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Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson, Jr

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Abstract

The prevalence of childhood cancer attributable to genetic predisposition was generally considered very low. However, recent reports suggest that at least 10% of pediatric cancer patients harbor a germline mutation in a cancer predisposition gene. Although some of these children will have a family history suggestive of a cancer predisposition syndrome, many others will not. Evidence from recent pediatric studies suggests that surveillance and early detection of cancer in individuals carrying a germline cancer predisposing mutation may result in improved outcomes. However, there is a lack of consistency in the design of cancer surveillance regimens across centers nationally and internationally. To standardize approaches, the Pediatric Cancer Working Group of the American Association for Cancer Research (AACR) convened a workshop, during which consensus screening recommendations for children with the most common cancer predisposition syndromes were developed. In general, we considered a 5% or greater chance of developing a childhood cancer to be a reasonable threshold to recommend screening. Conditions for which the cancer risk was between 1 to 5% were addressed individually. In a series of manuscripts accompanying this article, we provide recommendations for surveillance, focusing on when to initiate and/or discontinue specific screening measures, which modalities to use, and the frequency of screening. Points of controversy are also reviewed. We present the outcome of our deliberations for consensus screening recommendations for specific disorders in 18 position papers as Open Access publications and available on an AACR-managed web site.

Keywords

Cancer predisposition; genetic susceptibility; cancer surveillance; early tumor detection; and cancer genetics

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Tribute to Alfred G. Knudson, Jr

Dr. Alfred G. Knudson is considered by many to be the father of modern cancer genetics and heritable predisposition. Al passed away on 10 July 2016, as this workshop was still in its planning stages. It was the unanimous consensus of the workshop participants to dedicate our efforts to Al Knudson and his pioneering work in this field. In his initial statistical analysis of hereditary and nonhereditary cancer, he hypothesized that "*retinoblastoma is a cancer caused by two mutational events. In the dominantly inherited form, one mutation is inherited via the germinal cells and the second occurs in somatic cells. In the nonhereditary form, both mutations occur in somatic cells*" (1). This "two-hit theory" of the genetic origin of retinoblastoma was extended to other pediatric cancers, like neuroblastoma and Wilms tumor (2,3), as well as many cancers occurring in adults. Although this model may not explain the genetic etiology of all heritable cancers, it has been a guiding principle for cancer susceptibility and pathogenesis around the world for 45 years.

In addition to this and many other contributions to our understanding of the genetic basis of cancer, Al was also an "intellectual pollinator". He took great delight in going to meetings and visiting scientists around the world, and then sharing his insights with the other scientists that he encountered. He was a humble man who did not seek personal credit or acknowledgment for his contributions, but rather, he delighted in the successes of others. Nevertheless, Al certainly won his share of accolades, including the Charles Mott Prize from the General Motors Foundation in 1988, election to the National Academy of Sciences in 1992, the Karnofsky Memorial Award from American Society of Clinical Oncology in 1997, the Lasker Clinical Medical Research Award in 1998, the Kyoto Prize in 2004, and the Lifetime Achievement Award from AACR in 2005. However, his contributions to science and inspiration to many cannot be measured by awards or words. He was a gentle and inspiring giant in the field, and he will be deeply missed.

Pediatric Cancer Predisposition: Introduction

Cancer in children is generally considered a rare and sporadic event, and only a small percentage of cases were previously thought to result from a genetic predisposition. However, a number of features suggest that at least a subset of pediatric cancers result from a genetic predisposition. These include: 1) family history of the same or related cancers; 2) bilateral, multifocal, or multiple cancers; 3) earlier age at diagnosis than sporadic tumors of the same type; 4) physical findings suggestive of a predisposition syndrome; and 5) occurrence of specific tumor types that frequently occur in the context of genetic predisposition (4). A child presenting with any of these five features should be referred for evaluation to a cancer predisposition program [see Genetic Counseling Paper]. Examples of physical findings associated with specific cancer predisposition syndromes include café-au-lait macules in Neurofibromatosis type 1, macroglossia in Beckwith-Wiedemann Syndrome (BWS), or macrocephaly in PTEN hamartoma tumor syndrome, but these findings also occur in individuals without cancer predisposition. Examples of specific pediatric cancer diagnoses that are frequently seen in the setting of underlying cancer susceptibility include pleuropulmonary blastoma associated in DICER1 Syndrome, malignant rhabdoid tumors in Rhabdoid Tumor Syndrome, and adrenocortical carcinoma in Li-Fraumeni Syndrome (LFS).

