or spinal cord.
- Presents with symptoms of mass effect.

- Treatment: Surgical removal is usually curative (highly vascular but benign tumor). In VHL with multiple lesions, often multiple surgeries or sometimes consider anti-angiogenic therapy (like pazopanib, off-label).
- Prognosis: Excellent for individual tumor, but VHL patients get recurrences/new tumors over time.

Nerve Sheath Tumors

Intracranial nerve sheath tumors in pediatrics are uncommon except in genetic syndromes.

Schwannomas (Vestibular Schwannoma)

Vestibular schwannomas (acoustic neuromas) on CN VIII are classic in **NF2** patients, who often present in late adolescence or young adulthood with hearing loss[116]. Sporadic vestibular schwannomas in children are extremely rare.

Other cranial nerve schwannomas (trigeminal, etc.) can occur in NF2 or sporadically (very rare in kids).

Treatment: - Observation is an option if small and hearing intact (especially in NF2, one might delay intervention to preserve hearing). - Microsurgical removal if growing or causing brainstem compression. - Stereotactic radiosurgery is often used in adults; in NF2 kids, bevacizumab (VEGF antibody) has been shown to shrink vestibular schwannomas and improve hearing in some cases (an important medical therapy in NF2) – this can delay need for surgery[116]. - Outcome: benign tumor, so not life-threatening unless untreated large tumor causing brainstem compression. NF2 patients often have bilateral tumors.

Other Nerve Sheath Tumors

- **Plexiform Neurofibromas:** Occur in NF1 patients, often in peripheral nerves (plexiform in neck, brachial plexus, etc.). Occasionally NF1 can have intracranial nerve neurofibromas (like optic pathway glioma is glial, not nerve sheath; but trigeminal neurofibroma rarely).
- **Malignant Peripheral Nerve Sheath Tumors (MPNST):** Very rare intracranially (usually peripheral). NF1 patients can develop MPNST from plexiforms, usually in body, not in brain.
- **Schwannomatosis (SMARCB1/LZTR1 mutations):** multiple non-vestibular schwannomas; can include intracranial nerves. Typically adult onset.

In summary, nerve sheath tumors in pediatric CNS are largely NF2-associated vestibular schwannomas and maybe trigeminal schwannomas. These require multidisciplinary management (neurosurgery, ENT, audiology, sometimes Avastin therapy).

Tumor Predisposition Syndromes

Certain hereditary syndromes greatly increase the risk of pediatric CNS tumors. Recognizing them is crucial for appropriate screening and management[117][118]. Key syndromes:

Neurofibromatosis Type 1 (NF1)

Gene: NF1 (17q) – tumor suppressor encoding neurofibromin (Ras regulator). Autosomal dominant.

CNS tumor associations: NF1 patients frequently develop **optic pathway gliomas** (pilocytic astrocytomas of the optic nerve/chiasm)[117]. These occur in early childhood. They can also get other brain gliomas (astrocytomas elsewhere, brainstem gliomas) and have higher risk of malignant peripheral nerve sheath tumors (though those are peripheral). NF1-associated gliomas are usually low-grade (JPA), but occasionally can be higher grade in teens.

Features: Café-au-lait macules, axillary/inguinal freckling, cutaneous neurofibromas, Lisch nodules in iris, etc. Learning disabilities common.

Screening/management: Yearly ophthalmology exams in childhood for OPG. If symptomatic OPG (vision loss), treat with chemo (usually carboplatin/vincristine or now often MEK inhibitors like selumetinib) – NF1 gliomas often respond to MEK inhibitors[3]. NF1 gliomas tend to stabilize after puberty.

(Citations: NF1 predisposes to low-grade gliomas, especially optic gliomas[119].)

Neurofibromatosis Type 2 (NF2)

Gene: NF2 (22q) – encodes Merlin. Autosomal dominant.

CNS tumors: Hallmark is **bilateral vestibular schwannomas** (acoustic neuromas) typically by young adulthood[116]. Also multiple meningiomas and spinal ependymomas[116]. Can also get other cranial nerve schwannomas.

Features: Bilateral hearing loss in teens/20s, meningiomas causing seizures or deficits, skin schwannomas (but fewer café-au-lait than NF1).

