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Incorporating Genetic Counseling into Clinical Care for Children and Adolescents with Cancer

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Genetic counseling and genetic testing is becoming an increasingly key component of multi-disciplinary cancer care, as evidenced by inclusion of cancer risk assessment and genetic counseling in the clinical service standards of professional societies and accrediting bodies (e.g. The American College of Surgeons Commission on Cancer[1] and the American Society of Clinical Oncology[2]). Identification of patients at risk for hereditary cancer syndromes can provide opportunities to optimize care for the existing cancer, and guide surveillance for cancer survivors who may be at risk for second (or third) malignancies. Identifying patients with hereditary cancer syndromes also benefits their family members, who can then engage in cancer prevention strategies to improve outcomes. There are several known hereditary cancer syndromes that can present with childhood tumors, including Li-Fraumeni syndrome, hereditary paraganglioma, Von Hippel Lindau syndrome, and others, and pediatric oncology patients and their families can benefit from incorporating genetic services into existing care teams.

With increasing use of next generation DNA sequencing (NGS) technology in clinical diagnostic testing, pathogenic variants in cancer risk genes are being identified as secondary or incidental findings in children and adolescents who have sequencing completed for other

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reasons. In the first 104 patients with cancer enrolled in our Peds-MiOncoSeq population, 91 completed sequencing of paired tumor/normal DNA samples, and 9 (10%) had pathogenic germline variants associated with cancer risk[3]. The majority of the pathogenic germline variants findings (7/9) were not known prior to study participation and 4/9 had no family history to suggest potential risk for a familial cancer syndrome. Similarly, the Pediatric Cancer Genome Project found germline mutations in 8.5% of pediatric oncology patients completing genome or exome sequencing, and 60% of those with available family history information showed no evidence of inherited risk [4]. Even if sequencing is not performed on paired normal DNA, tumor sequencing can lead to identification of germline mutations[5], or identify mutational profiles strongly suggestive of underlying inherited risk, as with the ultra-hypermutant tumors seen in children with biallelic mismatch repair deficiency syndrome[6]. Molecular testing of germline DNA is frequently ordered in the diagnostic evaluation of cancer-free children with developmental delay, congenital malformations, and/or dysmorphic features, and can lead to secondary findings in cancer risk genes as well. One large study of array comparative genomic hybridization (aCGH) found that 0.34% of total results and 1.2% of abnormal results had a clearly cancer predisposing copy number variant.[7] Exome sequencing is taking precedence as a diagnostic test in pediatric patients with unexplained developmental delay or syndromic features, and a study of 2000 patients (88% pediatric) referred for clinical exome sequencing similarly found 1.25% had an incidental finding in a cancer predisposition gene[8], including those recommended for reporting by the American College of Medical Genetics[9].

The increased use of NGS in various clinical settings along with the potential implications for long term follow up for pediatric patients and family members affected by inherited cancer syndromes raises the important question of how to best meet the clinical need for timely genetic evaluation of these patients. Incorporating genetics services into pediatric oncology care teams offers several advantages, and there are some key steps that can help accomplish this goal.

Step 1 – Identifying patients who may benefit from genetic services

About 5–10% of cancer diagnoses in general are estimated to be caused by inherited risk. This number can be substantially higher for certain tumor types, including some cancers that occur in children or adolescents[10]. A single study of a childhood cancer survivor clinic evaluated 370 patients for criteria suggestive of inherited risk, and found that 29% could potentially benefit from genetic evaluation[11]. Among patients identified through this screening, 34% were identified based on personal history of a cancer diagnosis with known association to an underlying syndrome or clinical features of a syndrome. Referral for genetic evaluation has been suggested for individuals with specific tumor types [10], and it is likely that this list will grow over time. Although family history of cancer is frequently employed as a screen for hereditary syndromes, it is also worth noting that not all pediatric patients with genetic predisposition to cancer will have a family history of related cancers. Small family size, young ages of relatives, variable penetrance, and de novo mutations can make family history unreliable as a primary screening tool. Nearly half of Peds-MiOncoSeq participants with germline mutations in cancer risk genes had no suggestive family history

[3], emphasizing the importance of looking beyond the family history to recognize tumor types that suggest genetic risk.

Step 2 – Collecting and updating family histories

In the previously mentioned survivor clinic screening study, 66% of patients who could benefit from genetic evaluation were identified on the basis of reported family histories of cancer or other genetic conditions[11], emphasizing the importance of comprehensive family history collection. An ASCO expert statement recommends minimum elements for family history collection in the oncology setting, which includes: type of primary cancer and age at diagnosis for all first and second degree relatives (parents, siblings, children, aunts, uncles, and grandparents), ethnicity, and results of any previous genetic testing in the family.[12] Importantly, family histories are dynamic and new diagnoses of cancer within the family over time may become relevant in assessing risk. This is particularly important in the pediatric setting, where parents, aunts and uncles may be quite young, and may develop related cancers after the diagnosis in a child. For this reason, family histories must be updated as childhood cancer survivors are followed over time. Optimal collection and updating of family history could be improved with better tools that can be integrated into existing practice, particularly if the minimum recommended elements could be integrated into electronic health record systems. Options for direct patient data entry, and/or auto prompts for genetic counseling referral, could also streamline this process and improve identification of patients who may benefit from genetic evaluation.

Step 3 – Including genetic counselors as part of the multi-disciplinary team

There are many potential advantages to incorporating genetic counseling services directly into the multi-disciplinary care team for children and adolescents with cancer. The nature and complexity of cancer care can already mean multiple appointments with specialists on different days, creating barriers for children and their families/caregivers including more missed days of school or work, difficulties navigating a health system to correctly schedule visits, and even transportation needs. One study of outcomes in a multi-disciplinary pediatric cancer survivors' clinic with same day coordination of visits found that 26/130 participants (20%) had failed to follow up on a specialty referral in the past, and were able to complete these evaluations when they were offered as a same day service[13].

Direct involvement of a genetic counselor in the pediatric oncology clinic may also improve patient identification. Adding a genetic counselor to screen patients for suggestive tumor types and family histories in a pediatric survivors' clinic led to a significant increase in patient identification, from 6% referred prior to 29% after addition of genetic counselor.[11]

While there are more than 4000 trained genetic counselors in the United States[14], with about 30% identifying cancer genetics as their primary specialty (2014 National Society of Genetic Counselors (NSGC) Professional Status Survey[15]), not all clinics will have easy access to an on-site genetic counselor. Genetic counselors can be located by geographic area using the NSGC Find a Counselor feature[15] and clinics can also be located through the National Cancer Institute's Cancer Genetics Services Directory[16]. There are also increasing options for phone or video counseling to help meet demand for services in

underserved areas. The ASCO expert statement on family history collection recommends that all oncology teams should identify providers within or outside their practice with cancer genetics expertise who can provide appropriate counseling.[17]

In summary, identifying children and adolescents at risk for hereditary cancer syndromes creates opportunities to optimize cancer treatment and long term surveillance. A multi-disciplinary approach that incorporates genetic counseling services into the existing pediatric oncology team can increase patient identification, reduce barriers to services, and enhance patient centered care.

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