Recent reports using genome-scale germline sequencing of pediatric cancer cohorts not selected for genetic risk (5–7) suggest at least 10% of pediatric cancer patients harbor a germline mutation in known cancer predisposition genes. This is probably an underestimate, because there are also patients who fulfill clinical criteria for a cancer predisposition syndrome, but who lack identifiable germline mutation in the known gene(s) currently associated with those conditions. In addition, there are pediatric patients with cancer whose families exhibit a higher frequency of cancer than expected yet do not fit any patterns for a known predisposition syndrome. Furthermore, some individuals are predisposed to develop cancer on the basis of epigenetic changes (e.g., BWS or hemihypertrophy) that would not be detected by traditional DNA sequencing. Cancer genomes are increasingly scrutinized to identify variants that are actionable for targeted therapy, but changes or patterns of somatic mutation can sometimes be identified that may represent an unanticipated germline predisposition.

In addition, pediatric oncologists are increasingly sending patient samples for paired tumor/normal sequencing, with a primary goal to identify potentially targetable genetic lesions in the tumor. This analysis may also inadvertently lead to the identification of pathogenic variants that reflect germline mutations in cancer susceptibility genes, a possibility for which patients and their families do not always receive pre-test genetic counseling. It is likely that this type of systematic analysis of tumors (and paired germline) samples will become routine in pediatric oncology clinical care in the next few years, maybe even one day becoming the standard of care at diagnosis and even more likely at relapse. For example, the National Cancer Institute/Children's Oncology Group Pediatric MATCH trial will use such a study design for its sequencing. Overall, we expect that the proportion of cancer patients identified as carriers of cancer susceptibility mutations will increase as both targeted genetic evaluations and genomic analyses of cancer cells are implemented.

Individuals with cancer predisposition syndromes carry a significantly increased risk of developing one or more cancers. Therefore, focused surveillance on the types of cancer(s) to which the individual is most predisposed, and during the period of greatest risk, should substantially improve their outcome through early detection. Indeed, many centers are starting to follow proposed early tumor surveillance protocols that have been published for a few disorders like Li-Fraumeni Syndrome (LFS) and BWS-hemihypertrophy (8–10). However, even for these disorders, surveillance has not been performed consistently across different centers, and there are still many inherited cancer predisposition disorders for which either no protocols, or multiple published protocols, exist. This practice variability makes it difficult to compare studies from different centers or groups and creates uncertainty for clinicians caring for patients with these individually rare disorders.

An AACR-sponsored workshop was held in Boston, Massachusetts from 6–8 October 2016 to develop consensus recommendations for cancer surveillance of children and adolescents with heritable cancer predisposition. Sixty-five professionals from 11 countries were present, including 51 physician directors or co-directors of cancer predisposition programs (pediatric oncologists or medical geneticists), seven genetic counselors, three radiologists, three directors of adult cancer predisposition programs, and a pediatric endocrinologist. The main goal of this meeting and the post-workshop activities was to review the existing data

and practices, and to establish international consensus recommendations for cancer surveillance for the most common cancer predisposition syndromes. These pediatric cancer syndromes were organized into nine groups based on specific themes. Attendees were distributed into these groups based on prior experience and expertise.

Major Cancer Predisposition Syndromes

This AACR Workshop focused on the 50 most common syndromes that predispose to the development of cancer in the first 20 years of life. These syndromes were then divided into 9 major groups based on the major cancer types with which they are associated: 1) Li-Fraumeni syndrome, 2) Neurofibromatoses, 3) Overgrowth syndromes and Wilms tumor, 4) Neural tumors, 5) GI cancer predisposition, 5) Neuroendocrine syndromes, 7) Leukemia predisposition, 8) DNA instability syndromes, and 9) Miscellaneous syndromes. The disorders and associated genes for each of these categories are summarized in Table 1.

