Exploring the use of decision support tools to evaluate cancer predisposition syndromes in pediatrics

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Abstract

Background: Cancer predispositions syndromes (CPSs) are genetic conditions that increase the likelihood of developing cancer throughout a patient's lifetime. For pediatric cancer patients, CPSs are particularly relevant, as this population is less likely to develop malignancies from environmental exposures or other cancer-associated lifestyle factors. In fact, recent advances in the field of cancer genetics have elucidated the importance of recognizing the multitude of CPSs that may impact treatment plans, cancer surveillance and/or preventative measures for pediatric patients and their families. As a result, the last 20 years have seen a rise in decision-support tools (DSTs) that aim to guide health care practitioners in their evaluations of underlying CPSs. Currently, the scope of DSTs used to evaluate pediatric CPSs has yet to be described and their clinical application across Canadian institutions is not well understood.

Objectives: The primary goal of this thesis is to identify, describe and categorize the features of DSTs developed for the pediatric oncology population. The second goal is to establish how these tools are being adopted in clinical settings, by assessing their utility to pediatric hematologist-oncologists (PHOs) across Canadian tertiary-care hospitals.

Methods: An initial scoping review was performed to identify the pediatric-adapted DSTs that utilize the patient's clinical features to determine whether they are likely to have an underlying CPS. Using the Joanna Briggs Institute scoping review methodology, a systematic search strategy was developed and customized for MEDLINE and EMBASE databases. Subsequently, the tools identified in the scoping review informed a survey electronically distributed to PHOs across the 16 largest pediatric oncology departments in Canada. Their awareness and attitude towards DSTs were solicited on an anonymous basis.

Results: Fourteen DSTs were identified, of which (8/14) (57%) have been internally or externally validated for clinical use. Half of the DSTs were specific to one CPS (7/14); the majority were published in a paper-based format (11/14); developed to input the patient's tumour type (14/14), family history of cancer (12/14), non-malignant physical findings (8/14); and developed to output their recommendation in a dichotomous form (10/14).

With the online survey, a total of 36 responses from PHOs were recorded: 18/36 (50%) of the respondents had previously used a DST, while 15/36 (41.7%) had not, and 3 were uncertain. Users of DSTs did not solely rely on the tool's recommendation but used it as part of their decision-making process. Non-DST users were often unaware of the existence of these tools or how to gain access to them. Both DST users and non-users stated that a tool's ease-of-use, its accessibility, and its promotion by their academic institution constitute the most important features for a tool's adoption into their clinical practice.

Conclusion: Fourteen pediatric CPS DSTs were identified through a scoping review; these were developed with a wide range of input/output parameters, formats, and types of CPSs and malignancies being evaluated. Despite the need for additional resources, the use of DSTs in clinical settings is not prominent, as half of the surveyed physicians have not previously used a DST and most tools remain unknown to them. With further development of DSTs' ease-of-use, accessibility, and evidence of their clinical benefit, adoption of DSTs in clinical practices across the country may become more systematic and lead to the increased recognition of CPSs in pediatric patients.

Résumé

Contexte : Les syndromes de prédisposition au cancer (SPCs) sont des conditions génétiques qui augmentent la probabilité de développer un cancer au cours de la vie d'un patient. Pour les patients pédiatriques atteints de cancer, les SPCs sont particulièrement pertinents, car cette population est moins susceptible de développer des tumeurs malignes en raison d'expositions environnementales ou d'autres habitudes de vie associées au cancer. En fait, les progrès récents dans le domaine de la génétique du cancer ont mis en évidence l'importance de reconnaître la multitude de SPCs qui peuvent avoir un impact sur les plans de traitement, la surveillance du cancer et/ou les mesures préventives pour les enfants et leurs familles. En conséquence, dans les dernières années, plusieurs outils d'aide à la décision (OADs) ont été développés afin de guider les professionnels de la santé dans leurs évaluations des SPCs. À l'heure actuelle, la portée des OADs utilisés pour évaluer les SPCs pédiatriques n'a pas encore été décrite et leur application clinique dans les établissements canadiens n'est pas bien comprise.

Objectifs : Le premier objectif de cette thèse est d'identifier, de décrire et de catégoriser les caractéristiques des OADs développés pour la population pédiatrique en oncologie. Le deuxième objectif est d'établir comment ces outils sont adoptés en milieu clinique, en évaluant leur utilité pour les hémato-oncologues pédiatriques (HOPs) dans les hôpitaux tertiaires canadiens.

Méthodes : Une revue de la portée a été effectuée pour identifier les OADs adaptés aux enfants qui utilisent les caractéristiques cliniques du patient pour déterminer s'il est susceptible d'avoir un SPC. À l'aide de la méthodologie du *Joanna Briggs Institute*, une stratégie de recherche systématique a été élaborée et adaptée aux bases de données MEDLINE et EMBASE. Par la suite, les outils identifiés ont guidé le développement d'un sondage distribué électroniquement aux HOPs des 16 départements d'oncologie pédiatrique au Canada. Les connaissances et les attitudes des HOPs à l'égard des OADs ont été sollicitées de façon anonyme.

