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Genetic Counselor Recommendations for Cancer Predisposition Evaluation and Surveillance in the Pediatric Oncology Patient

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Abstract

As the understanding of the genetic etiology of childhood cancers increases, the need for the involvement of experts familiar with the provision of genetic counseling for this population is paramount. In October 2016, the American Association for Cancer Research organized the AACR Childhood Cancer Predisposition Workshop in which international experts in pediatric cancer predisposition met to establish surveillance guidelines for children with cancer predisposition. Identifying for whom, when, why, and how these cancer predisposition surveillance guidelines should be implemented is essential. Genetic counselors invited to this workshop provide a genetic counseling framework for oncology professionals in this article. Points of entry and recommendations regarding the provision and timing of the initial and subsequent genetic counseling sessions are addressed. The genetic counseling and testing processes are reviewed, and the psychologic impact related to surveillance is explored. Pediatric cancer genetics will continue to grow and evolve as a field, and genetic counseling services will be vital to ensure appropriate identification and management of at-risk children moving forward. *Clin Cancer Res; 23(13); e91–e97. ©2017 AACR.*

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Introduction

The field of pediatric cancer predisposition is rapidly growing as new genes and syndromes are discovered, the phenotypes of known syndromes are expanded, and new cancer screening and genetic testing technologies are developed. With the increasing use of large gene sequencing panels, genome-wide chromosomal microarrays, and whole exome/genome sequencing, more children with cancer predisposition syndromes are being identified (1). The use of somatic tumor testing in childhood cancers is also increasing and carries the potential to identify underlying germline pathogenic variants (2, 3). This highlights the growing need for both pediatric cancer predisposition programs and genetic counselors specialized in pediatric cancer to address the unique issues and challenges of this population. Genetic counselors are experts in risk assessment and the interpretation of genetic test results, and are uniquely qualified to address the complex genetic, ethical, legal, and psychosocial issues encountered in the pediatric cancer genetics clinic.

Special issues and challenges in pediatric cancer genetic counseling include obtaining informed consent and assent for minors undergoing cancer genetic testing, determining the optimal timing of genetics referral and testing for at-risk children, providing education and counseling over time as children mature, disclosing genetic test results after the death of the child from cancer, and assisting adolescents with successful transition to adult cancer predisposition care. Given the rarity of childhood cancer predisposition syndromes, there is a paucity of guidelines for the referral, diagnosis, and management of patients with suspected or confirmed cancer predisposition syndromes (2). In addition, incidental diagnosis of cancer predisposition syndromes in children is increasing with the use of genomic testing and involves its own distinct psychosocial issues and challenges (4–7).

In this position article, we present recommendations for addressing issues specific to pediatric cancer genetics, including referral to pediatric cancer genetics clinics, pretest counseling and informed consent and assent for cancer genetic testing of children, test selection and timing of testing, posttest counseling, and psychosocial aspects of cancer surveillance for children with hereditary cancer syndromes.

Points of Entry

Individuals with indication for hereditary cancer evaluation should be referred for genetic counseling.

There are several points of entry prompting a pediatric cancer genetics referral, including family history, physical features, high-risk tumor types, and incidental results from germline or somatic testing. The importance of family history in the identification of

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Table 1. Recommendations for pediatric solid tumors (diagnosed <18 years of age) warranting referral for genetic evaluation regardless of family history[a]

