

Using family history forms in pediatric oncology to identify patients for genetic assessment

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ABSTRACT

Objective We set out to identify and offer genetic testing to the 5%–10% of pediatric cancer patients who have been estimated to carry germline mutations in inherited cancer predisposition syndromes. Clinical genetic testing has become widely available, and thus in busy oncology clinics, tools are needed to identify patients who could benefit from a referral to genetics.

Methods We studied the clinical utility of administering a family history form in the pediatric oncology long-term follow-up clinic to identify patients who might have an inherited cancer predisposition syndrome. Genetic testing involved primarily Sanger sequencing in CLIA (Clinical Laboratory Improvement Amendments)–certified laboratories.

Results Of 57 patients who completed forms, 19 (33.3%) met criteria for referral to genetics. A significant family history of cancer was present for 4 patients, and 12 patients underwent genetic testing. Of 18 genetic tests ordered, none identified a pathogenic mutation, likely because of a small sample size and a candidate-gene approach to testing. Three families were also identified for further assessment based on a family history of breast cancer, with two of families having members eligible for *BRCA1* and *BRCA2* testing.

Conclusions Genetic testing in pediatric oncology patients is important to guide the management of patients who have an inherited cancer predisposition syndrome and to identify other family members at risk when mutations are identified. When no mutations are identified, that information is often reassuring to families who are worried about siblings. However, in the absence of an identified genetic cause in a patient, some uncertainty remains.

Key Words Cancer genetics, genomics, inherited cancer predisposition syndromes, pediatric oncology, family histories, pediatric genetic testing

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INTRODUCTION

More than 100 cancer predisposition genes have been shown to increase the risk of cancer¹, and up to 10% of pediatric oncology patients are thought to harbour a germline mutation². Advances in sequencing technology have made clinical genetic testing widely available, and large gene panels can be used to test multiple genes concurrently³. Many families want to know why their child developed cancer and are concerned about the risk for their other children. Genetic testing that identifies a hereditary cancer predisposition syndrome not only answers both of those questions, but is also important to establish the proper

management, screening, and risk counselling for other family members^{1,4}. Conversely, genetic testing that does not identify a pathogenic variant could reassure families that the risk of malignancy is low for siblings, although it does not rule risk entirely out.

Genetic testing for pediatric oncology patients is rapidly becoming a standard of care, and yet many clinicians are unclear about who would benefit, and currently, few guidelines outline referral criteria^{1,5}. To address that gap, studies have advocated for the addition of genetic counselling to routine care in pediatric oncology follow-up clinics.

Jongmans *et al.*⁶ recently published a checklist to assist clinicians in identifying children with cancer who should

be referred to genetics, and an interactive smartphone application is also currently under development (McGill Interactive Pediatric OncoGenetic Guidelines Project)⁷. An analysis of 370 patients attending the Cancer Survivor Center at Cincinnati Children's Hospital Medical Center found that the rate of referral to genetics increased to 29% from 6% after evaluation by a genetic counsellor or completion of a family history screening form⁴. Family history of cancer accounted for 61% of the referrals, followed by type of cancer (18%) and personal medical history (16%). The possibility of an unrelated genetic condition was identified in 6% of families.

Family history questionnaires are routinely used in adult genetics clinics to triage referrals for breast cancer testing⁸. The aim of the present study was to determine the clinical utility of a Cancer Family History Form, reviewed by a clinician with expertise in genetics, in identifying childhood cancer survivors who would benefit from genetics referral at our centre.

METHODS

All childhood cancer survivors presenting for their annual visit in the Pediatric Oncology long-term follow-up clinic during July–November 2014 were approached by their clinic nurse and asked to complete the Cancer Family History Form in the waiting room. Children with a history of brain tumours are followed in a separate clinic and were not included. Approval for the study was obtained from the research ethics board at the Children's Hospital of Eastern Ontario (CHEO), and informed consent was obtained from all participants.