Management: Annual MRI screening of brain and spine from teenage years. Treat tumors individually (surgery or radiosurgery). Bevacizumab can cause vestibular schwannomas to shrink and improve hearing in NF2[120] (Merlin pathway influences VEGF).

(Citations: NF2 predisposes to schwannomas, meningiomas, ependymomas[116].)

Tuberous Sclerosis Complex (TSC)

Genes: TSC1 (hamartin) or TSC2 (tuberin). AD, though many de novo.

CNS tumors: Subependymal Giant Cell Astrocytoma (SEGA) in up to 10-15% of patients[12]. These arise in lateral ventricles near Monro and can cause hydrocephalus. Also cortical tubers (developmental hamartomas causing epilepsy) and subependymal nodules.

Features: Skin (facial angiofibromas, ash-leaf spots, Shagreen patch), epilepsy (infantile spasms often), cognitive impairment, renal angiomyolipomas, cardiac rhabdomyomas[12].

Management: Monitor via MRI for SEGA growth (especially in childhood/adolescence). Treat growing SEGAs with **everolimus (mTOR inhibitor)** – often shrinks tumor and can obviate surgery[12]. Epilepsy management (often surgery for tubers or newer drugs like everolimus can help seizures too).

Li-Fraumeni Syndrome (LFS)

Gene: TP53 (p53) germline mutation. AD.

CNS tumors: High propensity for **high-grade gliomas** (especially in childhood, e.g. glioblastoma) and **Choroid plexus carcinomas** (particularly in infants, CPC is a classic LFS tumor)[55]. Also can see medulloblastoma (SHH subgroup with TP53-mutant)[61].

Features: Very broad cancer spectrum (sarcomas, breast cancer, leukemia, adrenocortical carcinoma, etc.) at young ages.

Management: Intense surveillance (per Toronto protocol for LFS). Avoid radiation if possible (since radiation-induced cancers are a risk). If a child of LFS family presents with CPC or HGG, LFS should be suspected.

(Citations: TP53 (LFS) predisposes to gliomas, medulloblastomas, choroid plexus carcinoma[55].)

Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome)

Genes: PTCH1 (mostly) or SUFU. AD.

CNS tumors: Predisposes to **medulloblastoma, SHH subtype**[121]. Specifically, infants with Gorlin have ~5% risk of medulloblastoma (usually desmoplastic nodular subtype SHH). SUFU mutation carriers have an even higher medullo risk in infancy (up to 20%).

Features: Multiple basal cell carcinomas (especially after radiation, so avoid XRT), jaw keratocysts, calcification of falx, bifid ribs, etc[76].

Management: If a medulloblastoma patient has Gorlin (or germline SUFU), one crucial point is **avoid cranial radiation** if possible (because they will get hundreds of BCC skin cancers in radiation field). Therefore, treat with surgery and chemo only, or proton therapy to minimize dose, and rigorous skin monitoring. For PTCH1 Gorlin kids, use chemo-intensive protocols for medullo to delay/avoid RT.

(Citations: Gorlin syndrome (PTCH1, SUFU) predisposes to SHH medulloblastomas[60].)

Turcot Syndrome (FAP and Lynch subtypes)

Turcot refers to familial polyposis syndromes with CNS tumor predisposition: - **APC gene mutation (Familial Adenomatous Polyposis)** – associated with medulloblastoma (usually WNT subtype)[122]. In childhood, if a FAP patient develops a brain tumor, it's classically medulloblastoma. This is sometimes called Turcot Type 2. - **Mismatch Repair gene mutations (Lynch syndrome or Constitutional MMR-D)** – associated with high-grade gliomas (astrocytomas/GBM) in children[122]. Constitutional MMR deficiency (biallelic Lynch mutations) often causes childhood glioblastomas (and leukemias, early GI cancers) – sometimes referred to as Turcot Type 1.

Management: For APC carriers, standard medulloblastoma treatment (they tolerate therapy normally). For CMMRD patients, treat HGG as usual but they have extreme toxicity to alkylators (and radiation) and often second cancers, so it's very challenging.

(Citations: APC/FAP predisposes to medulloblastoma; Lynch/CMMRD to high-grade gliomas[122].)