Résultats : Quatorze OADs ont été identifiés, dont 57 % (8/14) ont été validés (en interne ou en externe) pour une utilisation clinique. La plupart des outils étaient spécifiques à un SPC (7/14), publiés en format papier (11/14), développés pour saisir le type de cancer du patient (14/14), les

antécédents familiaux de cancer (12/14), les caractéristiques physiques non-cancéreuses (8/14) et développés pour émettre une recommandation sous forme dichotomique (10/14).

Le sondage en ligne a permis d'enregistrer 36 réponses de HOPs au total : 18/36 répondants avaient déjà utilisé un OAD, tandis que 15/36 (41,7%) ne l'avaient pas fait, et 3 étaient incertains. Les utilisateurs d'OADs ne se fiaient pas uniquement à la recommandation de l'outil mais l'utilisaient dans le cadre de leur processus décisionnel. Les non-utilisateurs d'OADs n'étaient pas au courant de l'existence de ces outils ou des moyen pour y avoir accès. Les utilisateurs et les non-utilisateurs d'OADs ont déclaré que la facilité d'utilisation d'un outil, son accessibilité et sa promotion par leur institution académique constituent les caractéristiques les plus importantes pour l'adoption d'un outil dans leur pratique clinique.

Conclusion : Quatorze OADs pédiatriques ont été identifiés ; ils ont été développés avec une grande variété de paramètres d'entrée/sortie, de formats, et de types de SPCs évalués. De façon similaire, une hétérogénéité a été remarquée dans leur application clinique dans les établissements canadiens. Malgré le besoin de ressources supplémentaires, l'utilisation des OADs en milieu clinique n'est pas très répandue, car la moitié des médecins interrogés n'ont jamais utilisé d'OADs et la plupart des outils leur sont inconnus. En améliorant la facilité d'utilisation et l'accessibilité des outils et en étudiant leur efficacité en clinique, leur adoption dans la pratique clinique par les établissements Canadiens pourrait devenir plus courante et standardisée.

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Contribution of Authors

Cristal Namuhoranye, BSc

I authored the entirety of the thesis. I lead the scoping review, created its search strategy, screened the studies, interpreted the results and drafted the manuscript. I developed the protocol, REB approval documents for the questionnaire in the second manuscript, interpreted the results and drafted the manuscript.

Catherine Goudie, MD

Dr. Goudie supervised my thesis. She conceived the topics of both manuscripts, contributed as the second reviewer of the scoping review, regularly provided insight on study design, analytical approach, interpretation of results, and reviewed all parts of the thesis.

Nandini Dendukuri, PhD

Dr. Dendukuri co-supervised my thesis. She provided guidance for the analysis of the data and reviewed all parts of the thesis.

Lara Reichman, MSc, (C)CGC

Lara Reichman contributed to the design of the questionnaire in manuscript 2, provided insight and clinical expertise in the interpretation of the results of both manuscripts. She contributed as a second reviewer to the scoping review, reviewed and edited all parts of the thesis.

Amy Bergeron, MISt

Amy Bergeron is the librarian at the McGill University Health Centre who helped to develop, test and review my search strategy for the scoping review (manuscript 1).

Thesis committee members : William Foulkes, PhD ; Jean-Baptiste Rivière, PhD ; Todd Lee, MD MPH

All thesis committee members offered clinical expertise and insight for the design of both manuscripts. They offered feedback and suggestions in order to provide focus for the research questions and clarify the interpretation of the results. They also provided supplemental resources to inform the interpretation of the results.

Abbreviations

BMF	Bone marrow failure
BWS	Beckwith-Wiedemann syndrome
C4CMMRD	European consortium ‘Care for CMMRD'
CMMRD	Constitutional mismatch repair deficiency
CNS	Central nervous system
CPS	Cancer predisposition syndrome
C^{17}	C^{17} council
DST	Decision support tool
EHR	Electronic health records
HBOC	Hereditary breast and ovarian cancer
HCP	Health care professional
LFS	Li-Fraumeni syndrome
MeSH	Medical subject headings
MIPOGG	McGill interactive pediatric onco-genetic guidelines
NF1	Neurofibromatosis 1
PHOs	Pediatric hematologists-oncologists
POGO	Pediatric oncology group of Ontario
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
TuPS	Tumor predisposition syndrome

Chapter 1: Literature review

1.1 Childhood cancer epidemiology

Childhood cancer remains the second leading cause of death among Canadian children aged 0-14 years old, and the third leading cause of mortality among adolescents, aged 14-19 years old[1]. Current epidemiological and surveillance databases estimate the cancer incidence rate among Canadian children <15 years old to be 156.05 (per 1,000,000) in 2020 [2].

1.2 The genetic basis of cancer: a historical perspective

It has become widely accepted that cancer develops due to the accumulation of cellular DNA damage involving genes implicated in cell proliferation, survival and repair mechanisms[3]. DNA damage is posited to originate from environmental exposures and/or due to random errors occurring during DNA replication [4]. For children, in particular, inherited and non-inherited genetic predispositions contribute to cancer development.

Clusters of cancers in families were the first indication that childhood malignancies may have a genetic etiology. In 1969, Drs. Frederick Li and Joseph Fraumeni noticed the increased frequency of cancers in relatives of children with rhabdomyosarcoma. In five particular families, an increased frequency of breast cancer in the young mothers of children affected by rhabdomyosarcoma, soft tissue sarcomas in their siblings or cousins and neoplasms in at least one grandparent, indicated the "plausibility of genetic mechanisms underlying the familial occurrences of sarcoma"[5].

