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REVIEW

Medulloblastoma: Molecular Classification-Based Personal Therapeutics

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Abstract Recent advances in cancer genomics have revealed 4 distinct subgroups of medulloblastomas, each with unique transcription profiles, DNA alterations and clinical outcome. Molecular classification of medulloblastomas improves predictions of clinical outcome, allowing more accurate matching of intensity of conventional treatments with chemotherapy and radiation to overall prognosis and setting the stage for the introduction of targeted therapies.

Keywords Medulloblastoma · WHO · MYC · SHH · WNT · Genomic · DNA methylation · Subgroups · Group 3 · Group 4

Introduction

Medulloblastoma is one of the most common malignant brain cancers in children and accounts for 8% to 10% of childhood brain tumors. Medulloblastoma research has also been on the leading edge of cancer genomics. The insights gained from genome-wide analysis of DNA alterations and gene transcription are starting to translate to the clinic. These studies have shown that medulloblastomas consist of at least 4 distinct subgroups that have unique transcription profiles, somatic DNA alterations, and clinical outcomes. An international consensus defining these subgroups has been accepted as the basis for diagnostic criteria by the World Health Organization (WHO), revealed in the recently published revised fourth edition of the WHO Classification of Tumors of the Central Nervous System [1, 2]. The WHO classification now includes medulloblastoma molecular subgroups that are of immediate prognostic value for patients, and set the stage for clinical trials of new targeted therapies (Table 1).

We and others first profiled the genomic mutation landscape of medulloblastoma in 2012 [3–5]. Three papers published back-to-back identified mutated genes, and delineated the extent to which these mutations were specific to the transcription- and copy number-based subgroups previously characterized [1, 6–9].

Now, nearly 5 years later, these findings are just starting to translate to clinical trials [10–14]. Standardization of the methods to define medulloblastoma subgroups in a "real-time" clinical setting remains a significant challenge, but the WHO guidelines will help to pull subgroup methods from the laboratory into the clinic more rapidly (Table 1). Accurate and timely clinical subtype assignments will be the basis for molecular subclassification-based personal therapeutics in medulloblastoma. With tumor subgroup in hand, it will plausible to more precisely risk-stratify patients and tune traditional treatment modalities, and identify candidates for emerging targeted therapies.

Medulloblastoma research is now moving into the postgenomic era of cancer research. Most cancer types have had large cohort sequencing studies published, and it is likely that the large majority of coding sequence oncogenic mutations have been discovered [15, 16]. Practical implementation of genomic methods is feasible owing to the plummeting cost from evolving DNA sequencing technologies [17]. However, knowing the population-wide genetic events in cancer has not yielded a corresponding systemic shift in survival rates.

Historically, the largest major leap forward in cancer survival for most solid tumors came in the 1950s—when radiation treatment became part of the standard of care for most

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Table 1 2016 World Health Organization (WHO) Histological Classification of Tumours of the Central Nervous System—medulloblastoma diagnosis (modified from [2])

WHO classification subgroup	Histology subtype	**Prognosis and demographic notes**
Medulloblastoma, WNT-activated	Classic	Low risk
	Large cell/anaplastic (very rare)	Uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53 mutant	Classic (rare)	High risk
	Large cell/anaplastic	High risk; prevalent in children aged 7–17 y
	Desmoplastic/nodular (very rare)	Uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53 wild type	Classic	Standard risk
	Large cell/anaplastic	Uncertain clinicopathological significance
	Desmoplastic/nodular	Low risk in infants; prevalent in infants and adults
	Extensive nodularity	Low risk in infants
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard risk
	Large cell/anaplastic	High risk
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard risk
	Large cell/anaplastic (rare)	Uncertain clinicopathological significance

WNT = wingless; SHH = Sonic hedgehog

cancers [18]. This was owing to the discovery of megavoltage linear accelerators (linac) machines. Linacs delivered radiation with more precision, at higher dosages, and with deeper penetrance than the previous technology [19]. Since the 1970s, the 5-year overall survival rate for all patients with cancer has increased by about 20% (American Cancer Society Cancer Facts and Figures 2016). These gains came from early diagnosis, and chemotherapy treatments. Some cancers, like prostate, testicular, and leukemias, have seen the biggest gains. Survival rates of other cancers have barely changed, such as lung cancer survival rates, which have only increased 3% to 16% [20].

