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The Future of Surveillance in the Context of Cancer Predisposition: Through the Murky Looking Glass

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Abstract

At least 10% of children with cancer harbor a disease-associated pathogenic variant in a known cancer predisposition gene. It is widely accepted that pathogenic variants affecting other genes, epigenetic factors, or abnormalities in additional gene products may contribute to the etiology of many more childhood cancers. Effective preventive measures exist for only a few cancer types associated with predisposing conditions, but the development and implementation of surveillance protocols aimed at reducing morbidity and mortality in at-risk children through the early detection of cancer has emerged as an important clinical tool. The articles in this *Clinical Cancer Research* series present international consensus generated recommendations for surveillance for a wide spectrum of cancer predisposition syndromes affecting children. In this article, we explore the challenges and opportunities for researchers and practitioners in the many fields affiliated with pediatric cancer, and we offer insights into what the future might hold as we continue our efforts to mitigate the impact of cancer susceptibility on children, their families and society. *Clin Cancer Res; 23(21); e133–e7. ©2017 AACR.*

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Introduction

With the advent of next-generation sequencing (NGS), there has been increased awareness and recognition of childhood cancer predisposition among practitioners, including general pediatricians, pediatric oncologists, clinical geneticists, and genetic counselors. As a result, the notion of tailored interventions to reduce mortality and morbidity in this high-risk population is gaining acceptance as an objective that is necessary and achievable. Traditionally, the concept of cancer prevention as applied to childhood cancer has not been given much credence or attention. However, early detection through rational surveillance protocols leading to effective and perhaps less toxic therapies could achieve an equivalent endpoint to primary prevention—namely, mitigating morbidity and mortality. Genetic tests, including multigene panels, as well as whole-exome or whole-genome sequencing continue to uncover pathogenic or likely pathogenic DNA variants in cancer susceptibility genes in children with a wide spectrum of malignancies. Before these unbiased approaches, most germline pathogenic variants were found in the context of a known cancer susceptibility syndrome, many of which are described in this unique series of articles. However, germline pathogenic variants are more frequently being discovered in the absence of a recognized constellation of congenital or cancer phenotypes in the child or family and will be done so at increasingly high rate as clinical large-scale sequencing becomes more common.

Therefore, the future of the rapidly expanding field of cancer predisposition and surveillance faces a number of challenges that we anticipate will be overcome by concerted multidisciplinary, multi-institutional efforts. The principles of mutual and robust cooperation and collaboration led to the American Association of Cancer Research (AACR) Pediatric Cancer Predisposition Workshop, and to the series of recommendations that derived from it, and were published in a series of articles in *Clinical Cancer Research*. This effort will guide future short- and long-term studies to ultimately improve on these recommendations and transform the care of children and family members deemed genetically susceptible to cancer. The directions of these research efforts are considered in this article. They are derived from: (i) common themes that arose during the workshop and preparation of these articles; (ii) ongoing efforts of investigators who participated in the workshop; and (iii) work being performed by clinical and basic researchers whose science informs the field.

Knowledge Translation and Communication

Several recent studies have concluded that at least 10% of children with cancer harbor a pathogenic germline mutation in a known "cancer predisposition gene," approximately 60% of which are believed to be directly linked to development of cancer (1, 2). However, the actual rate of genetic predisposition is likely to be higher. Within the medical community, information regarding cancer predisposition is not always sought, effectively disseminated or used to guide patient management (3). This gap in

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knowledge transfer and practice may be due in part to the limited education in genetic medicine in many medical school curricula and residency training programs, with most of the limited discussion focused on hereditary breast and colon cancer—leaving most practitioners at a disadvantage in terms of knowing how to interpret and/or use this information in a clinically useful way. Also, the primary goal of pediatric oncologists is to treat their patients in the most effective way possible to achieve the best clinical outcome. It is not unusual that some pediatric oncologists perceive genetic testing and ongoing surveillance for other tumors as submitting patients and their families to undue anxiety during what is already a highly stressful period in their lives. Furthermore, there is often a lack of expertise in genetic counseling for childhood cancer predisposition, particularly in smaller centers. This leaves a significant burden of responsibility on other health care providers, including nurses, nurse practitioners, and physicians who are generally not trained to provide genetic counseling, select the appropriate genetic test, obtain insurance authorization for and order germline genetic testing, and initiate tumor surveillance.