A more concrete understanding of the genetic pathophysiology of cancer began when mathematician Dr. Alfred Knudson demonstrated the "two-hit hypothesis" by analyzing familial cases of retinoblastoma (RB) in the 1970s. Through statistical methods, he hypothesized that hereditary RB requires at least two mutational events, with one mutation inherited (or occurring early in development), and the other occurring somatically. In hereditary cases, the first mutational event "the first hit" occurs in a germline cell, where the mutation will be present in all cells of this

individual. An additional mutational event in the retina "the second hit", usually occurring after birth, leads to tumorigenesis. In these hereditary cases, carriers develop cancers at an earlier age, are likely to develop bilateral RB and, are also, more likely to develop multiple cancers in their lifetime [6,7].

In 1986, the discovery of *RB1*, a tumour-suppressor gene inhibiting transcription and cell cycle progression, provided evidence of Knudson's two-hit hypothesis on a molecular level [8,9]. This finding became an important starting point for the search of genes associated with familial (or inherited) cancers. Shortly after, the early 1990s lead to the discovery of additional cancer-predisposing genes such as the *TP53* tumour suppressor gene associated with Li-Fraumeni syndrome (LFS), the *RET* gene associated with Multiple Endocrine Neoplasia (Types 2A and 2B), and *CDK4 or CDKN2A* in familial melanoma [10–14]. At the time, linkage analysis was often used to uncover the genetic basis of CPSs in cancer-prone families[15]; today, more than 100 genes have been deemed as cancer predisposing genes due to the development of more complex genetic sequencing methods, notably next-generation sequencing techniques applied for whole-exome and whole-genome sequencing [16,17]. There are likely many more cancer predisposing genes to be identified as sequencing technologies become more accessible, increasingly sophisticated and incorporate complementary methods such as RNA testing [18].

1.3 Pediatric-onset cancer predisposition syndromes

Cancer predisposition syndromes (CPSs) are defined as genetic conditions that increase an individual's risk of developing one or more cancers throughout life, with or without non-neoplastic clinical features (e.g. dermatological manifestations, congenital anomalies, developmental delays). Neurofibromatosis 1, for instance, is a dominantly inherited CPS estimated to be prevalent in 1/3,000 individuals and is associated with an increased risk of neurofibromas, optic pathway gliomas and brain tumours[19]. In addition, the syndrome is associated with non-neoplastic features such as cutaneous lesions 'café-au-lait macules', freckling in axillary or inguinal regions, learning disabilities, and musculoskeletal pathologies (e.g. dysplasia of the long bones, sphenoid wing dysplasia). [19,20]

In the past 30 years, over 100 cancer predisposing genes have been linked to tumour development in the pediatric and adult populations [20]. While many syndromes, such as LFS, can cause pediatric and adult malignancies, other syndromes are known as pediatric-specific (ex. constitutional mismatch repair deficiency, Wilm's tumour syndrome) and adult-specific (ex. hereditary breast and ovarian cancer, Lynch syndrome). A summary of the most common pediatric CPSs, their associated genes and cancer types can be found in Supplementary Table 1.1.

1.4 The prevalence of CPSs in pediatric oncology patients

The prevalence of CPSs in children with cancer is estimated to be 10%. Initial estimations were based on evidence provided by Zhang *et al.,* who found an 8.5% CPS rate in a group of 1120 children and adolescents with cancer, half of which were affected by leukemia, 20% by central nervous system tumours, ~9% by neuroblastoma, and the remainder affected by non-CNS solid tumours [21]. Similar estimates have been demonstrated by other research groups [22–24]. However, in subsequent studies, the proportion of germline pathogenic or likely pathogenic variants was evaluated between 6-18%, in a cohort of children, adolescents and young adults with solid tumours[25] or around 14.6% in a study conducted by Byrjalsen *et al*., who studied children affected by all tumour types [26].

Importantly, the prevalence of CPSs has been shown to vary according to tumour type. Up to 70% of cases of pleuropulmonary blastomas are associated with pathogenic germline *DICER1* variants[27]. Due to this strong association, the presentation of such tumours in clinical settings warrants a referral for CPS evaluation and genetic counselling [28,29]. In contrast, tumours such as neuroblastoma have been associated with germline variants in 1-2% of cases [30]. Even further, the prevalence of germline variants may also differ among subgroups of a certain tumour type, as demonstrated by Waszack *et al.*, where one medulloblastoma subgroup (MB_{SHH}) showed a CPS prevalence of 20%, while the other subgroup (MB_{WNT}) had a CPS prevalence of 8% [31]. In general, the prevalence of CPSs is noted to be highest in solid tumours, followed by brain tumours then leukemias [21,32].

Nevertheless, the current estimates of CPS prevalence in children with cancer have several limitations. Previous studies evaluating the prevalence of CPSs may not have taken into account the epigenetic mutations associated with CPSs (e.g. gain/loss of methylation associated with Beckwith-Wideman syndrome) or account for copy number variants [33–35]. This may have led to an underestimation of the prevalence of certain types of CPSs. These studies are also limited by the current repertoire of known cancer-predisposing genes, as some children meet CPS diagnostic criteria while having unremarkable genetic test results or variants of unknown significance. As genetic screening increases and NGS methods become more common, the rate of CPSs may be proven to be higher than it is currently estimated to be.