Central and peripheral nervous system tumors	Non-CNS solid tumors	Renal and genitourinary tumors (non-rhabdoid)
Acoustic/vestibular schwannoma	Adrenocortical carcinoma	Botryoid-type embryonal rhabdomyosarcoma
Atypical teratoid/rhabdoid tumor	Anaplastic rhabdomyosarcoma	Cystic nephroma
Choroid plexus carcinoma	Basal cell carcinoma	Gonadoblastoma
CNS hemangioblastoma	Carcinoid tumor	Gynandroblastoma
Malignant nerve sheath tumors	Cardiac rhabdomyoma	Juvenile granulosa cell tumor
Medulloblastoma (sonic hedgehog, desmoplastic, nodular)	Ciliary body medulloepithelioma	Large cell calcifying Sertoli-Leydig cell tumor (testicular)
Neurofibroma (two or more or one plexiform neurofibroma)	Gastrointestinal cancer	Ovarian Sertoli-Leydig cell tumor
Optic pathway glioma	Cribriform-morular variant of papillary thyroid cancer	Renal angiomyolipoma
Pineoblastoma	Desmoid tumor	Renal cell carcinoma
Pituitary blastoma	Endolymphatic sac tumors (ELST)	Renal sarcoma
Subependymal giant cell astrocytoma	Gastrointestinal stromal tumor (GIST)	Urothelial cell carcinoma
	Hepatoblastoma	Wilms tumor (bilateral/multifocal)
	Malignant rhabdoid tumor	
	Medullary thyroid cancer	
	Melanoma	
	Multinodular goiter	
	Myxoma	
	Nasal chondromesenchymal hamartoma	
	Osteosarcoma (dx <10 y)	
	Parathyroid carcinoma	
	Pheochromocytoma/paraganglioma	
	Pleuropulmonary blastoma	
	Retinal hemangioblastoma	
	Retinoblastoma	

Abbreviations: CNS, central nervous system; dx, diagnosis; y, years.
[a]Of note, these lists are not comprehensive of indications that may warrant automatic consideration for referrals. Referral practices may vary, and indications may change with time

children affected by cancer predisposition has been well reported (8–10), yet genetics evaluation can be indicated in the absence of family history, especially in the pediatric setting. Studies assessing the utility of next-generation sequencing (NGS) technologies in the detection of pediatric cancer susceptibility have revealed that family history alone does not adequately identify children with predisposition syndromes (11–14). Family history will not be revealing in the setting of *de novo* variants or parental germline mosaicism. Furthermore, low penetrance, recessive inheritance, and small and/or young families can mask an inherited syndrome that is being passed through the family. Referral recommendations and tools for providers to recognize appropriate referrals are available. Positive family histories, high-genetic risk solid tumor types (see Table 1), multiple primary tumors, additional physical or clinical features, and treatment toxicity (15–18) all should be factored into the referral process. In the future, however, genetic testing may be considered for all children with cancer given the limitations of current referral and genetic testing criteria.

Many non-oncologic physical findings should prompt referral for cancer predisposition evaluation. Examples include the classic lip pigmentation associated with Peutz–Jeghers syndrome; >3 café au lait macules associated with neurofibromatosis type 1 and biallelic mismatch repair deficiency; and multiple, bilateral congenital hypertrophy of the retinal pigment epithelium associated with familial adenomatous polyposis (16). In addition, incidental findings identified on germline genetic testing performed for other clinical reasons may initiate referral. This includes the disruption of cancer predisposition genes detected by chromosomal microarray technology (5–7) and secondary findings detected by exome sequencing (4). Referrals generated by non-oncologic physical findings or incidental findings on a genetic test can come with unique challenges in the discussion with both parents and clinicians given the unanticipated nature of the findings and their association with cancer predisposition.

Finally, the uptake of precision medicine and molecular tumor analysis by NGS increases the possibility of identifying somatic variants within cancer predisposition genes (19). Oncologists are increasingly challenged with interpreting whether a reported variant is an isolated somatic change or if it indeed represents germline susceptibility. A referral to the cancer genetics clinic for additional interpretation may be indicated when a variant identified on tumor testing is suspected to represent an underlying germline mutation (3).

Timing of the Genetics Referral

Referral for genetic counseling should be made at the time of tumor diagnosis so that genetic testing, if indicated, can be completed in a timely manner.

DNA banking should be considered if the genetic counseling appointment may occur after the initiation of treatment or if the child has a poor prognosis.

