Collaboration to Promote Research and Improve Clinical Care in the Evolving Field of Childhood Cancer Predisposition

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ABSTRACT

Germline pathogenic variants in cancer susceptibility genes are identified in up to 18% of all children with cancer. Because pediatric cancer predisposition syndromes (CPS) themselves are rare and underrecognized, there are limited data to guide the diagnosis and management of affected children and at-risk relatives. Furthermore, the care of affected children requires distinct considerations given the early onset of cancers, lifelong risks of additional cancers, and potential late effects of therapy. Herein, we discuss efforts to leverage existing infrastructure, organize experts, and develop a new consortium to optimize care and advance research for children with CPS. A 2016 workshop organized by the American Association for Cancer Research united many experts in childhood cancer predisposition and resulted in publication of multiple consensus guidelines for tumor surveillance. More recently, several of these authors established the Consortium for Childhood Cancer Predisposition (C^3P), a multi-institutional collaboration that provides a structure for systematic research in cancer predisposition, screening, and prevention in children. The Consortium intends to work with other cooperative groups to merge longitudinal data from children with CPS throughout the continuum of the cancer risk period, as well as cancer treatment and survivorship care, to optimize overall outcomes.

Introduction

Cancer predisposition syndromes (CPS) contribute to pediatric cancer onset to a much greater degree than previously appreciated (1–5). In multiple recent studies of children with cancer, rates of germline pathogenic/likely pathogenic variants in cancer predisposition genes ranged from 8% to 18% of individuals sequenced (5, 6). Furthermore, the rapid increase in somatic and paired germline/somatic sequencing of pediatric tumors has uncovered germline variants, which would not have been expected on the basis of tumor type, clinical features, and/or family history (5, 7–10). Altogether, it is now well established that genetic predisposition in pediatric patients remains an underrecognized and substantial contributor to childhood cancer development.

Recognition of underlying cancer predisposition may have immediate and future implications for children and their families. Improved cancer-related survival may be achieved by early tumor detection through systematic surveillance (11). In addition to enabling improvements in survival, decreasing cancer- and therapy-related morbidity is equally important in two respects. First, it is critical to avoid limiting effective therapy options for future cancers, and second, therapeutic agents may contribute to subsequent tumor risk (12–14, 15, 16), Further, cancer management itself may be modified in the presence of an underlying CPS, with need for careful planning around potential treatment-related toxicities, surgical approach, and choice of familial hematopoietic stem cell donor.

In addition to the clinical implications, the knowledge gained from the study of clinical and biological aspects of pediatric CPS should inform our understanding and treatment of childhood malignancy more broadly. For example, lessons learned from the application of circulating tumor DNA for early detection of primary cancers in patients with CPS could

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advance the use of this technology for relapse surveillance and tumor evolution in the general pediatric oncology population, and effective pharmaco-prevention strategies may influence the design of future therapeutic trials.

There is tremendous opportunity to improve outcomes for children predisposed to cancer through identification of CPS, early tumor detection, and eventually cancer prevention. However, several unique challenges have impeded successful research and systematic approaches to accomplish these goals. Herein, we outline some of these challenges, as well as some past, ongoing, and future efforts to optimize clinical care and promote research in CPS.

Historical Challenges in Studying Pediatric CPS

While genetic testing of pediatric patients was historically discouraged due to a lack of perceived benefit to children (17, 18), two recent developments have shifted clinical practice towards more systemic genetic testing and CPS identification: large scale tumor-normal sequencing studies, and efficacy of screening in Li-Fraumeni Syndrome (LFS) (5, 11). The introduction of paired germline/tumor sequencing into many large pediatric centers and cooperative group precision medicine studies have led to the identification of underlying CPS in a significant proportion of children, more so than were previously identified by guideline-based single gene testing or small targeted panels (5, 19–21). Furthermore, given the efficacy of tumor surveillance strategies, CPS programs have been established within pediatric cancer centers to enable genetic testing for early diagnosis and screening.