1.5 Clinical implications of CPSs identification

The approach to recognizing and confirming a CPS will be discussed further below (section 1.6). When a CPS is identified in an individual, several changes in clinical management may be considered such as therapeutic modifications, surveillance measures, preventative measures, familial risk assessment and counselling (Table 1.1).

The psychological impact of CPS diagnoses

When a child gets diagnosed with cancer, parents often seek to understand why the cancer developed. Uncovering a CPS may provide answers to these types of questions and may benefit the psychological well-being of relatives interested in understanding their risk as well. Although research into the psychological impact of CPS genetic testing is much more common in the adult population [48–50], emerging literature demonstrates that parents of children diagnosed with cancer may desire CPS genetic testing. Mitchell *et al.* reviewed the psychological impact of germline testing in pediatric patients [51]. Genetic testing for a CPS was sought out by parents and their families to gain a better understanding of why such a rare event (childhood cancer) had developed with their child in particular, and also, to understand the risk of cancer development for their other children. In a survey conducted with adolescent children undergoing Li-Fraumeni syndrome (*TP53*) genetic testing, surveyed participants reported that knowledge of their CPS status allowed them to feel prepared, reduced their anxiety and made them feel empowered [47,51–54]. However,

beyond the sphere of cancer genetics, the psychological impact of genetic testing in children has also raised some concerns. A systematic review by McGill *et al.* lists the negative psychosocial impact of testing: feelings of worry, regret, stigma; concern for privacy; misuse of results, and fear that disease prevention may not be feasible [55]. Parents also raise concerns about the effects of testing on their insurance, their children's future opportunities for employment and results leading to potential family dysfunction [54]. Although the positive psychological impact of CPS genetic testing is suspected, further research is needed to confirm its effect on pediatric patients and their parents.

Table 1.1 : Clinical implications of CPS diagnosis

Clinical implications of CPS identification	Example(s)
Prophylactic surgery	Thyroidectomy in children affected by multiple endocrine neoplasia type 2A to reduce the likelihood of medullary thyroid carcinoma[36,37]
Reduction of standard chemotherapy and/or radiotherapy dosage to avoid : (1) treatment-related toxicity (2) radiation-induced secondary malignancies	Relevant to patients affected by CPSs such as Bloom syndrome[38] , Ataxia-telangiectasia [39], Nijmegen breakage syndrome[40]
Enrollment in CPS-specific clinical trials	Ongoing clinical trials evaluating *MEK* inhibitors for the treatment of Neurofibromatosis type I associated tumours [41]
Avoidance of cancer therapeutics demonstrated to be ineffective or inappropriate for CPS-affected patients	Avoidance of O^6 methylators against T-cell non-Hodgkin's lymphoma for patients affected by Constitutional Mismatch Repair Deficiency[42]
Cancer surveillance programs leading to early cancer detection	Colonoscopic surveillance of children and adolescents affected by familial adenomatous polyposis starting at ages 12-14 years old. Subsequent follow-up every 1-3 years if adenomas are identified. [43] Toronto Protocol for patients affected by Li-Fraumeni syndrome[44]

Provision of genetic counselling and psychological support to patients and their family members	Allows for (1) informed decision-making (2) greater understanding of the nature and implications of a CPS diagnosis (3) dissemination of genetic testing results/ cascade testing of at-risk relatives (4) discussions about family planning[45,46]. Psychological support in patients with Li-Fraumeni syndrome has been demonstrated to contribute to psychological wellbeing [47]

Surveillance protocols

Children with CPSs are likely to develop one or multiple tumours throughout their lives. An important advantage of uncovering an underlying CPS is that it allows patients to undergo cancer surveillance protocols that aim to detect tumours at an earlier stage in the hopes of increasing the likelihood of an improved prognosis. Multiple CPS-specific surveillance protocols have been developed, but not all have demonstrated survival advantages in subsequent analyses[56]. The Li-Fraumeni syndrome (LFS) surveillance strategy developed by Villani *et al.*, otherwise known as the "Toronto protocol", demonstrated increased overall survival of pediatric LFS patients accepting to undergo recurring abdominal ultrasounds, urinalyses, blood tests and brain/total body MRIs at established monthly intervals. In fact, the 3-year survival rate of cancer patients in the surveillance group was 100% (7 patients) while that in the non-surveillance group was 20% (2/10 patients)[57]. Similar benefits were demonstrated in a longitudinal follow-up study, in which the overall survival of patients following the surveillance protocol was 88% and that in the non-surveillance group was 59.6%[44]. Other studies have modeled the cost-effectiveness of CPS surveillance strategies, such as the adoption of annual abdominal ultrasonography for children affected by Beckwith-Wiedemann syndrome (BWS), up until the age of 4, as demonstrated by McNeil *et al*.[58]. Using a simulation model, children with BWS undergoing abdominal sonography for the detection of Wilm's tumour is estimated to cost $9,642 per life year saved, which is comparable to other screening programs (e.g the cost of mammography for women, over 50 years old, at risk of breast cancer is $46,200 per life year saved). Further, surveillance strategies are becoming continuously refined as more genotype-phenotype correlations are uncovered. Specific genotypes are associated to higher tumour risk (e.g IC1 hypermethylation in BWS) or may be

associated with a particular subset of tumour types (for example, in BWS, those who harbour a germline variant in *CDKN1C* have a higher likelihood of developing neuroblastomas as compared to other subgroups of individuals with BWS)[59].