Genetic counselors or other genetics professionals are integral members to the patient's care team, and we recommend that referrals are made at the time of tumor diagnosis. The genetic counselor or genetic professional in consultation with the oncologist can decide when to see the family based on the child's prognosis, treatment plan, and psychologic well-being of the family. As the genetic counseling appointment may not arise immediately, DNA banking should be considered if available and if testing may be more difficult once treatment has started

(i.e., due to lowered lymphocyte counts following chemotherapy or difficulty of obtaining a germline sample after a patient has undergone donor bone marrow transplant) or if the patient has a poor prognosis. In addition, testing a child postmortem may be important for the care of relatives but is unfeasible if no DNA is banked. Every effort to organize genetic counseling before the child passes away should be made, as the cost of postmortem genetic testing often falls to the family and, therefore, may not be feasible even if a sample is available.

Pretest Genetic Counseling and Informed Consent

Children and their parents/guardians should meet with a genetic counselor or other qualified professional prior to undergoing germline cancer genetic testing.

Informed consent should be obtained from the parent(s)/guardian(s) of children undergoing germline cancer genetic testing. Verbal or written informed assent should be obtained from older children and adolescents undergoing germline cancer genetic testing and should be documented in the medical record. Younger children undergoing testing should also be included in the pretest discussions in a manner that is appropriate for their age and understanding.

Cancer genetic counseling is meant to increase family understanding of testing options, ensure that the most appropriate test(s) is ordered, allow for informed decision making, and ensure that families are prepared for the outcomes of testing. Genetic testing for adult-onset conditions in children should not be undertaken without medical and/or psychosocial justification and a discussion with family members, although pathogenic variants in adult-onset cancer genes may be revealed by large panels, tumor-based testing, or whole exome/genome analysis as an incidental finding (20). Genetic testing without genetic counseling has been linked with a variety of negative testing outcomes including a lack of informed decision making around testing; ordering of costly, unnecessary genetic testing; misinterpretation of genetic test results; inappropriate or inadequate medical management; violations of ethical standards; and adverse psychosocial outcomes (21–23). The informed consent process should include a discussion about the implications of the results to the patient (including discussion of the surveillance protocol, or lack thereof, for the child if found to have a hereditary cancer predisposition syndrome), psychosocial and ethical considerations, confidentiality and privacy concerns (which varies with the laws of different countries), the implications of the results for other relatives, logistics including a plan for disclosing results, and the option of deferring or declining testing (15, 24–26).

The trend toward openly discussing treatment plans and prognosis with children who have cancer has mirrored the trend toward involving children in a developmentally appropriate manner in pretest counseling discussions. Obtaining verbal or written assent from older children and adolescents further ensures that they have a voice in the decision-making process, allows them to have their fears or misconceptions addressed, and helps prepare them to learn their test results (27, 28).

Despite concerns about potentially exacerbating parental and patient anxiety, genetic counseling has been found to allay fears and to empower families by providing fact-based risk information and potential options for proactive risk reduction and/or early detection strategies if a gene mutation is identified (29, 30).

Genetic Testing

Genetic testing is an important tool for identifying individuals with hereditary cancer predisposition syndromes. Test selection should be undertaken with input from a genetic counselor or other qualified professional.

The transition to NGS platforms is the most significant recent development in genetic testing. This technology allows for the analysis of multiple genes or even whole genomes at moderately low cost and increases the ability to efficiently screen children with cancer for genetic predisposition.

When selecting a laboratory and a specific genetic test, it is important to consider inclusion of the gene(s) of interest, testing methodology and validation, variant interpretation and reinterpretation practices, cost, turnaround time, and the laboratory's policies regarding data sharing. The American College of Medical Genetics and Genomics (ACMG) proposed a five-tier variant classification structure that recommends reporting variants discovered during clinical testing as benign, likely benign, uncertain significance, likely pathogenic, and pathogenic (31). Although this system provides the clinician with insight into the classification decision, further tailoring is often needed to apply the findings from genetic testing to the clinical context of the patient. Testing with multigene panels and exome/genome sequencing results in a higher yield of both pathogenic variants and variants of uncertain significance (VUS; ref. 32) than with single-gene testing (Table 2).