Cancer Surveillance Considerations

Prior to the workshop, each group reviewed the published literature to determine current state of screening recommendations from experts, professional organizations or groups that care for such patients. Attendees also provided information from their own centers as well as personal experience with regard to cancer incidence and surveillance protocols. The groups frequently consulted additional experts on specific disorders for their input both before and after the workshop. In general, the recommend surveillance protocols are designed for asymptomatic individuals who are genetically predisposed to develop cancer, although some individuals are identified only after the development of their first cancer.

The first question addressed was whether or not it was appropriate to do cancer surveillance for children or adolescents with a given cancer predisposition syndrome. For this decision, the consensus of the group was that surveillance was recommended when there is a 5% or greater risk of developing cancer during the first 20 years of life, and when effective screening modalities existed. Surveillance was not recommended or considered worthwhile if the risk for an individual malignancy during the first 20 years of life was less than 1%. Conditions in which the cancer risk during childhood fell between 1 and 5% were discussed on an individual basis. We supported surveillance if the screening modalities were relatively cost-effective and noninvasive, and/or if the outcome was so poor for clinically detected tumors that any possibility for early detection might enhance survival. If screening was indicated, then the remaining questions for surveillance included: 1) what procedure(s) should be done?; 2) how often should screening be performed?; 3) at what age should screening start, and if/when should it stop?; and 4) should the screening procedures change over time, such as a change in frequency or type of screening with age to account for changes in cancer risk? We also asked if any evidence exists that the recommended surveillance leads to improved clinical outcome, but for most cases this will have to await the implementation of the recommendations proposed in the accompanying position papers for the respective disorders.

Evidence that Surveillance Improves Outcome

It is generally accepted that early identification of tumors when smaller and less likely to be metastatic will improve clinical outcome. This is the underlying principle that supports cancer surveillance approaches for adults (e.g. screening for colon, breast, prostate or other cancers, especially in predisposed individuals). However, relatively few studies of cancer surveillance have been published in children and adolescents. In a recent study, a clinical surveillance protocol was implemented using frequent biochemical and imaging studies for asymptomatic individuals with LFS (8,9). Forty subjects underwent surveillance whereas 49 did not, and the 5-year overall survival OS was 89% in the surveillance group versus 60% in the non-surveillance group. These data suggest that surveillance was associated with improved OS from tumors detected in patients with germline *TP53* mutations even after 11 years of follow-up (8,9).

Another group undertook a cost-benefit analysis of children with BWS undergoing screening for Wilms tumor and hepatoblastoma (10). Using a conservative model, they determined that screening for these tumors with abdominal ultrasound was predicted to be cost-effective. Although the focus of the study was not on outcome, screening also resulted in an improved survival (10). A review of characteristics and outcome of children with BWS and Wilms tumor treated on National Wilms Tumor Study Group protocols showed a trend towards smaller tumors over time that was not seen in non-BWS patients with Wilms tumor, suggesting that existing screening protocols led to earlier detection (11). Together, these data on cancer surveillance of LFS and BWS suggest that screening enables the detection of smaller tumors, allowing for less intensive therapy, less organ toxicity and better outcomes.

Consistent Approach to Pediatric Cancer Patients and Their Families

The primary goal of this series of articles is to develop consensus recommendations for the management of children at significant hereditary risk for cancer. However, a parallel issue discussed in more detail elsewhere [see Genetic Counseling Paper] includes the need for a consistent and thoughtful approach to genetic testing for these families. Training in pediatric hematology-oncology does not emphasize the importance and methods with which to obtain and record a complete family cancer history. Similarly, gaps exist in training around the appropriate methods for germline genetic testing, and the issues that should be addressed when obtaining consent for tumor testing. Genomic testing of tumor tissue can reveal mutations in genes that may also be present in the germline. Mutations present in the tumor at an allele frequency near 50% can be acquired or they may reflect a germline mutation (12). A number of studies have demonstrated that parents of children with cancer are concerned about a hereditary contribution to the cancer diagnosis in their child, with possible implications for other family members (13). Thus, education around germline genetic testing, disclosure of results, and identification and testing of at-risk family members, are essential activities that are integral to the training of current and future pediatric oncologists.