Lastly, uncovering a CPS allows for the child's biological relatives to assess their risk of harbouring the same variant, a process known as cascade testing. Relatives with CPS-associated gene variants may then follow the appropriate cancer surveillance protocols or risk-reducing surgery options, while tested non-carriers are provided with reassurance and notified that their cancer risk is at the same level as the general population. The knowledge that a CPS may be passed down to future offspring can also impact reproductive choices, inform family planning decisions and allow carriers to consider fertility preservation procedures [60,61]. There are also additional procedures such as pre-implantation genetic testing that may be of interest to patients with a molecularly confirmed CPS diagnosis [62]. With age-appropriate communication to relatives and the provision of psychosocial peer support, cascade testing (for hereditary breast and ovarian cancer and Lynch syndrome, in particular) has been demonstrated to increase life expectancy in a cost-effective manner [63,64].

Therapeutic considerations

The recognition of a CPS in a cancer patient permits clinicians to adjust cancer treatment plans in order to reduce harm and optimize their clinical benefits. For CPSs due to the impaired functioning of DNA repair mechanisms, affected patients are hypersensitive to common cancer therapies such as radiotherapy and chemotherapy. Bloom syndrome, for instance, is a rare autosomal recessive CPS, characterized by biallelic pathogenic variants in the *BLM* gene [65]. It is estimated that over one-third of individuals with Bloom syndrome develop cancer by 25 years old [38]. Current recommendations include reduced chemotherapy dosage and/or duration, avoidance or limited use of alkylating agents, avoidance of radiation, and replacement of CT scans with MRI or ultrasound examinations, whenever possible [66]. The reduction of standard chemotherapy doses and/or the avoidance of radiotherapy is also recommended for multiple other DNA damage repair syndromes affecting pediatric patients, as they are more susceptible to treatment complications and likely to develop subsequent primary malignancies from these treatments [67]. In addition, CPSs may also

cause tumour resistance to standard therapies. Constitutional mismatch repair deficiency (CMMRD), for instance, is associated with pathogenic variants in genes involved in mismatch repair mechanisms, rendering standard therapies (such as O^6 methylator) to be ineffective and increasing the chances of developing a second primary malignancy [42,68,69]. Lastly, the knowledge about a CPS will allow the introduction of targeted therapies (for example, the use of Sirolimus in the setting of tuberous sclerosis complex)[70].

1.6 Difficulty of CPS recognition

CPS may be difficult to recognize in clinical settings due to multiple factors. As general guidance, oncologists and geneticists typically consider certain features as suspicious for an underlying CPS: (1) family history of cancer (2) congenital anomalies or facial dysmorphisms (3) early age of cancer onset (4) specific cancer types that are strongly associated with CPSs (5) excessive toxicity to cancer therapy [71–73]. Importantly, these last three indications occur at the time of or *after* a cancer diagnosis, making the recognition of CPSs prior to tumour development strongly dependent on the clinician's cautious observation of family history and the presence of any morphological abnormalities. However, the absence of a family history of cancer does not exclude the possibility of an underlying CPS, as up to half of children with pathogenic germline variants in a cancer predisposing gene have an unremarkable family history [74]. In addition, young children tend to have young parents and family members, who may currently have an unremarkable cancer history but develop malignancies later in life. Some families lack knowledge of disease occurrence in second and third-degree relatives or forget valuable details surrounding their relative's disease (e.g. the age of cancer onset) making the construction of a detailed pedigree difficult or falsely reassuring. Affected children may also have de novo pathogenic variants which makes them the first CPS-affected member of their respective families and leads to an unremarkable family history of cancer. While the frequency of de novo mutations remains unknown in some CPSs, it has been shown to be especially common in others. Li-Fraumeni syndrome, for instance, is associated with TP53 de novo mutations in 7-20% of cases[85], while, in contrast, up to 50% of neurofibromatosis patients[86] and up to 90% of individuals with heritable retinoblastoma[87] are affected by de novo mutations. As the prevalence of de novo mutations continues to be elucidated with different CPSs, DSTs

heavily dependent on family history to predict the likelihood of such CPSs may be prone to miss the opportunity for early identification.

Similarly, the prevalence of morphological abnormalities (dysmorphic features, congenital anomalies) is variable and may be easier to identify in some CPSs compared to others. Noonan syndrome, for instance, is well characterized by dysmorphic facial features that are more pronounced in childhood (low-set ears, drooping of the upper eyelids, down-slant of palpebral fissures, short stature etc.), while some CPSs (e.g. Peutz-Jeghers syndrome) are associated with subtle dermatological manifestations, and others (e.g. Li-Fraumeni syndrome) are associated with tumour development without dysmorphic features [72,75].