There are 2 main reasons that have constrained cancer genomic insights from translating to improved therapies. First, as is the case for medulloblastoma, there are few druggable targets, in part owing to a lack of effective drugs, and also because of the striking heterogeneity of genomic alterations across patient tumors samples even within a subgroup. Second has been the instability of the disease with continued acquisition of new genetic abnormalities, which allows for rapid development of resistance to targeted therapies. Indeed, even for cancers with a large percentage of patients having the same genetic alteration that a targeted therapy can be designed against—V600E *BRAF* mutations in melanoma being an example—the tumors evolve rapid resistance to that targeted therapy vemurafenib (PLX4032) [21–23]. A clear exception to this is leukemia—specifically chronic myeloid leukemia (CML). CML proves that the right targeted therapy can restore normal life expectancy [24]. Close to 90% of all CMLs share the same BCR–ABL fusion, or so-called Philadelphia chromosome. The tip of the long arm of chromosome 9 breaks at the ABL gene and this becomes fused to another break in chromosome 22 at the BCR gene. This creates a novel oncoprotein BCR–ABL which functions to maintain constitutive tyrosine kinase activity. The tyrosine kinase inhibitor imatinib (Gleevec) inhibits phosphorylation of the BCR–ABL target [25]. Gleevec prevents the progression of CML into the fatal form, but it must be taken continuously [26]. As with other cancers, emergence of resistance in responsive tumors has been an issue, but further development of targeted therapies has enabled therapists to overcome this resistance in many cases. The success of Gleevec demonstrates that a well-characterized genetic lesion that is stable from patient to patient makes it a tractable system to find the best drug.

More heterogeneous cancers, like medulloblatoma, are going to require a new model for drug discovery that is based upon more of a personalized medicine approach, or at least a subgroup-focused approach based on within subgroup similarities. Subgroups based on histology were first reported in the 1980s, but they were found to predict poorly clinical behavior [27, 28]. In 2002, the analysis of genome-wide array-based expression data demonstrated that biologically distinct molecular subgroups exist and that gene expression profiles were more accurate for predicting clinical behavior than histologic or clinical criteria [9]. Further refinement of methods and increased tumor cohort size has led to the current classification schema, as noted above. Subgroup-specific approaches are being adopted for clinical trials, allowing modification of standard treatments, including changes in radiation dosage or chemotherapy schedules, and the inclusion of novel targeted interventions. Now is the time that we can start to increase survival rates that have held steady for nearly half a century while at the same time improve the quality of life of survivors by reduced toxicity of treatment, and this will be

done by finding the right treatments for the right group of patients.

Medulloblastoma Subgroups and Clinical Significance

Medulloblastoma comprises multiple molecular subgroups, which, importantly, have distinct prognoses [1, 6–9]. There is an international consensus that 4 major subgroups exist, and their names reflect our understanding of their mechanisms—WNT, SHH, group 3, and group 4 [1, 6, 29], but as this consensus was reached it was already clear that there are molecular subgroups within these subgroups that have clinical relevance, which was clearly reinforced in a retrospective meta-analysis of 402 tumors [6, 30]. These subgroups are durable and further recapitulated using other genome-wide data such as DNA methylation profiles [31].

