

Hicks D, Rafiee G, Schwalbe E, Howell C, Lindsey J, Hill R, Smith A, Crosier S, Joshi A, Robson K, Wharton S, Jacques T, Williamson D, Bailey S, Clifford S. [Subgroup-Directed Stratification of Risk in Infant Medulloblastoma.](#)

*In: 17th International Symposium on Pediatric Neuro-Oncology (ISPNO).  
12-15 June 2016, Liverpool, UK: Oxford University Press.*

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This is the authors' manuscript of an abstract of a paper that was presented at the 17<sup>th</sup> International Symposium on Pediatric Neuro-Oncology (ISPNO) and published in *Neuro-Oncology* by Oxford University Press.

**DOI link to published version:**

<http://dx.doi.org/10.1093/neuonc/now076.59>

**Date deposited:**

24/08/2016

**Embargo release date:**

01 June 2017



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## Subgroup-directed stratification of risk in infant medulloblastoma

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The molecular pathology of infant medulloblastoma (iMB) has not been systematically characterised, particularly in relation to the consensus molecular subgroups or outcomes, to inform contemporary treatments, risk-stratification and clinical trials. We assembled 208 iMBs (0-5yrs) with full central clinical and pathological review, subgroup assignment, and comprehensive profiling of copy-number and mutational features. iMB represented a three-subgroup disease with MB<sub>SHH</sub> and MB<sub>Grp3</sub> predominant (41% each; MB<sub>Grp4</sub>, 17%). MB<sub>SHH</sub> significantly associated with DN/MBEN pathology (72% (50/69);  $p=6.8 \times 10^{-19}$ ), but also contained classic (CLA;  $n=15$ ) and LCA ( $n=4$ ) tumours (28%; 19/69) throughout the age-range. Multivariate survival analysis identified sub-total resection (STR; HR 6.3,  $p=3.1 \times 10^{-5}$ ) and DN/MBEN (HR 0.1,  $p=0.004$ ) as independent prognostic factors, however metastatic (M+) disease and other established biological features were not associated with outcome. A novel MB<sub>SHH</sub> survival model defined CLA/LCA and/or STR tumours as very high-risk (44% (27/61); 10yr OS, 24%), with 18.8-fold relative-risk compared to favourable-risk totally-resected DN/MBEN disease (56% (34/61); 10yr OS, 93%). MB<sub>Grp3</sub> was strongly associated with LCA (23%, 14/62) and *MYC* amplification (19%, 12/62). Presence of either feature defined a very high-risk group (27% (18/62); 10yr OS, 23%), with common rapid progression on current therapies and an 11.7-fold relative-risk than remaining MB<sub>Grp3</sub> tumours (73% (45/62); 10yr OS, 74%; standard-risk). Only MB<sub>SHH</sub> DN/MBEN tumours showed potential of rescue at relapse following initial therapy (56% survival post-relapse); other relapses were almost universally fatal. Combined diagnostic assessment of iMB subgroup, pathology and molecular biomarkers will be essential to direct improved risk-stratified therapies, and novel approaches for very high-risk patients.