A brief description of the study and the questionnaire was provided by the clinic nurse, genetic counsellor, or summer student. The Cancer Family History Form used for the study was modified from the one used in our established adult cancer genetics program. Specific questions related to the presence of birth defects or other medical problems in the child, and history of cancer in both first-degree and more distant relatives. Forms were presented in both French and English given that patients are seen at CHEO in both languages.

A medical geneticist and a genetic counsellor reviewed the forms and identified patients who could benefit from an evaluation at the Hereditary Pediatric Cancer Genetics clinic. Specific criteria included the type of cancer diagnosed (those with known germline mutations, or mutations that are part of a spectrum of tumours seen in cancer predisposition syndromes), pediatric onset of adult-associated malignancy, multiple malignancies, associated comorbidities, and family history suggestive of inherited cancer predisposition.

Candidate genes for testing were selected based on the gene most likely to carry a mutation in patients with the presenting diagnosis, as determined by the clinical geneticist seeing the patient. Single-gene tests were done by Sanger sequencing in CLIA (Clinical Laboratory Improvement Amendments)–certified laboratories. Beckwith–Wiedemann testing included methylation and copy number analysis at the genomics laboratory of The Hospital for Sick Children in Toronto. Microarray testing by Affymetrix

CytoScan HD assay (Thermo Fisher Scientific, Waltham, MA, U.S.A.) was done at the CHEO cytogenetics laboratory in Ottawa.

RESULTS

Of 75 families or patients approached for the study, 57 consented to participate [Figure 1(A)]. The patients were representative of the distribution of pediatric cancer in Canada [Figure 1(B)]. In almost all cases, a parent completed the questionnaire. A few older patients completed it themselves, possibly with the help of parents.

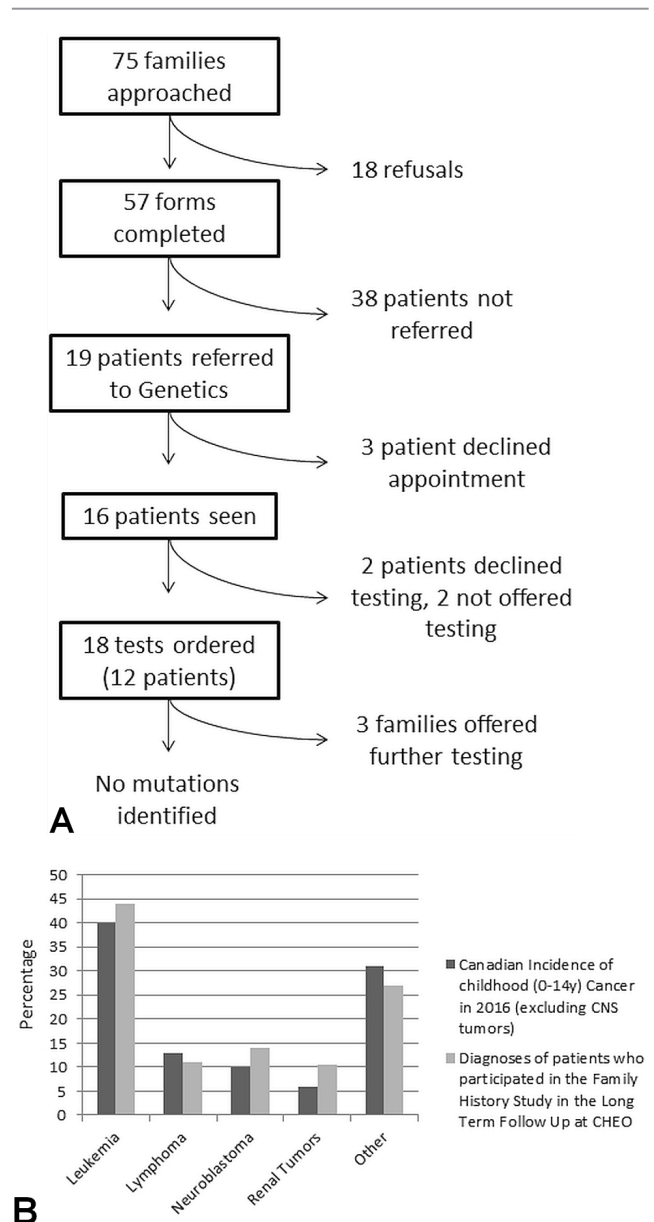


FIGURE 1 (A) Flowchart of participating families. (B) Distribution of pediatric cancer diagnoses in Canada [central nervous system (CNS) tumours excluded] and in our long-term follow-up clinic. CHEO = Children's Hospital of Eastern Ontario.