Current treatment regimens for medulloblastoma patients have stayed largely consistent for the last 2 decades. For children > 3 years of age, it is based on external beam radiation to the brain and spine with a boost to the tumor bed, together with combinations of multidrug chemotherapy [32, 33]. Medulloblastoma has 2 main treatment stratification levels based on clinical criteria—average risk and high risk [34]. Average-risk medulloblastomas have < 1.5 cm^2 residual tumor following surgical resection and no metastases, while high risk are metastatic at diagnosis and/or > 1.5 cm^2 residual tumor [35]. Average-risk tumors are treated with 23.4 Gy craniospinal irradiation, with a boost to the tumor bed of 55.8 Gy. Higher risk increases the craniospinal irradiation radiation to between 36.0 and 39.6 Gy, depending on extent of metastasis. Both average and high-risk patients receive a multidrug chemotherapy regime of four 28-day cycles of cyclophosphamide, cisplatin, and vincristine [34, 36, 37]. Children < 3 years of age are treated are differently. For these children, a major goal is the elimination or great reduction of radiation to the brain and spine, which have been shown to be particularly devastating to the developing brain in these early years of life. Indeed, high-dose chemotherapy in young children and infants without radiation gives nearly 75% overall 5-year survival for favorable subgroups such as the desmoplastic nodular variant [38].

This treatment scheme has led to excellent overall survival rates in medulloblastoma—85% overall 5-year survival for average risk and 70% for high risk [11, 39]. Unfortunately, these treatments can be devastating to the survivors. Surgery itself has many complications such as cerebellar mutism syndrome, which causes detrimental effects on speech, cognition, and behavior of the patients [40]. Radiation is even more devastating to the quality of life in the survivors [13, 41]. Medulloblastoma is generally more radiosensitive than other brain cancers such as glioblastoma, but radiation dosages have not been able to be further reduced without negatively affecting survival [42–44]. Radiation reduces IQ and the magnitude of the reduction is inversely related to the age of the patients. The youngest patients can lose up to 40 IQ points [45]. Many of these children do not grow up to live independently as adults [41, 46, 47]. Radiation can cause secondary cancers, hearing loss, and radiation-induced vasculopathy and strokes [48–51]. There is a desperate need for improved therapies in medulloblastoma that could help to reduce the amount of radiation needed, and especially in the youngest of patients.

Central to the goal of reducing radiation is to identify improved targeted therapies in medulloblastoma. Targeted therapies are likely to be predicated on medulloblastoma subgroups. Having the 2016 WHO guidelines for medulloblastoma diagnosis incorporate subgroups will be a major leap forward toward these goals (Table 1). Here we list the WHO subgroups, give their defining features from molecular and genomic studies and summarize the current therapeutic opportunities these may have.

Wingless Activated

Wingless (WNT) signaling activated subgroup tumors are the least common of the medulloblastoma subgroups, accounting for just 11%. Overall, medulloblastoma afflicts boys more often than girls, but the WNT subgroup affects both sexes equally. The peak age of diagnosis for WNT tumors is 6 to 10 years of age [52]. WNT is also remarkable for its very favorable prognosis. Nearly 90% of patients survive for more than 5 years [53]. WNT tumors are named because they are dominated by a WNT signaling and activated β-catenin (*CTNNB1*) signature. Indeed, the DNA sequencing studies identified that almost every tumor in the subgroup harbors a stabilizing point mutation in *CTNNB1* [4, 5]. The majority of WNT subgroup tumors share similar genomic events; in addition to *CTNNB1*, almost universally they have monosomy chromosome 6. The WNT activated subgroup can be clinically diagnosed by nuclear accumulation of catenin beta 1 (CTNNB1) immunohistochemistry of tumor sections [54]. Furthermore, half of all WNT tumors contain mutations in X-linked RNA helicase *DDX3X*. *DDX3X* has subsequently been found in to be recurrently mutated in a number of other cancers, including head-and-neck, mesothelioma lung cancer, lymphoma, and leukemia [55–59]. As seen in medulloblastoma, *DDX3X* is on the X chromosome and it appears to have also have a strong sex bias for mutations [60, 61].