As the number of long-term survivors of childhood cancer increases, it will be essential for survivorship clinics to incorporate genetic counseling and testing of adult survivors,

including those who were identified as children to carry a cancer predisposing mutation, or who may be at risk for an inherited syndrome but have never been tested. This allows adult survivors the opportunity to learn about the implications of the genetic findings for ongoing cancer (and other health) risks, the adult survivor's risk of having affected children, and the opportunity for prenatal or postnatal testing. Similarly, long-term survivors who previously had a malignancy that is now recognized to be associated with a substantial germline genetic risk (e.g. adrenocortical carcinoma or hypodiploid acute lymphoblastic leukemia) would benefit from a genetic consultation, as this information might not have been available when they were diagnosed.

Importance of Consensus Protocols

Identification of children with an underlying cancer predisposition syndrome provides critical information for testing otherwise healthy appearing family members, in particular siblings of childhood age, to identify whether or not they also carry the same genetic risk. If identified, these family members may have asymptomatic tumors found through the initiation of tumor surveillance protocols. With this increase in systematic assessment of germline status, it becomes increasingly important for both primary and specialty clinicians to have ready access to consensus protocols in order to undertake appropriate surveillance. It also will become important to understand the nuances of early tumor findings and how to appropriately interpret any indications of a possible early cancer.

As described throughout the papers in this series, the working groups strove to reach consensus by careful review of existing guidelines from professional organizations, prior publications, cancer risk estimates and assessment of the potential side effects associated with screening, balanced against the potential morbidity and mortality of clinically detected tumors of more advanced stage. For some newly described or rare disorders, no prior guidelines existed, so the committees endeavored to develop consensus recommendations as to whether surveillance was indicated, and what tests and schedule would be a good starting point for surveillance recommendations, based on the principles described above. If substantial differences of opinion existed, these differing viewpoints are described in the individual papers as well. However, there was unanimous agreement among all workshop participants that providing surveillance recommendations where none existed would provide a foundation on which to make rational decisions for the management of children with cancer predisposition going forward. Gathering data from prospective experience with these consistent approaches worldwide will facilitate future revisions of the proposed recommendations and evolution of surveillance protocols.

The major focus of the cancer surveillance protocols proposed in this series of manuscripts was on individuals with a germline predisposition who have not yet developed their first cancer. We did not address the implications of the underlying disorder for therapy of tumors that develop, or for second cancers and subsequent surveillance. This will likely be very syndrome specific, e.g., a greater risk of therapy-related cancers in Li-Fraumeni Syndrome, retinoblastoma predisposition or DNA instability syndromes, etc., and less so in individuals with certain other syndromes (14–16). The recommendations will likely need substantial personalization, as the surveillance recommendations will depend on the child's risk of a

second tumor, while taking into account their risk of recurrence, the therapy that they received, and the biological nature of the predisposition syndrome.

Pediatric Cancer Predisposition: Conclusions

Consistent approaches to surveillance will allow clinical experience and research from different centers, groups and countries to be compared. These recommendations will also provide a standardized approach to patients and families with disorders that are encountered infrequently by centers with limited experience. The outcome of this AACR-sponsored Workshop is to provide position papers on surveillance recommendations for the major cancer predisposition syndromes likely to be encountered in children and adolescents. These position papers will be published online as Open Access publications, so they will be broadly available to the medical community. They will also provide a broadly accepted international consensus of surveillance that may be useful for obtaining third-party coverage of the recommended tests. Nevertheless, these recommendations are likely to change over time, as more experience and information becomes available. New syndromes, as well as more specific information about genotype-phenotype associations and gene-gene or gene-environment interactions, will allow screening recommendations to be further customized. Finally, newer technologies in molecular detection and diagnostic imaging will likely provide less costly, increasingly effective, and noninvasive approaches for early cancer detection, which in turn could dramatically reduce required treatment, decrease systemic toxicity, and improve patient outcome.