Systematic methods for CPS clinical recognition

An important question that remains to be answered in the field of pediatric CPSs is whether children with clinically actionable CPSs (exemplified in Table 1.1) are being adequately and time-appropriately referred for genetic evaluations. Although this is difficult to determine due to the rare nature of CPSs and pediatric cancers, evidence that many CPSs (whether clinically actionable or not) are going unnoticed is demonstrated through the incidental findings of CPSs in genetic research initiatives[23]. In addition, initiatives implementing systematic screening methods (through clinician educational modules, family history questionnaires, and decision support tools) for CPS identification have shown an increase in CPS diagnoses, which indicates that more systematic approaches to CPS identification should be considered [76–78].

1.7 Decision-support tools

The use of tools to assess the probability of a clinical event is used in many healthcare sectors to provide evidence-based support, systematic decision-making, reproducibility or agreement among clinicians' choice of action. These tools are referred to in many different ways in the literature, including 'decision-support tools', 'risk assessment tools', 'decision aid', 'clinical decisional algorithm' etc. These tools serve many different clinical goals and can be adapted for clinician or patient use. This thesis will continue with the terminology 'decision-support tool' or DST, which

will be referring to clinician-facing tools that estimate the risk of a clinical event given a patient's individualized characteristics.

In the context of pediatric oncology, where the recognition of CPSs is rendered difficult by the complexities of family history collection and variable genetic expressivity, clinician-facing evidence-based tools can play an important role in improving the clinical recognition of CPSs. The first researchers to develop tools that assist in the recognition of CPSs proposed family history collection tools and questionnaires that allowed for the systematic ascertainment of familial patterns of cancers[79–82]. DSTs solely based on family history, despite their utility in certain settings, overlook many important aspects of CPS diagnosis and do not help in the identification of patients with *de novo* CPSs [81].

In more recent years, the development of tools that ascertain the risk of hereditary breast and ovarian cancer (HBOC), involving the *BRCA1* and *BRCA2* genes, has been popularized. Unlike their predecessors, tools such as BRCAPRO[A] incorporate the patient's personal history (age at menarche, cancer history, physical measurements etc.) into more complex statistical models, allowing them to be better predictors of *BRCA1/2* mutations and breast cancer risk in diverse populations. In fact, BRCAPRO has become a widely used DST. It is continuously updated to improve calibration and detection rates, has become inclusive to women of different ethnic backgrounds and may also be used as a prediction model for male breast cancer patients[83–85]. When assessing its performance, it was demonstrated to have equivalent sensitivity and higher specificity than experienced clinicians for CPS detection [86]. There now exists an array of such clinical DSTs which vary based on the type of CPS and tumours being considered, as well as their target population.

A study conducted by Schwermer *et al.* in 2021 provided evidence that the systematic implementation of clinical DSTs developed by Jongmans *et al.* was effective in identifying a greater number of children harbouring CPSs[71,72,87]. In 287 children with cancer, a trial period of systematic DST use led to the identification of CPSs in 9.4% of the group, compared to the 5.3%

[A] https://projects.iq.harvard.edu/bayesmendel/brcapro

identified during the control period (non-DST use). This is the first study to provide evidence that the systematic use of DSTs leads to a higher detection rate of CPSs in patients.

Given the recent evidence of their effectiveness, it is unknown how many new DSTs have been developed and how they compare to one another. In addition, clinicians' attitude and knowledge about such tools have not been explored. As such, the focus of this thesis will be the exploration of the current literature regarding DST use for the recognition of pediatric CPSs. In addition, we will conduct a survey to gain a better understanding of whether such tools are known, used and well-adapted for clinicians.

Chapter 2 : Introduction to original thesis work

2.1 Objectives

This thesis contains two primary objectives :

1. To identify, describe and categorize DSTs that assist clinicians in their recognition of pediatric patients likely harbouring a CPS
2. To first, determine Canadian PHOs' familiarity with the previously identified DSTs and second, establish whether the tools may be adequately adapted for clinical use

2.2 Thesis overview

This thesis will begin with a scoping review that addresses the first objective, that is, the identification, description and categorization of DSTs for pediatric CPSs. It will be prefaced by an introductory section that will rationalize the methodology of the scoping review. Chapter 3 will begin with a transition text that will explore the link between both manuscripts and explain why we decided to pursue a national survey to answer the second research question. Chapter 4 will discuss the implications of both manuscripts, linking their findings and relating them to the current literature on DSTs for CPS recognition. Lastly, Chapter 5 will summarize and provide the main conclusions of this thesis.