Of the 57 patients, 19 (33%) met our criteria for a referral to the Hereditary Pediatric Cancer Genetics clinic. Of 6 patients referred based on reported family history of cancer, only 4 patients still had significant family histories of cancer after assessment (breast or ovarian cancer, or both, in first- and second-degree relatives in 3 patients; kidney and pituitary tumours in the parent of the patient with synovial sarcoma). Another 13 patients were referred based on their type of cancer, and 2 patients were referred for both indications. We ordered a total of 18 genetic tests for 12 patients and did not identify any pathogenic mutations (Table 1). Beckwith–Wiedemann syndrome testing was performed for patients who had demonstrated additional features seen in that condition. Genetic counselling for a family history of breast cancer was offered to the families of 3 patients based on their reports of breast or ovarian cancer, or both, in the family, and affected members in at least 2 families were eligible for *BRCA1* and *BRCA2* testing and were encouraged to elicit a referral from their primary care physician.

One third of the patients who participated in the study were not referred to the genetics program because of one or a combination of a cancer diagnosis thought to be sporadic, lack of an identified predisposition gene available for testing, or a family history that was not suggestive of an inherited genetic predisposition (Table 1). Those patients were sent a letter outlining the reasons that a genetics evaluation was not recommended at the present time and advising them to contact their physician if their personal

or family history changed, because the change might alter our assessment. Interestingly, 24% of families chose not to participate in the study and did not complete the family history form. Most of those families (56%) explained that they were not interested, which might reflect a lack of understanding of the relevance of a family history to clinical care. Only 1 patient in that group had previously been referred to genetics, and that family declined to participate in the present study for that reason.

DISCUSSION

Vogel *et al.*⁹ reported that more affected family members with cancer were identified with self-administered questionnaires than with a patient's electronic medical record, which might be the reason that some patients in our study had not previously been referred to genetics. However, administering a family history questionnaire also has limitations. Confirmation of the information being provided by family members is not sought until after the patient has been referred⁴, and parents might not report their entire family history of cancer if they consider adult-onset cancer to be unrelated to their child's cancer¹⁰. Family histories also change over time, making the timing of information collection and requests for regular updates very relevant⁴. The presence of a genetic counsellor or informed oncology nurse to introduce and explain the questionnaire should help to mitigate some of those limitations.

TABLE 1 Clinical details of patients referred to the Hereditary Pediatric Cancer Genetics program

| Diagnosis | Age at diagnosis | Family history | Genetic testing | Follow up suggested as a result of genetic assessment |
|------------------------------|------------------|----------------|--|--|
| Acute lymphoblastic leukemia | 4 Years | Yes | None offered | Referral for family members eligible for <i>BRCA1/2</i> testing |
| Atypical melanoma | 10 Years | No | Declined appointment | |
| Breast cancer | 12 Years | No | Declined testing | |
| Hepatoblastoma | 6 Months | Yes | <i>CDKN1C</i> , ^a <i>TP53</i> | Referral for family members eligible for <i>BRCA1/2</i> testing, and colonoscopies for parents |
| Hepatoblastoma | 15 Months | No | <i>CDKN1C</i> ^a | |
| Neuroblastoma | 5 Years | No | <i>ALK</i> | |
| Neuroblastoma | 4 Months | No | <i>ALK</i> | |
| Neuroblastoma | 3.5 Years | No | <i>ALK</i> | |
| Neuroblastoma | 6 Years | Yes | <i>ALK</i> | Family will try to obtain more details about paternal cancer history |
| Neuroblastoma | 3.5 Years | No | Declined appointment | |
| Neuroblastoma | 18 Months | No | Declined appointment | |
| Neuroblastoma | 10 Days | No | <i>ALK</i> | |
| Neuroblastoma and autism | 1.5 Years | No | <i>ALK</i> , microarray | |
| Ocular melanoma | 14 Years | Yes | <i>BAP1</i> | Referral for relative with breast cancer for genetic risk assessment |
| Pleuropulmonary blastoma | 3.5 Months | No | <i>DICER1</i> | |
| Sex cord stromal tumour | 15 Years | No | <i>DICER1</i> | |
| Synovial sarcoma | 13 Years | Yes | Declined testing | Parent to send the pathology for their kidney and pituitary tumours for review |
| Wilms tumour | 2.5 Years | Yes | None offered | |

