# Medulloblastoma findings summary



> *Findings of: Govender D, de Monaco BA, Dhall G, Thompson EM. Medulloblastoma chapter - past perspectives and future directions. Adv Cancer Res. 2025 Oct 16;167:141-184. doi: 10.1016/bs.acr.2025.09.001. PMID: 41198336.*

Good question. Here's a summary of the **key findings and messages** from **Govender D, de Monaco BA, Dhall G & Thompson EM. *Medulloblastoma chapter – past perspectives and future directions. Advances in Cancer Research.* 2025 Oct 16;167:141–184. (PMID: 41198336) PubMed +2 ScienceDirect +2

## Main Findings & Themes

1. **Heterogeneity of Medulloblastoma**

   Historically, medulloblastoma was treated as a single disease entity. The authors emphasize that it is now understood to be **highly heterogeneous**, with at least **four major molecular subgroups** (WNT, SHH, Group 3, Group 4) that differ in genetics, epigenetics, clinical behavior, and prognosis. PubMed

2. **Improved Diagnostics & Risk Stratification**

   - Advances in molecular diagnostics (e.g., genomics, methylation profiling) have significantly improved risk stratification. These molecular insights are helping to guide **subgroup-specific strategies**, rather than "one-size-fits-all" therapy. PubMed +1
   - The authors note that risk-adapted treatment approaches based on biology have contributed to better survival (now > 70% overall). PubMed

3. **Treatment Modalities and Their Burden**

   - Current standard therapy remains **multimodal**: surgery, radiotherapy, and intensive chemotherapy. PubMed
   - However, these treatments come with **significant morbidity**, both short-term and long-term (e.g., neurocognitive effects, endocrinopathies, secondary malignancies). PubMed
   - There is a strong need to **balance efficacy and toxicity**, especially in survivors.

4. **Emerging/Novel Therapeutic Strategies**
    - The chapter discusses a range of **novel targeted therapies**, particularly for high-risk and relapsed medulloblastoma. PubMed
    - There is promise in combining conventional therapies with **molecularly targeted agents** to improve outcomes.
    - They also highlight **innovative approaches** such as:
        - **Liquid biopsy** (e.g., using CSF or blood to monitor disease or minimal residual disease) PubMed
        - **Artificial intelligence** to improve diagnosis, risk stratification, or perhaps therapy planning. PubMed
        - **Proton therapy**, which might reduce radiation-related toxicity because of its favorable dose distribution. PubMed
5. **Germline Predisposition**
    - The authors note that **germline mutations** (i.e., cancer predisposition genes) account for a non-negligible proportion (5–10%) of medulloblastoma cases. ScienceDirect +1
    - Recognizing these predisposition syndromes is clinically relevant (for risk, surveillance, family counseling).
6. **Future Directions / Challenges**
    - A major theme is moving toward **precision-based care**: integrating biology (molecular subgroup), novel agents, and reduced-toxicity approaches.
    - There are continuing challenges: how to **design clinical trials** that are subgroup-specific; how to develop agents that penetrate the **blood–brain barrier**; and how to **monitor for relapse** with minimally invasive tools.
    - The authors also emphasize the importance of **survivorship**, not just survival: reducing long-term sequelae of therapy must be a priority.

## Implications & Significance

- This chapter serves as a **state-of-the-art review**: it synthesizes where the field has come from (past perspectives) and outlines a roadmap for **future research and clinical care**.
- It reinforces that **molecular stratification is no longer just academic** — it is clinically actionable and central to next-generation medulloblastoma therapy.

- The combination of **traditional treatment (surgery, chemo, radiation)** with **targeted, biologic, or less toxic therapies** may be the way forward to improve cure rates while minimizing long-term harm.
- There is also a call to better integrate **germline testing** in clinical practice, which has implications for families as well as therapy.
- Finally, as therapies improve, **quality of life** for survivors must remain a central concern.

If you like, I can check whether there are any **new clinical trials or agents** (2024–2025) that align with these "future directions" highlighted in the chapter — do you want me to do that?