An international group of experts in pediatric cancer predisposition, supported by the AACR, met and developed extensive and comprehensive recommendations for surveillance of children with a wide spectrum of cancer predisposition syndromes (4). These recommendations are outlined in a series of 17 articles that have recently been published as open access in *Clinical Cancer Research* as a new Pediatric Oncology Series. Notwithstanding these publications, there may be limited awareness and access by most clinical pediatric oncologists, pediatricians, genetic counselors, geneticists, medical oncologists or general practitioners. As a first step to broaden the audience that will read and act upon these recommendations, the AACR will work with other relevant discipline-based societies and organizations to disseminate the contents of this series. These include, but are not limited to, the American Society of Clinical Oncology (ASCO), American Society of Pediatric Hematology/Oncology (ASPHO), American Society of Hematology (ASH), Society of Pediatric Radiology (SPR), American Society of Human Genetics (ASHG), American College of Medical Genetics and Genomics (ACMG), American Association of Pediatrics (AAP), National Society of Genetic Counseling (NSGC), and their equivalent European and Asian counterparts. A wide net must be cast through various links to this online series of articles (and future updates thereof). Indeed, discussions with the National Comprehensive Cancer Network (NCCN) should occur, and incorporation of these recommendations into NCCN guidelines should be encouraged, as these recommendations represent an international consensus and interpretation of peer-reviewed published evidence from a large number of wide-ranging experts across relevant disciplines.

Although these recommendations will undoubtedly evolve over time—as do virtually all other principles of Medicine—they represent an important starting point from which new modifications will evolve. Such an evolution will be possible only if these surveillance recommendations are generally followed, the results of collaborative, multi-institutional surveillance efforts in the form of prospective studies are reported, and these data are periodically examined to identify gaps and redundancies in current surveillance efforts, taking into consideration potential morbidity from the surveillance regimens. In addition, technological changes in imaging techniques, blood tests, "liquid" biopsies, and other surveillance tools will likely impact on recommended surveillance practices in the future. To accomplish the current recommendations and be effectively poised to update them as needed, all relevant medical practitioners must be made familiar with the current recommendations, incorporate the principles of surveillance into their practice, and engage in dialogue in the field of pediatric cancer predisposition.

Refining Surveillance Protocols

The majority of recommendations across all disease groups represented here are based on conventional imaging studies, biochemical or metabolic assays and routine physical examination and history. In some instances, such as the use of whole-body magnetic resonance imaging (WB-MRI), significant constraints may be encountered in funding and insurance coverage, challenges in expertise of reading the images, potential risks associated with sedation in young children, and/or technological availability particularly in underserved regions of the world (5). In other instances, incidental findings resulting from the recommended studies may lead to additional and possibly more invasive diagnostic tests, which may not confirm a malignancy (false positives), or subtle findings initially interpreted as incidental or "benign" that subsequently turn out to be malignant (false negatives). These challenges in developing more precise interpretations of radiologic features to guide appropriateness of further intervention will be best addressed through collaborative efforts with the radiology community. It will be important to focus on findings that are likely to represent early evidence for a malignancy to which the individual is predisposed, and to learn to not to aggressively pursue every incidental finding. This point is highlighted in recent analyses of the use of surveillance for early tumor detection in the context of Li-Fraumeni syndrome (6, 7), which highlight the patient and family burden of frequent testing and anxiety pending results, as well as financial and medical challenges of intervention for non-malignant disease.

Furthermore, a variety of new early tumor surveillance approaches are envisioned; in fact, they are already being explored through new research efforts to develop more specific and sensitive surveillance tests. Among the most promising of these is the use of circulating tumor DNA (ctDNA) as a surrogate marker of disease (8, 9). Several different technical approaches are being pursued, virtually all of which are designed to detect early traces of malignant cells whose rapid turnover leads to "shedding" of free "tumor-specific" DNA into the circulation, to the extent that tumor-specific DNA changes are known. These are not confined to solid tumors, for even in the context of myelodysplastic syndrome and AML predisposition, there are ongoing efforts to identify cooperating mutations that may be informative in the future. Measuring nanogram levels of circulating DNA offers an intriguing approach to detect tumors early, and importantly for our pediatric patients, an approach that is relatively non-invasive and does not require anesthesia. Other approaches, such as measurement of tumor-derived exosomes offers the promise of detection of expressed gene products and circulating free DNA (cfDNA), which may reflect quantitative differences that represent tumor DNA for which no specific tumor marker is known (10). The long-standing clinical use of biomarkers such as alpha fetoprotein or βhCG to monitor hepatoblastoma or germ cell tumors, respectively, suggests that new efforts to identify other tumor

markers such as proteins, glycoproteins, and other molecules through proteomic approaches may also find value as surveillance and early tumor detection markers.