When pathogenic or likely pathogenic variants are identified, that information can be used to tailor management and perform targeted testing for at-risk family members. Typically, the identification of a VUS should not influence medical management decisions, and relatives should not be tested for these for the purposes of risk assessment and clinical management. However, variant tracking may be performed for informative relatives to assist with variant interpretation. The family and treating oncologist should be aware that interpretation of this variant may change over time. Periodic rereferrals for genetic counseling are recommended for individuals with a VUS or negative/uninformative genetic test results but continued suspicion for a cancer predisposition syndrome. Periodic reevaluation for these patients allows families to be updated on new information and changes in family history to be incorporated into the assessment.

Although NGS testing of multiple genes increases identification of pathogenic variants, many individuals with features suggestive of familial risk will not have an identifiable pathogenic variant. The sensitivity of genetic testing for identifying the underlying mutation varies quite significantly with >95% for some conditions (e.g., von Hippel-Lindau syndrome) and less than 50% for juvenile polyposis. For these families, risk assessment and management will be based on empiric data and clinical judgment.

Posttest Genetic Counseling

Genetic counseling for children diagnosed with a hereditary cancer syndrome should be an ongoing process to reinforce information, address age-specific risks and management, ensure

Table 2. Genetic testing approaches

Type of genetic testing	Level of analysis	When used	Advantages	Limitations/disadvantages
Familial variant testing of a single gene	Analysis of a single variant	Known familial variant	Least expensive Very accurate Results are definitive	May miss a cancer-predisposing mutation in a different gene not previously identified in the individual or family (a rare circumstance) Testing should be performed in the same lab that identified the mutation in a family member, or a positive control sample should be sent
Single gene[a]	Sanger sequencing or NGS coding sequence and intron/exon borders of the selected gene +/− copy number analysis for intragenic deletions/duplications	Phenotype fits a known cancer syndrome caused by one or a few genes	Highly specific Lower risk for VUS	May not identify certain types of variants (i.e., deep intronic variants) May miss variants in more rarely associated genes not tested with this approach Additional testing may be required if initial testing is negative or inconclusive
Multigene panel[a]	NGS of coding sequence and intron/exon borders of the selected genes May include targeted panel of genes associated with specific cancer type or broad panel of genes associated with cancer predisposition +/− copy number analysis for intragenic deletions/duplications	Phenotype that does not clearly fit with a specific syndrome Patients suspected to have a condition that can be associated with variants in multiple genes (e.g., pheochromocytoma/paraganglioma)	Increases the chance of identifying a causative variant Cost-effective	May identify incidental findings/VUS Depending on nature of the panel, may identify moderate-risk genes for which limited surveillance recommendations may be available
WES/WGS[a]	NGS technology to evaluate coding areas (exons and intron/exon borders only) or entire genome (exons and introns)	Patients with unclear cancer phenotypes or multisystem phenotypes Patients with negative/uninformative results on prior single-gene or multigene testing Research settings identify novel genetic associations	Cost of WES/WGS is approaching the cost of multigene panels and may be the most cost-effective approach in the future Data can be reanalyzed as new genetic associations are made	Not all platforms will have adequate coverage of the genes of greatest interest for a patient Sequencing technology may miss intragenic copy number variants Greatest chance for incidental findings/VUS Ethical considerations regarding possible identification of variants associated with adulthood disease risk Challenges in storing and reinterpreting data and communicating implications over time Increased time to obtain informed consent and determine preference for possible result types NGS technologies not consistently available as a clinically certified test
SNP Microarray	Genome-wide microarray to detect large chromosomal deletions/duplications	Patients with developmental delays/intellectual disability/autism spectrum disorder and/or congenital abnormalities that may be indicative of a chromosomal deletion/duplication Patients identified by single-gene or multigene testing to have a whole gene deletion	Identifies large deletions or duplications that may be missed by single-gene, multigene, or WES/WGS testing Defines size of deletion or duplication and genes included	Chance of incidental findings (including consanguinity)/VUS Will not identify balanced chromosomal rearrangements Will not identify sequence alterations or deletions/duplications below a certain size

