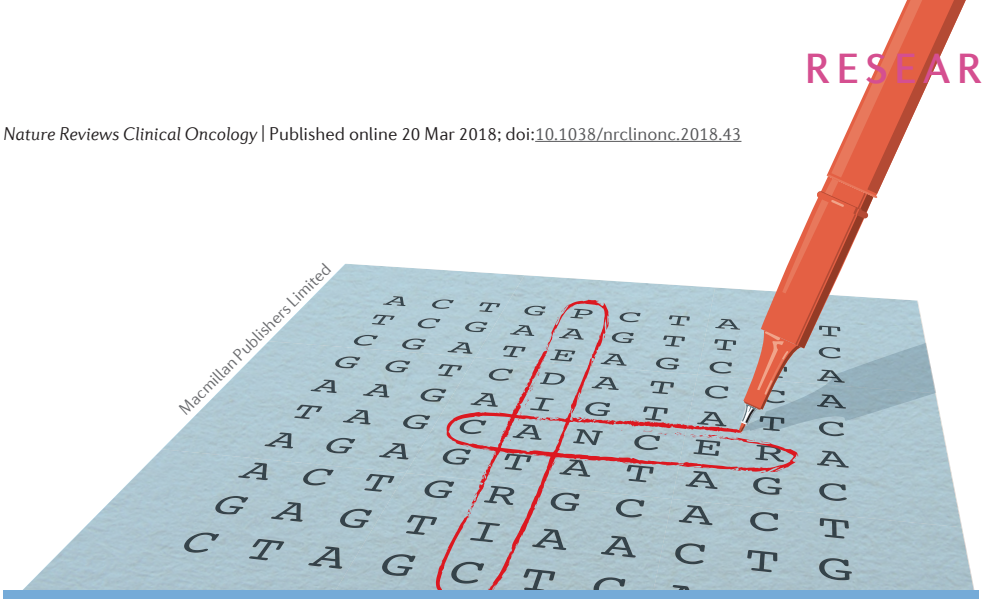
Nature Reviews Clinical Oncology | Published online 20 Mar 2018; doi:10.1038/nrclinonc.2018.43



PAEDIATRIC CANCER

Pan-cancer genomic analyses uncover molecular drivers

Pan-cancer genomic studies have resulted in a substantially improved understanding of diverse malignancies in adults and have facilitated precision medicine. Two studies recently published in *Nature* describe similar studies of whole-genome sequencing data, but for paediatric cancers.

Previous genomics studies of paediatric cancers focused on one particular tumour type, and the two new pan-cancer studies provide opportunities to directly compare the data for different childhood malignancies, as well as adult cancers. "This approach substantially helped in identifying new aspects of individual tumour types but, more importantly, we now have a much better idea of how different paediatric tumours are from adult cancers, how important hereditary predisposition is in paediatric oncology, and how common putative drug targets are across the various paediatric malignancies, with the latter information being extremely important for clinical trial planning," explains Stefan Pfister, co-supervisor of one of the studies.

Pfister and colleagues analysed 961 tumours, encompassing 24 different molecular subtypes, from children, adolescents, or young adults. They identified aberrations in 149 putative driver genes, which could be separated into two classes accordingly to whether they were small focal mutations versus structural or copy number alterations. "We have (again) confirmed that paediatric tumours, on average, are much less genetically complex than adult tumours; thus, we think that the precision medicine paradigm of 'a single driver matching an effective drug' can be applied perfectly to some childhood tumours," Pfister summarizes. Indeed, most of the commonly mutated genes were mutually exclusive across tumour types, unlike in adult cancers, including potentially druggable mutations that were identified in >50% of patients, most commonly in components of the MAPK, cell-cycle, or DNA-repair pathways.

~8% of tumours were associated with predisposing germline mutations, mostly in DNA repair genes, potentially creating opportunities for immunotherapy in a subset of these patients. Notably, certain glioma subtypes with such mutations had high mutation burdens. "We hope that eventually the paediatric (and adult) oncology community will recognize the importance of agnostic germline testing in order to identify patients with hereditary cancers, who very often require fundamentally different treatment approaches," Pfister adds.

In the second study, led by Jinghui Zhang, 1,699 paediatric leukaemias or solid tumours, of six histotypes, were evaluated and alterations affecting 142 driver genes were identified. "62% of the driver variations are copy number alterations and structural variations, indicating that a genome-wide approach is required to identify pathogenic genomic abnormalities of paediatric cancer in clinic," explains Zhang. Interestingly, in keeping with data from the first study, "only 45% of the driver genes in paediatric cancers match those found in adult cancers, indicating the need to develop paediatric cancer-focused precision medicine," she continues, adding that "new drugs are required to target genomic aberrations that are unique to paediatric cancer." Furthermore, the functional roles of many 'paediatric-specific' mutations in oncogenesis remain unclear, necessitating further research. Moreover, Zhang plans to "expand this work to gain more insights into the effect of non-coding variants, which can cause epigenetic dysregulation, as our current study was focused exclusively on alterations that cause protein changes."

Despite the need for more extensive research, rapid breakthroughs might be possible. "We now have quite a good idea of the frequency of many drug targets across childhood cancers, and it is a great time to systematically test these drugs in suitable models representing the entire genetic spectrum of these diseases," Pfister opines. Indeed, a number of interesting public–private partnerships have been launched in North America and Europe to systematically evaluate potential targets and matched drugs preclinically, in order to prioritize the development of new drugs for paediatric cancers. "We are trying to coordinate these efforts in the best interest of our patients," Pfister concludes.

David Killock

> "new drugs are required to target genomic aberrations that are unique to paediatric cancer"

ORIGINAL ARTICLES Gröbner, S. N. et al. The landscape of genomic alterations across childhood cancers. *Nature* https://doi.org/10.1038/nature25480 (2018) | Ma, X. et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* https://doi.org/10.1038/nature25795 (2018)