However, even as these genome-based detection technologies continue to improve, it is important to recognize that although they infer the presence of a tumor, they cannot localize it anatomically. For this, critical improvements in development of ever more precise imaging modalities to take advantage of detection of the molecular fingerprint of the tumor are required. Some of these radiogenomic approaches are addressed in the series article by Greer and colleagues (5). These improvements include refinements in MRI technique, MR spectroscopy, positron emission tomography (PET)-MRI, and other molecular imaging techniques in which tumor-specific molecular targets may be labeled and home to specific malignant lesions.

A further challenge to be explored with use of molecular biomarkers and novel imaging modalities is the approach to identify benign tumors that can, by their location and growth patterns, cause striking morbidity. These include cerebellar or spinal hemangiomas in Von Hippel-Lindau (VHL), paragangliomas in the pheochromocytoma-paraganglioma syndrome, cystic nephromas in DICER1 syndrome, and others. The growth patterns of these lesions are often unpredictable—and timing of intervention is frequently more of an art than a science. Even in the context of other diseases such as Li-Fraumeni syndrome in which virtually all tumors are ultimately malignant, growing evidence suggests that many tumors initially present as lower-grade lesions but, at some point, irreversibly transform (6). Timing of intervention is not always clear, particularly for those tumors that arise in surgically challenging sites. Over the next several years, we envision that surveillance protocols will incorporate components of ctDNA or other circulating molecular biomarkers, novel radiogenomic approaches to imaging, better understanding of the factors influencing transformation, as well as the influence and timing of surgical excision.

Genotype: Phenotype Correlations

To complement the expansion and incorporation of molecular markers into the toolbox of surveillance for early tumor detection, emerging data across many syndromes suggest particular genotype:phenotype relationships. Although some of these have been recognized for some time, such as domain-specific mutations in the *VHL* gene associated with higher risk of pheochromocytoma or renal cell carcinoma (11), or domain-specific mutations in the *APC* gene associated with variable penetrance in familial adenomatous polyposis (12), for the most part similar relationships in other diseases are poorly understood—especially in the pediatric setting. Furthermore, genes continue to be identified through genome-wide screens that explain certain cancer predisposition phenotypes, and new cancer predisposition syndromes (or associations of cancers in constellations not previously well defined) continue to be described. These discoveries have important implications in many aspects of clinical care, including early detection.

Perhaps most importantly, with wider recognition of these cancer predisposition syndromes, more genetic testing will be performed, the results of which can be incorporated into larger-scale registries that can then be interrogated for additional genotype:phenotype relationships. Without centralization of data collection, it will be very challenging to recognize such patterns. Even the largest academic centers with a focus on cancer genetics do not typically have a large enough patient population in which to perform these sorts of correlative studies for even the most common pediatric cancer syndromes. Currently, most surveillance regimens are not modified in any significant way across the pediatric age spectrum or based on the specific germline genotype. This is changing somewhat in the context of diseases such as DICER1 syndrome and, to some degree, the SMARCB group of disorders in which particular components of the surveillance protocol are incorporated or removed at different ages, reflecting the differences in tumor spectrum across the age spectrum (13, 14). However, much research is still required for virtually all other cancers that present in the context of a predisposition syndrome to further refine the protocols based on the specific genetic change identified in the patient. Identifying and understanding the molecular biomarkers that arise along the benign to malignant continuum will serve to not only act as useful clinical markers to detect cancers, but also provide us important clues to the genetic and biologic mechanisms of cancer progression.

Recent advances in our understanding of the role of genetic modifiers of cancer risk—that is, the role of cooperating epigenetic or genetic events that modify the phenotype conferred by the primary gene mutation—suggest that incorporation of these events will also need to be taken into account when calculating cancer risk and designing surveillance protocols to effectively account for these complex interactions. Ultimately, it is hoped that surveillance protocols can be comprised of component assays that are specific to the tumors that occur in particular syndromes, that are age-specific, that are minimally invasive, and that identify lesions at biologically low grade and clinically low stage. With all of these conditions met, one can envision a remarkable reduction in morbidity and mortality for patients with these diseases.

