Hereditary cancer syndromes are estimated to account for up to 10% of all new cancer diagnoses in children and adults [1–4]. Given the current incidence of pediatric cancer, this translates to greater than 1,300 children in the United States and Canada diagnosed each year with a cancer related to a hereditary cancer syndrome. However, this widely quoted 10% rate is just an estimate extrapolated from the most common cancers known to be associated with inherited mutations and has not been systematically investigated. One publication last year described the population prevalence of familial cancer and common hereditary cancer syndromes based on 33,197 eligible respondents ages 18–64 years old in the 2005 California Health Interview Survey [5]. The investigators who conducted this survey assigned 14.6% of the cohort as having moderate familial risk associated with a twofold increase in cancer, and 7.7% of the cohort as having strong familial risk with a five to sevenfold increase in cancer. A similar type of population-based prevalence study to determine the true estimate of hereditary cancer in children has yet to be performed. Moreover, one could easily speculate that cancer in children is much more likely to be due to underlying genetic causes than in older adults who have diminishing DNA repair capability and longer environmental exposures.

One of the best ways to identify children with an inherited cancer predisposition syndrome is to obtain an accurate family history. Due to the immediate life-threatening nature of a new cancer diagnosis in children (and its accompanying emotional toll), discussions with a newly diagnosed pediatric cancer patient’s family must focus on treatment strategies, and rightly so. Following a new cancer diagnosis, the coordination of staging CT scans, port placements, and chemotherapy orders often reduces the time needed for clinicians to obtain a very detailed cancer family history. However, collection of a more accurate family history ultimately could identify children and families who would benefit from a clinical cancer genetics referrals and even potentially participate in research.

In addition to the family history, pediatric hereditary cancer syndromes can be suggested by a specific type of tumor or pattern of multiple cancers in a single individual [6–8]. For example, an extremely high percentage of patients with bilateral Wilms tumor will have a mutation in one of the WT genes (Wilms Tumor Syndrome). More than 80% of children with adrenocortical carcinomas (ACCs) will have TP53 germline mutations (Li-Fraumeni Syndrome), and this percentage is even higher in children with choroid plexus carcinomas. Eighty percent of children with bilateral retinoblastoma and 20% of children with unilateral retinoblastoma will have a germline mutation of the RB gene. Over 70% of pediatric patients with metastatic paragangliomas or pheochromocytomas may harbor underlying SDHB mutations (Familial Pheochromocytoma/Paraganglioma Syndrome). Approximately one-third of newly diagnosed patients with rhabdoid tumor will have an inherited INI1/SMARCB1 mutation (Rhabdoid Predisposition Syndrome). Twelve percent of pediatric gastrointestinal tumors (GISTs) have been described to have mutations in one of the SDH genes. Even hepatoblastoma has been associated with a 10% risk of carrying an APC mutation (Familial Adenomatous Polyposis [FAP] Syndrome). Cancers diagnosed in children that are usually seen in older adults such as colorectal or thyroid cancer also can indicate an inherited cancer predisposition syndrome. The list of pediatric tumors associated with hereditary cancer syndromes seems to grow longer every day.

In this issue of Pediatric Blood & Cancer, Knapke et al. publish one of the first systematic pediatric hereditary cancer risk assessments by embedding a certified genetic counselor within in a pediatric oncology follow-up clinic. Using this approach, they accurately determined the total percentage of 370 childhood cancer survivors who were appropriate for referral for cancer genetic counseling. As Knapke and her colleagues report, with the help of their dedicated genetic counselor, they could identify a surprising 29% of childhood cancer survivors who qualified for genetic counseling. The majority of these referrals (61%) were based on family history, while tumor type accounted for 18%. The study was not designed to determine the mutation results for the 109 patients eligible for genetic testing, so we do not know how many referrals actually resulted in a hereditary cancer syndrome diagnosis for patients or their families. Nevertheless, the fact that they found over a quarter of all childhood cancer survivor patients met eligibility for cancer genetics referrals is remarkable. Moreover, this study population consisted of patients at least 5 years from their diagnosis and may underestimate the true percentage of pediatric patients eligible for genetic testing due to early deaths of certain patients. For instance, no patients were identified for...
referral based on tumor type of ACC, choroid plexus carcinoma, or rhabdoid tumors (presumably because these patients died).

Why does this study matter? If children at risk for an inherited cancer syndrome are identified early based on a suggestive family history or individual tumor type, then they and their families can be screened for genetic mutations and appropriate cancer surveillance can be implemented [1,9]. Early cancer detection in this high risk population leads to both improved survival and treatment outcomes [2,4,9]. Villani et al. [10] recently demonstrated in families with Li-Fraumeni Syndrome (TP53 mutations) that biochemical screening combined with regular imaging studies resulted in 3-year overall survival of 100% in the surveillance group versus 21% (95% CI 4–48%) in the non-surveillance group ($P = 0.0155$). Another example of successful intervention includes children and teenagers with FAP who now can be enrolled on chemoprevention trials with celecoxib to reduce colorectal polyp formation and delay colectomies, drastically improving quality of life.

In addition to our patients, identifying children who carry the diagnosis of an inherited cancer predisposition syndrome has immediate consequences for siblings, parents, and extended family members. These pediatric relatives may be considerably younger than relatives of adult patients with hereditary cancer syndromes and therefore, the affected parent of a newly diagnosed child with a cancer syndrome may not have yet presented with his or her first tumor. This provides an excellent opportunity to initiate early cancer surveillance programs in family members in order to detect tumors at a very early stage even before they become symptomatic.

This study by Knapke et al. demonstrates that if you look for inherited cancer syndromes in pediatric cancer patients, you will definitely find them. This especially holds true if you have a certified genetic counselor that has the time and resources available to identify eligible patients. The question now remains how to integrate these genetic counselors into our busy clinics from the first day of diagnosis in order to find the over 1 in 4 children (and their families) who may benefit from referral for genetic testing and early cancer surveillance.

REFERENCES