Abbreviation: WES/WGS, whole exome sequencing/whole genome sequencing.
[a]NGS-based testing has the ability to detect mosaicism due to a *de novo* mutation.

information is disseminated to at-risk relatives and, evaluate needs for additional psychologic support. We recommend that in addition to genetic counseling at the time of initial assessment, children diagnosed with hereditary cancer syndromes should revisit genetic counseling in the mid- to late teenage years and again at times of family planning.

Incorporating cancer predisposition test results into lifelong cancer risk management and understanding of reproductive implications is particularly challenging when this information is initially received in early childhood (2). Children's psychologic needs may also change with age as they become more aware of the implications of having a hereditary cancer risk and

as they reach an age at which physical features or cancers may begin to manifest. Evaluation of psychologic and emotional support needs for children and their caregivers is imperative, and processes for referring to support services should be in place (28). Revisiting genetic counseling in the mid- to late teenage years and again at the time of the family planning is also vital to ensure that patients understand their diagnoses, medical management recommendations, and reproductive risks and options.

Discussion of results and their implications with at-risk relatives should be encouraged and facilitated. When a pathogenic variant is identified, the inheritance pattern of the condition will determine which relatives are at risk and in need of testing. For autosomal dominant cancer syndromes, first-degree relatives have an up to 50% risk of having the pathogenic variant and the associated increased cancer risks. Disseminating information to relatives can be a daunting process for families also dealing with a cancer diagnosis. Genetic counselors can provide guidance and assistance in this process.

Risks for future children in the family should be addressed, and discussion should include options for preimplantation genetic diagnosis; prenatal diagnosis; testing children after birth; adoption; and/or utilizing donor eggs, sperm, or embryos.

Finally, the results of genetic testing should be incorporated into the management planning of the patient and at-risk relatives. Even in the context of a clearly pathogenic variant, surveillance recommendations may need to be tailored on the basis of personal and family history and genotype–phenotype correlations. In the absence of an identified genetic cause for the patient's personal and/or family history of cancer, families and referring physicians should be encouraged to follow up periodically with their local cancer genetics clinic to be informed of new genetic testing options and/or surveillance recommendations (see Table 3).

Psychosocial Issues Related to Surveillance

The family, in concert with multidisciplinary team, should be involved in decision making and coordination of tumor surveillance plans and be monitored for psychosocial impact of such plans on their overall quality of life.

As surveillance protocols for an increasing number of cancer-predisposing conditions are established, the importance of balancing the scientific merit with the psychologic burden needs to be carefully studied on a large scale. The efficacy of many cancer surveillance protocols for rare cancer syndromes has not been determined for many syndromes, although some data are beginning to accumulate (33–36), and for many pediatric cancers, no established surveillance exists. Clinicians and families must weigh the desire for early detection with possible negative outcomes of surveillance, which include risks from invasive medical procedures, procedures requiring sedation or general anesthesia, false positive results, incidental findings, cost, and psychologic burden.

Table 3. Circumstances in which surveillance recommendations should be followed

Pathogenic variant detected in cancer-predisposing gene
Clinical criteria met for a syndrome, but genetic testing not pursued
Clinical criteria met for a syndrome, but no pathogenic variant detected
50% risk (e.g., parent/sibling with syndrome), but genetic testing not (yet) pursued
50% risk (e.g., parent/sibling with syndrome), but informative genetic testing not available

Cancer-related distress is associated with impaired quality of life, reduced satisfaction with care, and worse overall survival (4, 37). At this time, only a few small studies have attempted to address the psychosocial factors associated with tumor surveillance in pediatric-onset cancer syndromes (38–45). A multidisciplinary approach with clear surveillance recommendations and support from providers has been demonstrated to improve adherence to surveillance protocols (39, 43).