Psychologic Studies/Intervention—"scanxiety"

Clinically important advances in the molecular, biochemical, and radiological sciences that would lead to improved surveillance and improved outcomes will not come quickly. Even when they do, the anxiety elicited by surveillance—both the anticipation of the particular test and the wait to receive results—will not likely lessen. Even the most well-resourced cancer genetics programs are severely under-resourced in psychology support beyond that, which may be provided by a genetic counselor or the primary treating oncology team. The concept of "scanxiety," the anxiety provoked by surveillance scanning or testing, is not unique to cancer susceptibility; it is an issue for oncology patients in general—waiting for the next test to determine whether their tumor is responding or recurring (15). The adult oncology world has long since reported anxiety issues with lung, breast, colon, and prostate screening; in fact, in some of these cases, lack of compliance is often attributed to the worry of the test and waiting for the results. To reduce the time to results, many centers make every effort to coordinate follow-up clinic visits to occur on the same day as the scans, preferably the same day immediately after the tests are performed so that at least preliminary results can be reported back. If this is not feasible, then reporting as quickly as possible is strongly recommended.

Recognizing signs of anxiety, adjusting clinical management to the patient and family, and acknowledging the fact of anxiety

goes a long way to alleviating it. Patients and parents consistently describe living with a cancer predisposition syndrome as having a "Damocles sword" hanging over their head (16). To them, the surveillance protocols, even with their current recognized deficiencies in sensitivity and specificity, provide a certain safety net on which to hang some hope. Furthermore, a sense of empowerment in having at least some control in the absence of a preventive measure is defined by many as important. At the same time, it becomes important for patients and families to not falsely assume that "clean scans" mean that the patient does not have a tumor, but rather that no tumors could be seen with the current level of detection. There is a fine balance between how much surveillance is "too much" versus "not enough." This refers not only to the technical aspects as described in this series of articles as well as any future modifications, but also to the psychological impact on patient, parents and family.

Future Directions

A brief look back at the history of medicine reveals that advances are generally iterative, and although "breakthroughs" such as discoveries of insulin and antibiotics, or the structure of the DNA double helix deserve all the credit they are given, none arose as a singular event. All these medical advances developed after years or decades of cumulated evidence. In the context of cancer predisposition and surveillance, a few important questions for the future remain.

- *Is surveillance medically and fiscally responsible?* We argue that it is. However, to date, there are limited data from consistent studies in large populations of patients to either support or refute the premise. It is critical to define the cost-benefit ratio of these interventions to effectively guide health policy in the global use of early detection surveillance strategies, and to determine a rational approach to cover their costs to reduce the financial burden for patients, families and society.
- *Will early tumor detection techniques improve?* Without a doubt, the answer is "yes." The technological advances in molecular biology, NGS and radio-imaging have been spectacular in the last decade, and they will continue to inform innovative approaches to surveillance. However, we do not know if we will begin to detect "early tumors" that might otherwise never have caused problems in the patient.
- *Does clinical surveillance for children at genetic risk of cancer save lives?* We would argue that it does. Cumulative evidence across multiple studies and in several syndromes in children and adults points to this conclusion (17).

Notwithstanding advances in cancer surveillance, future research endeavors should also focus on tumor prevention in genetically at-risk patients. The use of animal models to perform large-scale chemical/drug screens to identify agents that might mitigate or eliminate cancer risk is an active area of exploration. Adapting these studies to humans to measure either reduction in tumor incidence or changes in metabolic or biological parameters of health will be inherently complex. Similarly, lifestyle choices and environmental factors should be explored to determine their effects on reducing tumor risk in these families. Large-scale, multi-institutional, multi-international trials will be necessary to effectively address these questions.

Predicting the future is often a fruitless exercise; but hoping for a better one is what ties patients and health care workers together. Mitigating the morbidity and mortality of cancer in children can be achieved, in the context of genetic risk, through the judicious use of innovative and evolving surveillance techniques. To reach this goal, it is important to work with insurers and health care systems to better enable access to and coverage of the costs of surveillance. It behooves us to not ignore this important and expanding branch of oncology clinical care and research. It will perhaps transform not only the lives of those who live with a Damocles sword, but also our understanding of the molecular and biological basis of human cancer. Although stopping this sword of cancer from falling may be years away, we may be able to help our patients today by improving our ability to predict when it will fall, where it will land, and how to slow its descent, thus minimizing its damage through the safety net of advances in early tumor detection and treatment.

Disclosure of Potential Conflicts of Interest

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