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Commentary

Genetics and childhood cancer
Commentary on: inherited cancer in children: practical/ethical problems and challenges

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As convincingly presented in Drs. Tischkowitz and Rosser's comprehensive Review [1], identification and clinical management of children and families with inherited cancer syndromes can assist in early detection and, possibly, prevention. However, some complicating issues exist. First, as the authors note, some of these malignancies lack sensitive screening methods. Imaging strategies for Wilms', neuroblastoma, and rhabdomyosarcoma are controversial [2], making it unclear what to recommend for children at high risk. Further, because the familial component of these malignancies often comprises only a very small proportion of those affected (as Tischokowitz and Rosser note, only 1% of neuroblastoma is estimated to be familial), the benefit of widespread screening of siblings is not established. Finally, in addition to the ethical and family dynamic issues surrounding presymptomatic testing in childhood, are its implications for health insurance. Without universal coverage, as is the case in the United States, genetic testing of families raises questions about possible denial of health insurance, or at least, denial of treatment for pre-existing conditions [3]. Despite these issues, the discovery of familial cancer syndromes has been extraordinarily informative in defining general mechanisms of paediatric tumorigenesis and in identifying the responsible genes.

A promising future endeavour may be the on-going follow-up of families of children with cancer. Most children who develop cancer are members of young families that have yet to be characterised by a syndrome. Adult survivors of childhood cancer are often no longer seen by specialists who may be best equipped to recognise a familial cancer syndrome. For optimal on-going surveillance, comprehensive paediatric cancer registries are required. In North America, the Children's Oncology Group (COG) is forming the Childhood Cancer Research Network (CCRN) to register all parents and their children newly diagnosed with cancer at COG member institutions. Over 90% of all children diagnosed with cancer in the United States [4] are treated at COG institutions. COG investigators plan to use the CCRN for a study on cancer incidence in 1st- and 2nd-degree relatives. Pathological diagnosis and age at diagnosis will be confirmed through medical records. Family histories will be re-assessed at five-year intervals to identify evolving familial cancer syndromes. Moreover, genome-wide analysis will be conducted using biological specimens obtained from families of interest, with the expectation of discovering new information on major candidate genes in malignancy and familial syndromes.

As important as the continued identification of major gene effects is for understanding paediatric cancer, equally important is the investigation of gene-environment interactions. With current evidence associating less than 5% of all childhood cancers with a familial syndrome [5], for most children, the aetiology of cancer is probably multifactorial, a combination of host susceptibilities and exposures to carcinogens. Many childhood cancers are associated with the stochastic acquisition of genetic alterations in cell growth and viability pathways (as seen in familial cancer syndromes) leading to malignant transformation. Many of these genetic alterations have been linked with exogenous mutagens, such as

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alkylating agent therapies and secondary leukaemias presenting with losses of chromosomes 5 and/or 7; as well as DNA topoisomerase II inhibitor therapies (e.g., epipodophyllotoxins) and secondary leukaemias presenting with MLL gene rearrangements [6]. Further, interactions between host genetic susceptibility (i.e., genetic polymorphisms) and environmental factors have also been implicated in several common cancers [7], perhaps providing clues to the role and function of important genes. Lastly, the timing of steps in the carcinogenic pathway may be key to understanding basic biological mechanisms in paediatric oncology. For example, evidence suggests genetic alterations occuring *in utero* may be sufficient for some childhood leukaemias, but not for others [8]. In fact, observations from studies of gene-environment interactions may even aid in identifying new cancer genes and inherited childhood cancers.

Conflicts of interest statement

None declared.

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