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Table 1

Major Subgroups of Pediatric Cancer Susceptibility Disorders Reviewed

Predisposition Group	Specific Disorders Reviewed
Li-Fraumeni Syndrome	Li-Fraumeni syndrome—LFS (*TP53*)
Neurofibromatoses	Neurofibromatosis type 1 (*NF1*), type 2 (*NF2*), Schwannomatosis (*SMARCB1, LZTR1*), Meningioma predisposition (*SMARCE1*)
Overgrowth Syndromes, Wilms tumor	Beckwith-Wiedemann syndrome/hemihypertrophy (11p15.5), Wilms-Aniridia-GU-anomaly-Retardation (WAGR) syndrome, Denys-Drash and Frasier syndromes (*WT1*), Perlman syndrome (*DIS3L2*), Bohring-Opiz syndrome (*ASXL1*), Mulibrey Nanism (*TRIM37*), Simpson-Golabi-Behmel syndrome (*GPC3, GPC4*)
Neural Tumor Syndromes	Hereditary retinoblastoma (*RB1*), Hereditary neuroblastoma (*ALK, PHOX2B*), Gorlin syndrome (*PTCH1, SUFU*), Malignant rhabdoid tumor syndrome (*SMARCB1, SMARCA4*)
GI Cancer Syndromes	Familial adenomatous polyposis (*APC, MUTYH*), Juvenile polyposis syndrome (*SMAD4, BMPR1A*), Peutz-Jeghers syndrome (*STK11, LKB1*), Lynch syndrome (*MSH2, MSH6, MLH1, PMS2, EPCAM*), congenital mismatch repair syndrome—CMMRD (see Lynch syndrome genes)
Neuroendocrine Syndromes	Multiple Endocrine Neoplasia (MEN)-1(*MEN1*), MEN2A (*RET*), MEN2B (*RET*), MEN4 (*CDKN1B*), von Hippel Lindau (*VHL*), hereditary paraganglioma/ pheochromocytoma syndrome (*SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX*) familial thyroid cancer (*RET, NTRK1*), parathyroid cancer syndrome (*CDC73*)
Leukemia Predisposition Syndromes	LFS, CMMRD, Susceptibility to ALL 3 (*PAX5*), *GATA2*-associated predisposition to myelodynsplasia/acute myeloid leukemia (AML), *CEBPA*-associated predisposition to AML, thrombocytopenia, type 5 (*ETV6*), Familial platelet disorder with associated myeloid malignancy (*RUNX1*), Ataxia-pancytopenia syndrome (*SAMD9L*), Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy (*SAMD9*)
DNA Instability Syndromes	Ataxia telangiectasia (*ATM*), Bloom syndrome (*BLM*), Fanconi anemia (*FANCA-V, RAD51C*), Xeroderma pigmentosum (*XPA, XPC, ERCC2, POLH, DDB2*), Nijmegen breakage syndrome (*NBN*), Diamond-Blackfan syndrome (*RPS7, -10, -17, -19, -24, -26; RPL5, -11, -19, -35A*), Dyskeratosis congenita (*DKC1, TINF2, TERC, TERT, NHP2, NOP10, WRAP53*), Rothmund-Thompson syndrome (*RECQL4*)
Miscellaneous Syndromes	PTEN hamartoma tumor syndrome (*PTEN*), pleuropulmonary blastoma syndrome (*DICER1*), Noonan syndrome (*PTPN11, SOS1, RAF1, RIT1, KRAS*, others), and Costello syndrome (*HRAS*), Sotos syndrome (*NSD1*), Weaver syndrome (*EZH2*), Rubenstein-Taybi syndrome (*CREBBP, EP300*), Schinzel-Giedion syndrome (*SETBP1*), NKX2-1 syndrome (*NKX2*-1), hereditary leiomyomatosis and renal cancer syndrome (*FH*), metabolic disorders (*L2HGA, FAH*)