A comprehensive understanding of individual CPS remains challenging due to their relative rarity. Existing knowledge is based on epidemiologic and disease-specific studies that, due to ascertainment bias, likely represent those with the most penetrant disease, limiting our understanding of the true cancer risk. Assessment of genotype/phenotype correlations and the impact of genetic modifiers are also limited, leading to imprecise management plans and minimal stratification of care.

This lack of precision has led to a variability among providers in evaluation and management of at-risk children. Until recently, there has been little consistency in the identification of at-risk children and associated management and surveillance practices. As discussed below, this has been addressed with consensus guidelines for tumor surveillance, but data to inform the most effective surveillance approaches remain preliminary for most CPS.

Perhaps most importantly, the study of children at high risk for cancer has yet to be prioritized by major pediatric cooperative groups in the United States or elsewhere for many reasons, including the relative rarity of individual CPS, ethical concerns about the genetic testing of children, and difficulty obtaining insurance coverage of testing. As a result, the ability to perform large-scale trials in this population, such as cancer prevention trials, has been limited, despite promising risk reduction strategies for adult onset tumors, such as hereditary breast cancer (22, 23). Furthermore, systematic, large-scale efforts to collect comprehensive medical information and bank germline and somatic tissues from patients with CPS have been limited, restricting our understanding of potential differences in pathogenesis of germline-driven cancers compared with their sporadic counterparts.

These challenges have been recognized within the fields of genetics and pediatric oncology, and efforts are underway to address them systematically. For several individual CPS, particularly the rare disorders where diagnosis is made based on syndromic features before cancer develops, there have been important institutional and collaborative efforts that have moved the field forward (11, 24–28), but this has not extended more broadly, particularly across the increasing number of disorders where the diagnosis is not recognized until the child develops cancer.

Establishing the Framework for the Study of Childhood Cancer Predisposition

A Workshop organized by the American Association of Cancer Research represented an early effort to organize the development of cancer risk management guidelines for many pediatric cancer predisposition syndromes (10). The workshop included 65 experts from 11 countries with diverse backgrounds, including pediatric and adult oncology, genetics, genetic counseling, endocrinology, and diagnostic imaging. The group reviewed approximately 60 of the most common CPS and established consensus guidelines for tumor surveillance in childhood and adolescence. The systematic and consensus-forming approach led to the publication of open access guidelines for these CPS (https://aacrjournals.org/collection/57/Pediatric-Oncology-Series). This meeting and the resulting guidelines symbolized the establishment of a collaborative, multi-disciplinary field in childhood cancer predisposition. Several opportunities and challenges were recognized, including the need to establish a network of centers with expertise in cancer predisposition and an inclusive registry and biorepository through which robust, prospective clinical and translational research could be undertaken (29).

The Children's Oncology Group (COG) supported the establishment of a Cancer Predisposition Working Group (CPWG) to formalize a group of experts as a resource for the Disease and Discipline Committees. The mission of the CPWG is to promote the implementation of best practices and consensus guidelines for this population and to promote and facilitate research into the germline genetics, cancer prevention, tumor surveillance, quality of life, and treatment outcomes in children with CPS. More than 100 pediatric oncologists and other specialists, including geneticists, epidemiologists, and genetic counselors, have volunteered to contribute, highlighting the high level of interest in this field. However, as effective as the COG is in conducting childhood cancer research, it does not currently have the mechanisms or

infrastructure to include studies predominantly focused on children who do not have cancer.

Establishment of the Consortium for Childhood Cancer Predisposition (C^3P)

The C^3P was established to address the need to study children with genetic predisposition to cancer. Currently, C^3P consists of representatives from seven large academic centers with well-established pediatric cancer predisposition programs, with leadership through a Steering Committee that includes emerging and established experts in the field. A Memorandum of Understanding (MOU) documents the purpose, structure, and governance of the Consortium, which includes the processes for adding additional institutions. Data and material transfer agreements formalize the collaboration, and policies and procedures are established for new project proposals and appropriate attribution of investigators in publications. Human subjects' protection is overseen by a centralized review board, with special attention paid to the unique protections required for sharing of germline data. Data will be collected locally, stripped of identifiers, and shared with a central data repository, which will undergo periodic audits for data integrity. A data dictionary has been created to collect detailed, standardized clinical data, in alignment with established pediatric cancer data commons (below). Germline variants will be centrally reviewed and annotated using standardized nomenclature.