TABLE II Diagnoses of patients not referred to the Hereditary Pediatric Cancer Genetics program

| Cancer diagnosis | Patients (n) |
|--------------------------------------|--------------|
| Acute lymphoblastic leukemia | 18 |
| Acute myeloid leukemia | 2 |
| Acute promyeloid leukemia | 1 |
| Burkitt acute lymphoblastic leukemia | 1 |
| Leukemia (unspecified) | 2 |
| Wilms tumour | 4 |
| Ewing sarcoma | 3 |
| Hodgkin lymphoma | 2 |
| Non-Hodgkin lymphoma | 2 |
| T-Cell lymphoblastic lymphoma | 1 |
| Diffuse large B-cell lymphoma | 1 |
| Osteosarcoma | 1 |
| TOTAL | 38 |

In our study, and in our general practice, new diagnoses of cancer occur in the family such that the family history becomes suspicious for an inherited predisposition years after the initial presentation. Regularly updating the family history at follow-up appointments is important to ensure that care providers are aware of significant changes. Newly identified genes, better access to genetic testing, and new interest from families to pursue a genetics referral were other factors leading to a referral now for some patients, but not at the time of the initial diagnosis.

No disease-causing mutations were identified in any of the 18 genetic tests ordered for 12 patients. That information was relayed to the families, who were reassured to learn that the risk of further cancer diagnoses because of an inherited cancer predisposition syndrome was likely low in their child, and therefore low in their siblings as well. However, without identifying the precise genetic cause of a patient's cancer diagnosis, we cannot eliminate the risk of an inherited cancer predisposition gene segregating in the family, nor the presence of a *de novo* mutation in an untested gene in the patient. Given the small number of genetic tests done, it is possible that we missed pathogenic mutations in other genes.

As more nonbiased testing is offered (using larger gene panels or whole exome sequencing), we will continue to identify new disease–gene associations in childhood-onset cancer. A recent study of 1120 pediatric cancer patients who underwent either whole-genome or whole-exome sequencing identified germline mutations in cancer-predisposing genes in 8.5% of the children studied¹¹. Interestingly, pathogenic mutations were identified in genes not typically associated with the presenting type of cancer. In the past 2 years, for example, 5 new Fanconi anemia genes have been identified through whole-genome or whole-exome sequencing: *RAD51 (FANCR)*¹², *BRCA1 (FANCS)*¹³, *UBE2T (FANCT)*¹³, *XRCC2 (FANCU)*¹⁴, and *REV7 (FANCV)*¹⁵. Those recent studies of novel disease-genes, which identified and expanded known phenotypes, highlight how much more work is needed to understand

cancer predisposition in children and underscore the value, for many patients, in less-biased testing methods than a candidate-gene approach.

CONCLUSIONS

We have demonstrated that it is feasible for families to complete a family history screening form while waiting for their annual visits in a survivorship clinic and that the family history screening form is effective in identifying patients who would benefit from a referral to our Hereditary Pediatric Cancer Genetics program. Our study also highlights the need for targeted family histories and a working knowledge of hereditary cancer predisposition syndromes to well-serve pediatric oncology patients and families. The lack of mutation identification in our patients is likely a result of the small sample size and the limited number of genes tested, suggesting that larger gene panels might have identified pathogenic mutations in our patients. Use of a larger gene panel is an approach to consider in the future as the cost of genetic testing continues to decline.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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