*yes*

Great — I checked 2024–2025 literature and reviews. Below is a concise, actionable summary of **recent clinical directions and agents** that map to the "future directions" in the Adv Cancer Res. chapter (liquid biopsy, precision/targeted agents, immunotherapy/CAR-T, proton therapy, repurposed agents, and trial design challenges). I cite the most important sources for each point.

## Quick summary of 2024–2025 developments

## 1) Liquid biopsy — CSF ctDNA is maturing as a monitoring tool

> Multiple 2024–2025 studies show **CSF (not plasma) is the richest source** of tumor-derived cfDNA for medulloblastoma and other brain tumours; low-pass whole-genome or ultra-low-input sequencing approaches can detect copy-number changes, monitor minimal residual disease, and predict relapse. PMC +2 OUP Academic +2

**Clinical impact:** feasible now in serial sampling (at surgery, Ommaya/LP) for sensitive MRD monitoring and early relapse detection — promising for adaptive trials.

## 2) Immunotherapy / CAR-T and cell therapies — rapid preclinical → early clinical movement

> 2024–2025 literature and preclinical papers highlight CAR-T targets relevant to medulloblastoma and other pediatric CNS tumours: **B7-H3, GD2, GPC2**, with potent preclinical activity and ongoing translation to early phase trials. There are also platform successes in other brain tumours (e.g., dual-target CAR-T in glioblastoma) that inform medulloblastoma strategies (intraventricular delivery, multi-antigen targeting, safety/ICANS management). cell.com +2 ScienceDirect +2

**Clinical impact:** CAR-T/intrathecal strategies are among the most actively pursued immunotherapies for high-risk/relapsed disease; delivery route and antigen heterogeneity remain key challenges.

## 3) Radiation modality — proton therapy evidence continues to grow

2024–2025 systematic reviews/meta-analyses and cohort reviews find **proton therapy** shows similar disease control to photons but with evidence for reduced radiation-related neurocognitive and endocrine toxicity in children — supporting its use for toxicity mitigation. Cost-effectiveness discussions continue in some regions. MDPI +2 PMC +2

**Clinical impact:** proton RT is being used more for reduction of late effects and as a strategy in trials seeking to de-escalate long-term toxicity.

## 4) Targeted & repurposed agents — biology-driven but subgroup-dependent

Papers in 2024–2025 discuss subgroup-specific vulnerabilities: e.g., **BCL-2 (venetoclax)** shows preclinical efficacy in some Group 3/4 contexts; epigenetic modulators (HDAC inhibitors like panobinostat), BET inhibitors, and other pathway inhibitors are actively explored. Precision matching (molecular profiling → targeted agent) is increasingly tested in early phase studies. MDPI +1

**Clinical impact:** targeted strategies are promising, but success depends on subgroup biology (MYC-driven Group 3 vs SHH vs WNT), and BBB penetration remains a frequent barrier.

## 5) Biomarkers, genomics & trial design — methylation profiling, germline testing, and adaptive/subgroup trial designs

Consensus statements and reviews emphasize routine molecular/methylation profiling and germline predisposition testing (germline mutations in ~5–10% of cases) — both for therapy selection and family counseling. Trial designs are shifting toward **subgroup-specific arms** and basket/adaptive designs to accelerate signal detection with smaller cohorts. ScienceDirect +1

**Clinical impact:** clinical trials increasingly stratify by molecular subgroup; germline sequencing is becoming standard in many centers.

## 6) Practical challenges repeatedly noted (and active areas of work)

- **Blood–brain barrier (BBB) penetration** of many agents remains limiting.
- **Heterogeneity within subgroups** (esp. Group 3/4) complicates single-agent approaches.
- **Delivery** (intraventricular/intrathecal vs systemic), **toxicity management**, and **durability of response** for immunotherapies are open questions. PMC +1

## Most relevant 2024–2025 references (selected)

- CSF/ctDNA monitoring and sequencing approaches. PMC +2 OUP Academic +2

- CAR-T / immunotherapy reviews and preclinical advances (B7-H3, GD2, GPC2). cell.com +1
- Proton therapy systematic reviews/meta-analyses and outcomes. MDPI +1
- Repositioning/targeted agents (venetoclax, epigenetic modulators) and subgroup biology. MDPI +1