Individuals with expertise in pediatric oncology, clinical genetics, cancer genetics, and pediatric CPS are included among the C^3P leadership, with representation across the United States and Canada, including both metropolitan and rural communities (**Fig. 1**). This will allow participation of a diverse population in the Consortium, with attention to diversity in ancestry and cultural background. Additional contributions are anticipated from individuals with expertise in genetic counselling, psychology, and medical ethics, to ensure appropriate incorporation of varied perspectives.

The C^3P will collaborate with other pediatric cancer consortia, patient advocacy groups, and community partners to ensure coordination of research efforts. Colleagues in Europe are similarly organizing to study childhood CPS through a registry and biorepository, and trans-Atlantic collaborations have begun. C^3P worked with the National Cancer Institute Thesaurus, to establish and refine data dictionaries to ensure harmonized terminology and is participating in the Pediatric Cancer Data Commons, an international effort to harmonize clinical and biorepository data. Finally, C^3P aims to engage patient advocates and existing consortia, to ensure that patient perspectives and priorities are carefully considered as research plans are developed. Similarly, eventual expansion of C^3P to other centers, including small and/or rural centers, will broaden input and expand the reach of expertise.

C^3P Priority Research Aims and the Childhood Cancer Predisposition Study

The C^3P has identified several research priorities for patients with CPS and their families (**Fig. 2**), to include improved identification of children with CPS, optimization of cancer surveillance, characterization of tumor biology in the setting of CPS, and understanding the psychosocial impacts of CPS. To begin to address these priorities, C^3P has developed the Childhood Cancer Prevention Study (CCPS; NCT04511806), a multicenter, longitudinal, observational study that will collect clinical and biological data and specimens from children with CPS and their relatives. The objectives of the CCPS are (i) to establish and maintain a framework for recruitment, participation, and surveillance of children with CPS; (ii) to define the natural history of disease in children with CPS; and (iii) to evaluate the clinical impact and effectiveness of standard and emerging tumor surveillance strategies. The inclusion of family members, who will provide biologic samples and patient-reported data, will strengthen the ability to study life-long tumor risk, phenotypic heterogeneity, and genetic modifiers. The CPS cohort established through this protocol is anticipated to be one of the largest to date, allowing for unique opportunities to expand the spectrum of diseases associated with specific genetic abnormalities, including those thought of as only contributing to adult-onset tumors.

A Look to the Future: New Opportunities for Exploration and Impact

Beyond the scope of the CCPS, researchers will be able to address these research priorities through the C^3P infrastructure and additional collaborations.

Identification of children with CPS

Prior studies suggest that a significant proportion of patients with pediatric cancer have an underlying CPS, and individual institutional workflows have been developed to identify these patients (30, 31). However, there is no large-scale strategy to harmonize and implement CPS screening in this population. Efforts of collaborators, specifically the McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG), may standardize and expedite identification of children with CPS through the use of tumor-specific algorithms, with diagnostic accuracy on par with routine clinical oncology care (32). Universal screening strategies are advocated for by some, however access and ethical considerations of broad sequencing approaches need to be considered. New genetic predispositions continue to be discovered, including in new high-penetrance genes, modifiers, low penetrance genes/polygenic risk, and epigenetic modifications, necessitating an adaptable approach.

Figure 1.
C^3P member institutions (as of March 2022). Included in the consortium are seven large pediatric tertiary referral centers, with pathway for entry for other interested pediatric cancer programs caring for pediatric CPS.

Tumor surveillance strategies

The CCPS will prospectively evaluate the value of tumor surveillance, based on published guidelines, in children with the most common CPS. These studies will examine the clinical impact, effectiveness, and feasibility of the longitudinal cancer screening methods and serve as a baseline for comparison with novel screening strategies developed by the C^3P investigators and collaborators. Early plans for novel strategies include analysis of plasma specimens for circulating tumor DNA (ctDNA; ref. 33) and microbiome profiling, to build on data generated from adult patients with CPS (34).