"Scanxiety" (46) has been described in cancer patients and refers to the often-debilitating anxiety patients experience in the period surrounding imaging studies to identify cancer. Scanxiety can be compounded by a fear of future tumor development amongst cancer survivors. Undergoing imaging and/or laboratory studies as part of a cancer surveillance protocol may also cause potentially unnecessary worry for individuals with cancer predisposition syndromes (43).

Some patients have fears and anxiety related to specific aspects of surveillance such as confined spaces in an MRI, anesthesia, or blood draws. Uncertainty can arise when tumor surveillance reveals ambiguous findings, necessitating additional imaging or biopsy. Certain types of screening, such as whole-body MRI, may have high rates of incidental or false positive findings (34–36). Ultimately families can become frustrated with the lack of information regarding optimal surveillance protocols, high frequency of exams, inconclusive outcomes, and the challenges and costs of coordinating complex specialty care. Adolescents and young adults, who are more likely to be uninsured, have less stable employment and less social support and may be at greatest risk for discontinuing screening, often as they are reaching an age where cancer risk may increase. Detailed discussions with parents and teens about these issues of access to health care should be started in the later years of high school to decrease the possibility of a lapse in needed cancer surveillance.

Conversely, tumor surveillance plans can provide psychologic benefits. Families may feel a sense of empowerment and control with a proactive surveillance approach (38). A negative test can provide relief, especially in an organ with high cancer risk or for a tumor type known to be in the family. Relationships formed over time with the surveillance team can generate a sense of trust and support, especially when a new tumor diagnosis is made. Understanding the impact of intensive, long-term cancer surveillance programs on families is necessary to ensure adherence and positive psychologic adjustment.

Several unique situations may arise which require careful consideration by the family and care team. Examples include the continuation of surveillance for other malignancies when a tumor is diagnosed or when a known tumor progresses; modification of a surveillance plan for children with intellectual disability, developmental delays, or other comorbid conditions; and the ideal timing and preparedness training for transferring adolescents to adult tumor surveillance providers.

Conclusions

The model for a referral to cancer genetics programs is an ever-changing landscape. This is particularly evident in pediatric settings. Traditionally, practitioners often relied on a significant

family history of cancer to evaluate the risk for the presence of a hereditary cancer predisposition syndrome in the family. Family history is still an important tool in the initiation of some referrals to cancer genetics programs and should be taken at the initial tumor diagnosis and reviewed periodically (47). However, mounting evidence supports a review of this historical referral paradigm (11–14). Relying on family history alone could mean missing an early diagnosis and, therefore, the benefits of evaluation, diagnosis, and surveillance for the patient and family members.

If a referral for genetic counseling is indicated, we recommend this take place at diagnosis even if the genetic counseling appointment is deferred. The genetics professional and oncology team can decide on the best time for the evaluation to occur. At a minimum, the genetic counselor can help to facilitate DNA banking, when possible, before the initiation of treatment or if the child has a poor prognosis. Genetic counseling empowers children and families to be involved in the decision-making process surrounding genetic testing and tumor management.

When a hereditary cancer predisposition syndrome is identified, families are faced with the distress and anxiety of a new diagnosis of cancer in their child, along with information about increased risks for developing future cancers in the child and a risk for other family members. This distress can be mitigated in part by comprehensive pre- and posttest genetic counseling.

Genetic counselors and other genetic professionals will increasingly be integral members of the pediatric oncology team, providing expertise to help diagnose hereditary cancer syndromes, addressing the unique challenges associated with genetic evaluation in childhood, and helping families use information about cancer risk to plan screening and prevention strategies. Genetic counseling should be an ongoing process, and we recommend that patients receive repeat genetic counseling in their mid- to late teenage years and again when family planning. The field of hereditary cancer predisposition continues to evolve, and iterative genetic counseling will be vital to ensure that patients are kept abreast of new developments and options as they arise.

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