Supplementary Table 1.1 Summary of pediatric cancer predisposition syndromes, the associated mutated gene (second column) and associated tumours (third column). NB: Unconfirmed tumours, those with conflicting evidence of their association with the CPS or cancers reported very rarely in individuals with the CPS may not be included in this list. AD = Autosomal dominant ; AR = Autosomal recessive ; RCC = Renal cell carcinoma; BCC = basal cell carcinoma; RMS = rhabdomyosarcoma ; HB = Hepatoblastoma; NB = Neuroblastoma; PGGL = pheochromocytoma and paraganglioma

Cancer Predisposition Syndrome	Inheritance Pattern	Associated Cancer Predisposing Gene	Associated Tumours
Ataxia-Telangiectasia	AR	biallelic *ATM* pathogenic variants	mostly associated with leukemia and lymphomas. Less frequently associated with ovarian, gastric, breast, melanoma, leiomyomas, sarcomas [1] and thyroid cancers [2]
***BAP1* tumour predisposition syndrome**	AD	heterozygous germline pathogenic variants in *BAP1*	uveal melanoma, malignant mesothelioma, cutaneous melanoma, RCC and BCC [3]
Beckwith-Wiedemann syndrome	AD	alterations in 11p15.5 region (*IGF2, H19, CDKN1C, KCNQ1, KCNQ1OT1*)	embryonal tumours (Wilm's tumour, HB, NB, RMS) and ACC [4-6]
Birt-Hogg-Dubé syndrome	AD	heterozygous pathogenic variants in *FLCN*	renal tumours (hybrid oncocytoma/chromophobe, chromophobe, clear cell subtypes are most common while papillary carcinoma is less common) [7,8]
Bloom syndrome	AR	biallelic pathogenic variants in *BLM*	leukemia, lymphoma, Wilm's tumour, oropharyngeal, upper gastrointestinal, colorectal, breast and skin cancer [9]

BRCA1 and BRCA2- associated hereditary breast and ovarian cancer	AD	heterozygous pathogenic variants in *BRCA1* or *BRCA2*	breast and ovarian cancer; prostate, pancreatic and melanoma [10]
Carney syndrome	AD	heterozygous pathogenic variants in *PRKAR1A*	myxomas (cutaneous, cardiac), endocrine tumours (primary pigmented nodular adrenocortical disease, growth-hormone producing adenoma, testicular tumour, thyroid adenoma/carcinoma), psammomatous melanotic schwannoma and breast ductal adenoma [11]
Constitutional mismatch repair deficiency (CMMRD)	AR	biallelic pathogenic variants in *MLH1*, *MSH2*, *MSH6, PMS2*	mainly colonic adenomas; leukemia, lymphoma, high grade gliomas, supratentorial primitive neuroectodermal tumours, MB [12]
Congenital central hypoventilation syndrome	AD	heterozygous pathogenic variants in *PHOX2B*	NB, ganglioneuroblastoma, ganglioneuroma [13]
Costello syndrome	AD	heterozygous pathogenic variants in *HRAS*	RMS, NB, urothelial carcinoma [14]
Diamond-Blackfan anemia	AD or X-linked	heterozygous pathogenic variants in >20 genes that encode ribosomal proteins (*RPL5*, *RPL11*, *RPS19 […]*) and non-ribosomal proteins (*GATA1*, *TSR2[…])*	acute myelogenous leukemia, myelodysplastic syndrome (MDS) and solid tumours including osteosarcoma [15,16]

DICER1 syndrome	AD	heterozygous pathogenic variants in *DICER1*	pleuropulmonary blastoma, ovarian sex-cord stromal tumours, cystic nephroma, embryonal RMS, pineoblastoma, pituitary blastoma, ciliary medulloepithelioma [17,18]
Dyskeratosis congenita	X-linked, AD or AR	associated with ~19 genes to date, most commonly : *DKC1*, *TINF2, TERC, RTEL1, TERT,* and *CTC1*	acute myeloid leukemia (AML), squamous cell carcinoma of the head/neck, anogenital malignancies [19, 20]
Familial acute leukemia / myelodysplastic syndromes	AD	Biallelic pathogenic variants in: *ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, SRP72*	hematologic malignancies (mostly AML) [21]
Familial adenomatous polyposis (FAP)	AD	heterozygous pathogenic variants in *APC*	MB, gastrointestinal adenoma/carcinoma, HB, desmoid tumours, thyroid cancer, Gardner fibroma, osteoma, odontomas [22,23]
Familial chordoma	AD	T Brachyury gene duplication	chordoma [24]
Familial isolated pituitary adenoma (FIPA)	AD	heterozygous pathogenic variants in *AIP*	pituitary adenoma [25]
Familial myofibromatosis	AD or AR	heterozygous pathogenic variant in *PDGFRB* or *NOTCH3*	infantile myofibromatosis [26, 27]

Family isolated hyperparathyroidism (FIHP)	AD	heterozygous pathogenic variants in *CDC73 (HRPT2)*, *CaSR*	parathyroid tumours [28,29]
Fanconi anemia (FA)	AD, AR or X-linked	biallelic pathogenic variants in 21 associated genes (leads to autosomal recessive FA) ; heterozygous pathogenic variants in *RAD51* (autosomal dominant FA)*;* hemizygous pathogenic variant in *FANCB* (x-linked FA)	AML, Wilm's tumour, NB, MB, head and neck squamous cell carcinoma, skin and genitourinary tract tumours [30]
Germline pathogenic variants in ALK	AD	heterozygous pathogenic variants in *ALK*	NB, ganglioneuroblastoma, ganglioneuroma [31]
Gorlin syndrome (or nevoid basal cell carcinoma syndrome)	AD	heterozygous pathogenic variants in *PTCH1* and *SUFU*	MB, BCC, cardiac and ovarian fibromas in females, rhabdomyomas [32]
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	AD	heterozygous pathogenic variant in *FH*	RCC, ovarian tumours, leiomyosarcoma [33,34]
Hereditary papillary renal cell carcinoma	AD	heterozygous pathogenic variants in *HPRC* (*MET* protooncogene)	type 1 papillary renal cell carcinoma [35]