Tumor biology, response to therapy, and care across the cancer continuum

As differences in tumor biology, treatment response, and outcomes have been reported in specific CPS-related tumors compared with their sporadic counterparts (35, 36), more targeted approaches to CPS-related treatment modifications, second cancer risks, and modifications to CPS surveillance and post-cancer survivorship care need to be considered (37, 38). For example, immunotherapy may be specifically employed for tumors in patients with germline disruption of DNA mismatch repair pathways, among others (39, 40).

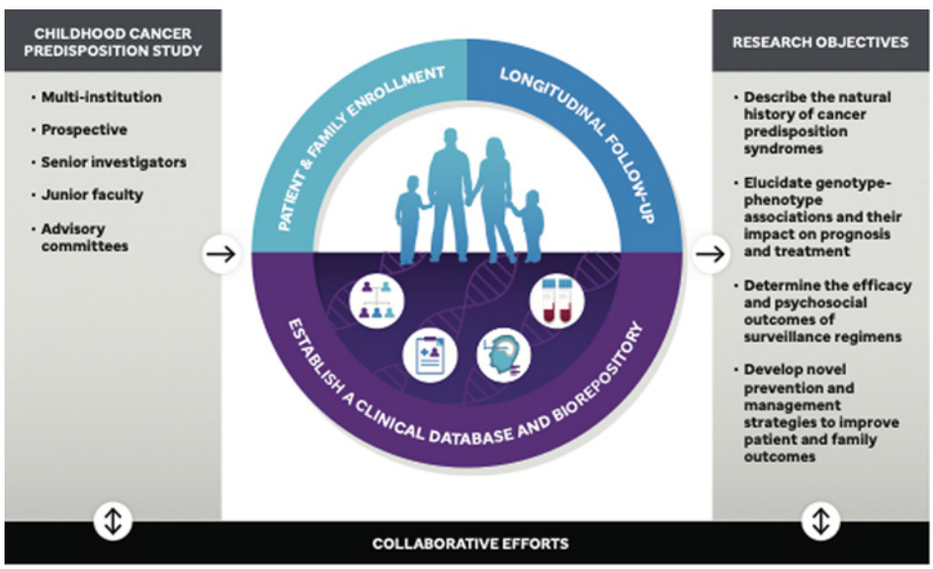

Figure 2.
C^3P organization and flow pathway. Included in the building of a new consortium is a dedicated clinical database and bio-repository available for specific research aims, with collaboration possibilities open to outside hospitals, investigators, and syndrome consortia.

Cancer prevention

Individuals at the highest risk of cancer represent an ideal population to study cancer prevention strategies. Although there are certain populations for whom cancer prevention is possible through prophylactic surgery (41, 42), for most CPS effective methods of cancer prevention remain unrealized. Strategies proposed include the use of medication prophylaxis for patients with CPS; for example, C^3P collaborators are investigating the use of metformin in adult patients with LFS, and several chemopreventative agents have been studied in children with familial adenomatous polyposis (43–45).

Psychosocial impacts

It has been consistently shown in adults with CPS that the majority of patients prefer knowing their genetic diagnosis and focus on the benefits of screening, despite the distress that may accompany these (46). However, analogous studies in children and their parents remain limited (47, 48). This is of particular importance in the pediatric population considering the invasiveness of screening, which may include sedation for imaging, and venipunctures for serum diagnostics, as well as the financial burden to families and interruption of schooling. In addition, there are unique perspectives when multiple siblings require screening, or as patients enter adolescence and adulthood. CCPS efforts to characterize the psychosocial impacts influencing immediate and long-term adherence and quality of life for affected patients and their families will enable the elaboration of developmentally appropriate measures to address these.

Conclusions

Pediatric CPS pose unique challenges to providers, given their perceived rarity and the complexities of evaluation and management of pediatric cancer risk. Through formation of the C^3P and many ongoing collaborations, children with CPS in North America will be systematically enrolled and followed over time. Through coordinated, multi-institutional research, we hope to accelerate improvements in survival and treatment outcomes for this at-risk population.

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