Germline mutations can be associated with WNT medulloblastoma, but these are rare events. A small cohort study, including 10 WNT tumors, identified 2 patients with germline lesions in anaplastic lymphoma kinase gene (*ALK*), a tyrosine kinase receptor, [62]. A separate case study had previously reported a germline *ALK* mutation in a medulloblastoma

tumor of unknown subgroup [63]. ALK mutations lead to constitutive activation of nuclear factor kappa B pathway, which may indirectly activate WNT through crosstalk of the pathways [64, 65]. Germline mutations in another WNT pathway regulator can also lead to medulloblastoma. Turcot syndrome with familial adenomatous polyposis is an inherited cancer predisposition syndrome that is caused by loss-of-function mutations in adenomatous polyposis coli (APC) [66]. Familial adenomatous polyposis is associated both with colorectal adenomas and medulloblastoma. APC downregulates β-catenin directly through phosphorylation events; consequently, its mutations lead to increased WNT signaling [67]. Somatic mutations in APC have also been identified in spontaneous medulloblastoma [68].

Recent work has suggested that the favorable prognosis in WNT tumors is because they have a very leaky vasculature, which allows for improved delivery of chemotherapy agents to the tumor cells [69]. The breakdown in the blood–brain barrier in WNT tumors is thought to be because they secrete the diffusible WNT antagonists, WIF1 and Dickkopf-related protein 1. Inhibiting WNT signaling to the surrounding vasculature disrupts its integrity as WNT is required for proper angiogenesis in the central nervous system [70]. Clinical trials are currently underway to leverage these insights so that patients with WNT subgroup medulloblastomas can be effectively treated with less chemotherapy and/or less radiation (ClinicalTrials.gov identifiers NCT01878617 and NCT02212574). There is some preliminary evidence to support that patients with WNT tumors treated with less radiation do, indeed, preserve more of their intellectual capabilities [13].

Drugging the WNT pathway for treatment of cancers, not just medulloblastoma, has been a vexing problem [71, 72]. WNT signaling is used so ubiquitously for key functions in the human body that its inhibition is not without risks and side effects. For example, it is required for bone formation and its reduction can lead to osteoporosis. Furthermore, the signal transduction pathway has so many multilayered points of regulation it is not always clear what level in the pathway is best to target for precise and durable benefit. As WNT-activated medulloblastoma tumors are nearly universally driven by stabilizing mutations in *CTNNB1*, targeting its interaction with another transcription factor, CREB binding protein (CREBBP), to inhibit transcription of their target genes would be a rational approach. PRI-724 is a CREBBP:CTNNB1 interaction antagonist that is being investigated in phase I clinical trials in pancreatic and liver cancers (ClinicalTrials.gov identifier NCT02413853).

In medulloblastoma, drugging the WNT pathway will need to be done with caution. It is worth noting that WNT medulloblastoma tumors can also harbor mutations in CREBBP, and the extent to which this may affect the efficacy of the drug in these tumors is unknown [4]. More troubling is that inhibiting WNT could actually make the tumors more resistant to the chemotherapy treatments. If the elevated intratumor WNT signaling is, indeed, driving the leaky vasculature and better delivery of chemotherapy, it is possible that inhibiting that intratumoral WNT signaling could improve the integrity of the blood–brain barrier and make the tumors more resistant to the chemotherapy.