Rhabdoid Tumor Predisposition (SMARCB1/SMARCA4 mutations)

Germline mutation of SMARCB1 (INI1) causes **Rhabdoid Tumor Predisposition Syndrome**. Affected infants can develop ATRT in the brain and/or rhabdoid tumors in kidney (RTK) or other sites.

- **SMARCB1** mutation: Often new in the child (parents phenotypically normal).
- **SMARCA4** germline: Causes a syndrome of ovarian small cell carcinoma in females and ATRT-like tumors.

Management: If an infant presents with ATRT, germline testing is indicated (up to 35% have germline SMARCB1/4)[80]. Family planning and sibling testing can be done as well. No preventive measures except vigilant early imaging if known mutation.

(Citations: 35% of ATRT patients have germline SMARCB1/SMARCA4[80].)

DICER1 Syndrome

Germline DICER1 mutation leads to a tumor predisposition syndrome with a variety of rare tumors: - CNS: **Pineoblastoma** (DICER1 is found in ~20% of pineoblastomas), **Pituitary blastoma**, and **intracranial sarcoma** with DICER1 mutation. - Others: Pleuropulmonary blastoma (lung), cystic nephroma, ovarian Sertoli-Leydig cell tumors, thyroid goiter or carcinoma.

Management: If child with pineoblastoma or pituitary blastoma, consider DICER1 testing. Typically inherited in families with other DICER1 tumors. Surveillance recommendations exist (chest imaging for lung tumor, US for thyroid etc.).

Cowden Syndrome (PTEN Hamartoma Syndrome)

Gene: PTEN (AD). **CNS association: Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease)** – essentially a hamartomatous overgrowth in cerebellum that can cause mass effect in young adults (rare in actual kids). PTEN mutations also slightly raise risk of other brain tumors (some gliomas reported) but not a strong link like others above. **Features:** Macrocephaly, trichilemmomas, breast/thyroid/endometrial cancers.

Management: MRI if LDD suspected. Otherwise no routine brain screening beyond clinical exam.

Von Hippel–Lindau (VHL) Disease

Gene: VHL (AD). **CNS tumors: Hemangioblastomas** of cerebellum, brainstem, spinal cord – typically starting in teenage years or 20s[123]. Also endolymphatic sac tumors in inner ear. **Features:** Retinal hemangioblastomas (vision loss), renal clear cell carcinoma, pheochromocytoma, pancreatic cysts/neuroendocrine tumors. **Management:** Annual MRI from adolescence. Remove hemangioblastomas when symptomatic (to prevent neuro deficits). They can recur/new ones form lifelong.

(Citations: VHL can present with medulloblastoma and hemangioblastomas in some contexts[124] – though medulloblastoma link is less direct, sometimes mentioned historically, hemangioblastomas are classic.)

Constitutional Mismatch Repair Deficiency (CMMRD)

This is essentially the biallelic form of Lynch syndrome – inheriting two mutated MMR genes (PMS2, MLH1, MSH2, MSH6). **CNS tumors:** Very high risk of childhood glioblastomas (often multiple), sometimes Lynch syndrome type brain tumor called gliomatosis. Also hematologic malignancies, and GI cancers in childhood. **Features:** Café-au-lait spots (can mimic NF1), consanguinity often in parents, childhood cancers. **Management:** Extremely difficult, but hypermutability means they sometimes respond to immunotherapy (PD-1 inhibitors) in trials. Avoid alkylator chemo if possible (they often fail it anyway).

(Turcot syndrome type was historically applied to CMMRD for glioma predisposition[59].)

Conclusion: This reference has compiled the spectrum of pediatric CNS tumors per the WHO 2021 classification (including newly defined entities)[5][125], along with key diagnostic criteria (clinical presentation, imaging, histology, molecular markers) and standard treatments drawn from current protocols (NCCN, COG, SIOP, etc.). Pediatric brain tumor management is increasingly risk-adapted, incorporating molecular features into therapy decisions[126]. Multidisciplinary care and attention to long-term effects (endocrine, neurocognitive, etc.) are essential for survivors. All data is up-to-date as of 2025 and sourced from authoritative guidelines and studies.

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