Sonic Hedgehog-Activated

The Sonic hedgehog (SHH) subgroup is also named for the signaling pathway that dominates these tumors. SHH tumors have a bimodal age distribution and they afflict both the youngest and oldest patients with medulloblastoma, but spare the middle of childhood [52]. The SHH subgroup of medulloblastoma comprises 25% of all cases [73]. Overall survival for the group at large is 70% [6]. However, some key features affect outcome, specifically *TP53* status. *TP53*-mutant cancers have a much worse prognosis with roughly a 40% 5-year overall survival rate *versus* 80% in *TP53* wild-type SHH tumors [74]. *TP53* mutation status elevates the patients to high risk as these tumors are more resistant to therapy and frequently reoccur. Therefore, the WHO criteria define 2 subclasses: SHH-activated and *TP53* mutant, and SHH and *TP53* wild-type. In some cases, *TP53* mutations have been found to be germline in medulloblastoma [74]. Li-Fraumeni syndrome, caused by germline mutation of *TP53*, is an inheritable or spontaneous genetic disorder that increases lifetime cancer risk, especially in pediatric cancers [75, 76]. Because of TP53's checkpoint role for DNA damage, repair, and cell death, radiation treatment can help to accelerate the tumors and this is of keen importance in patients with Li-Fraumeni syndrome [77]. Interestingly, *TP53* mutations occur in the WNT subgroups, but this does not decrease survival [74]. *TP53* mutant SHH tumors also have a higher rate of *MYCN* locus amplification and chromothripsis [74, 78].

SHH tumors also can be linked to inheritable or spontaneous germline mutations in SHH pathway member proteins—including protein patched homolog 1 (PTCH1)—which cause Gorlin's syndrome [79]. Other mutations in the SHH pathway found in the tumors are the SHH receptor, smoothened (SMO), and transcription factor GLI2 [3–5]. Patients with Gorlin's syndrome have a lifetime risk of developing cancer of > 90% and radiation exacerbates this. Radiation treatment in patients with medulloblastoma with Gorlin's syndrome should be avoided as it can cause many secondary cancers such as basal cell carcinoma and meningiomas [80, 81].

The SHH subgroup itself can be further subdivided into other up to 3 subclasses using transcriptome and DNA methylation data, and it is age that is the underlying feature that stratified these subclasses [82, 83]. Infant, childhood, and adult SHH medulloblastoma have unique expression profiles and genomic lesions [83]. Overall, infant SHH has a much

lower mutation rate than childhood and adult SHH tumors, as expected. The 2 most common mutations in infants are PTCH1 and SUFU, and nearly half of the SUFU mutations are germline events. Children aged 4 to 17 years commonly have TP53 or PTCH1 mutant cancers, and the TP53 mutations are frequently germline. Co-occurrence of *GLI2* and *MYCN* loci amplification are also common in childhood SHH tumors. Childhood SHH medulloblastoma have a high rate of copy number aberrations, which is thought to be caused by a genome-wide shattering event known as chromothripisis. These patients have the worst outcome in the SHH subgroup, and are generally treated with high-risk protocols. Owing to the high rate of germline TP53 mutations in this subgroup, the increased use of radiation needs to be applied with caution. The WHO criteria for SHH considers TP53 status for diagnosis so this will start translating directly into the clinic as the new guideline are adopted (Table 1). Adult patients with SHH medulloblastoma, in contrast, are the population that may benefit most from SHH-targeted therapies as > 80% of adult SHH medulloblastoma are driven by either PTCH1 or SMO mutations [83]. It has been a tantalizing idea to inhibit SHH signaling as a treatment option for this subgroup, and specifically in the adult cases. SMO is a transmembrane protein that in its wild-type state is tonically inhibited by PTCH. All other elements of the SHH pathway are downstream of SMO. The best inhibitors to the SHH pathway are SMO antagonists. Mutations in proteins downstream to SMO, including intracellular activators and transcription factors, are immune to SMO-inhibiting drugs. Indeed, a recent phase II clinical trial for vismodegib in 12 SHH subgroup medulloblastomas found that the patients who responded to the treatment were those with PTCH1 mutations [84, 85]. Vismodegib (Erivedge®) is a synthetic SMO inhibitor based on cyclopamine, the naturally occurring SMO receptor inhibitor found in *Veratrum californicum* (California corn lily), which famously causes cyclopia birth defects [86, 87]. Patients with *SUFU* and *GLI1* mutations were not affected by the drug. In conclusion, SMO inhibitors act only on tumors with genetic mutations that are upstream of *SMO* in the pathway. Adult SHH are the best candidates to benefit from this therapy in contrast to childhood and infant patients with SHH medulloblastoma [83].

Non-WNT/Non-SHH (Group 3)

Group 3 medulloblastomas are defined by their expression of MYC, photoreceptor, and γ-aminobutyric acid-ergic gene signatures [1, 6]. Group 3 comprises close to 25% of all cases and peak diagnosis is between 3 and 5 years of age. With a 50% overall survival rate this is the deadliest subgroup of medulloblastoma. MYC signature activation is associated with poor outcome in this subgroup, and just 20% of those patients survive for 5 years [6, 7]. MYC activation is driven by *MYC* loci amplification, *PVT1–MYC* genomic rearrangement, or another unknown mechanism [7, 88, 89]. Group 3 also commonly has isochromosome 17q, *GFI1* enhancer activation, and *OTX2* amplification. Imbalances in chromosome 17 have been linked to poor-outcome medulloblastoma, mainly when it occurs together with *MYC* amplification [54, 90]. Group 3 tumors relapse via metastasis and rarely with recurrence of tumor at original location [91].

Group 3 medulloblastomas have been a major focus for experimental therapeutics because of their dismal prognosis. However, there has not been a clear path to targeting a transcription factor like MYC [92, 93]. Novel BRD4 bromodomain inhibitors such as JQ1 have been recently developed to interrupt the hyper-transcriptional activity of MYC-driven medulloblastoma cell lines and xenografts [94, 95]. As yet, there are no bromodomain inhibitors with Food and Drug Administration approval for use in adults. Currently, there are ongoing phase I clinical trials in other bromodomain inhibitors such as CPI-0610 and MK-8628 in adult cancers.

The Food and Drug Administration-approved breast cancer drug palbociclib has been recently nominated for use of MYC-driven medulloblastoma in preclinical testing using a large-cohort *in silico* drug screen and medulloblastoma cell-line models [96]. Palbociclib is a cell-cycle checkpoint inhibitor (CDK4/6) and MYC-driven medulloblastomas appear to depend on CDK4/6 for their proliferation. Palbociclib is currently being investigated in a clinical trial for medulloblastoma and other pediatric brain cancers (ClinicalTrials.gov identifier NCT02255461).

Non-WNT/Non-SHH (Group 4)

Group 4 medulloblastomas remain the most mysterious of all. It is the most common subgroup and comprises 35% of all cases and is more likely to affect males. They were first defined by their enrichment for γ-aminobutyric acid-ergic and neuronal gene sets. Group 4 medulloblastoma have a high burden of chromosomal copy number variations. Unlike MYC-amplified group 3 tumors, isochromosome 17q does not equate to poor outcome in group 4. Patients with group 4 tumors with either i17q or chromosome 11 loss have improved outcomes compared with group 3 patients with i17q [97]. Group 4 medulloblastomas have an excellent prognosis, ranging from 88% to 95%, depending on risk group [11]. Metastasis at is the main indicator of high risk in patients with group 4 tumors [30, 97].

Chromatin remodeler *KDM6A* mutations are the only subgroup-specific recurrently mutated genes and only found in 13% of patients with group 4 [98]. *KDM6A* is a lysine demethylase and preferentially demethylates H3K27me3 during differentiation [99, 100]. *KDM6A* loss of function mutations lead to a retention of these marks and a resistance of

differentiation. Group 4 tumors without *KDM6A* mutations can reach a similar state by overexpressing the methylase *EZH2*, which puts down the H3K27me3 mark [4]. *EZH2* is overexpressed in group 4 tumors via loci application, and these are mutually exclusive of the *KDM6A* mutations, which suggests this epigenetic inflexible state may be a more common feature of the subgroup.

Future Directions

Epigenetic mechanisms are altered across every subgroup of medulloblastoma and are emerging as a major theme across the cancer landscape following the results of large-cohort sequencing studies [17, 101]. Because of this universality, there have been major efforts to identify treatments that target epigenetic regulators [102]. Medulloblastoma has recurrent mutations in histone modifiers [MLL2/3; KDM6A; CREBBP; histone deacetylase (HDAC)], co-repressor complexes (BCL6 corepressor, nuclear receptor corepressor 2, G protein pathway suppressor 2, LIM domain binding 1), and RNA helicases (DDX3X) [17]. Research to develop drugs that target dysregulated epigenetic mechanisms is in progress. Indeed, large-scale *in vitro* studies have found cancer cell lines to be sensitive drugs targeting chromatin regulators such as HDAC and enhancer of zeste homolog 2 inhibitors [103, 104]. There are many challenges, including an often narrow therapeutic window, owing to the targeting of epigenetic mechanisms in normal cells, as well as those in tumors, and a tendency for inhibition to be cytostatic rather than cytotoxic. Drug combinations that combine cytostatic and cytotoxic properties will almost certainly be needed for efficacy in cancer treatment. For example, *in vitro* testing of mouse-model group 3 medulloblastoma tumors has nominated a combination of antifolate drug pemetrexed and nucleoside analog gemcitabine for treatment of this devastating subgroup [105]. A similar study identified MYC-amplified group 3 tumors to be sensitive to a combination of HDAC and phosphoinositide 3-kinase inhibitors [106].

Recent studies have sought to more carefully address key prognosis questions in medulloblastoma that are outside of any one subgroup with a goal of finding minor ways to tune treatment to have the maximum benefit on outcome—both in overall survival and quality of life. Average- and high-risk medulloblastomas, for example, have been chiefly defined by the amount to residual tumor left behind from surgical resection. A large and extensive study of 787 medulloblastomas found no significant increase in survival from maximal surgical resection compared with remaining residual disease in WNT, SHH, and group 3 patients [14].

The chief cause of death in medulloblastoma is from metastatic disease. Medulloblastomas are rarely resected at recurrence, which has made study of metastatic disease difficult. Recent studies have started to shed light on this largely unknown component of medulloblastoma. Metastatic recurrent medulloblastoma tumors have the same molecular subgroup as the primary tumors [107]. However, the genomic lesions in the metastatic tumors can be different from the primary tumor site [108]. Recurrent disseminated medulloblastoma share a common ancestor to the primary tumor but are not a direct lineage descendent of the primary tumor using molecular clock modeling of the genomic lesions in the primary and metastatic tumors samples. The metastatic tumors share some, but not all, alterations found in the primary tumor [108].

The next major strides in translating medulloblastoma genomic studies to the clinic will come from improved and rapid methods to diagnose the subgroups, and broaden the breath of preclinical *in vitro* and *in vivo* models for identifying and testing new therapeutics. Next on the horizon is how to diagnose these subgroups in a clinically tractable manner. Indeed, towards achieving this future a recent consensus article authored by the global collaborative community of pediatric neuro-oncologists behind many of these key studies outlined clinical questions that should be prioritized and proposed design of future trials [10]. Methylation status, as mentioned previously, can classify the tumor types [31]. DNA methylation status can be obtained from fixed slides of formalin-fixed paraffin-embedded tissue, which are stored and stable at room temperature for long periods of time [109, 110]. Looking to the future, this seems like the most favorable method for rapid and reliable subgroup diagnosis. Currently, clinical diagnostics are limited to copy number changes with array technologies, immunohistochemistry, and targeted sequencing [10]. However, these can only identify or rule out specific subgroups and cannot equally identify all tumor subgroups. Now solidly in the postgenomic era of medulloblastoma, we are starting to build the bridges to transfer the research findings to the clinic, and break down the major barriers that have limited this [17].

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