Hereditary paraganglioma-pheochromocytoma syndrome	AD	heterozygous pathogenic variants in *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD* or *TMEM127*	PGGL, gastrointestinal stromal tumours, pulmonary chondromas, renal clear cell carcinoma [36]
Hyperparathyroidism jaw tumor syndrome (HPT-JT)	AD	heterozygous pathogenic variant in *CDC73* (*HRPT2*)	parathyroid adenoma and carcinoma, ossifying fibroma of the jaw, uterine benign and malignant tumours [37,38]
Juvenile polyposis syndrome	AD	heterozygous pathogenic variant in *SMAD4* or *BMPR1A*	colorectal cancers, cancers of the stomach, upper gastrointestinal tract and pancreas [39]
Klinefelter syndrome	Not inherited – Additional X chromosome	47, XXY karyotype (most commonly) ; others with mosaicism (47,XXY/46,XY)	germ cell tumours (ovary, testis, non-CNS, non-gonadal) [40]
Li-Fraumeni syndrome (LFS)	AD	heterozygous pathogenic variants in *TP53*	ACC, leukemia, lymphomas, breast cancer, CNS tumours, osteosarcomas, soft-tissue sarcomas, gastrointestinal cancers [41]
Multiple echondromatosis (Ollier disease)	AD	Somatic mosaic mutations in *IDH1*, *IDH2*	enchondromas, chondrosarcoma [42]
Multiple endocrine neoplasia type 1	AD	Heterozygous pathogenic variants in *MEN1*	parathyroid, pituitary, pancreatic, neuroendocrine tumours and non-endocrine tumours (angiofibromas, ependyomas, meningiomas..) [43]

Multiple endocrine neoplasia type 2	AD	heterozygous pathogenic variants in *RET*	medullary thyroid carcinoma, PPGL, parathyroid tumours [44]
Multiple endocrine neoplasia type 4	AD	heterozygous pathogenic variants in *CDKN1B*	parathyroid and pituitary tumours [45]
Multiple hereditary exostoses (HME)	AD	heterozygous pathogenic variants in *EXT1* and *EXT2*	osteochondromas, chondrosarcoma [46]
MUTYH-associated polyposis (MAP)	AR	biallelic pathogenic variants in *MUTYH*	colorectal adenoma and carcinoma; ovary and bladder cancers [47]
Neurofibromatosis Type I (Von Recklinghausen Disease)	AD	heterozygous pathogenic variants in *NF1*	neurofibromas, brain tumours (especially optic gliomas), malignant peripheral nerve sheath tumours, leukemias, lymphomas, neuroendocrine tumours, RMS, PPGL [48]
Neurofibromatosis type II	AD	heterozygous pathogenic variant in *NF2*	schwannomas, meningioma, ependymoma and astrocytoma [49]
Nijmegen breakage syndrome	AR	biallelic pathogenic variants in *NBN*	lymphomas, other solid tumours (MB, glioma, rhabdosarcoma) [50]

Noonan / Noonan-like syndromes	AD	Heterozygous pathogenic variants in *PTPN11, SOS1, RAF1, RIT1, KRAS*, *BRAF, MAP2K1, NRAS* and biallelic pathogenic variants in *LZTR*	leukemias, RMS, NB, tenosynovial giant cell tumour [51]
Perlman syndrome	AR	heterozygous pathogenic variant in *DIS3L2*	Wilm's tumour [52]
Peutz-Jeghers syndrome	AD	heterozygous pathogenic variant in *STK11*	colorectal and gastric cancers, breast cancer, sex cord-stromal tumours, pancreatic cancer [53]
PTEN hamartoma tumor syndrome (PHTS)	AD	heterozygous *PTEN* pathogenic variants	breast, thyroid, endometrial, gastrointestinal, RCC, cutaneous melanoma and brain tumours [54]
Retinoblastoma predisposition	AD	heterozygous pathogenic variants in *RB1*	retinoblastoma, pineoblastoma [55]
Rhabdoid tumor predisposition syndrome type 1 & 2	AD	heterozygous pathogenic variants in *SMARCB1* or *SMARCA4*	atypical teratoid/rhabdoid tumour, extracranial malignant rhabdoid tumour, rhabdoid tumour of kidney, small-cell carcinoma of the ovary, hypercalcemic type; meningiomatosis, schwannomatosis [56]
Rothmund-Thomson syndrome	AR	biallelic pathogenic variants in *RECQL4* or *ANAPC1*	osteosarcoma, BCC, squamous cell carcinoma and hematological malignancies [57]

Rubinstein-Taybi syndrome	AD	heterozygous pathogenic variant in *CREBBP* or *EP300*	NB, RMS, MB and hematological malignancies [58]
Schwachman-Diamond syndrome	AR or AD	biallelic pathogenic variants in *SBDS, DNAJC21, EFL1* or heterozygous pathogenic variant in *SRP54*	acute myelogeneous leukemia [59]
Simpson-Golabi-Behmel Syndrome type 1	X-linked	Hemizygous pathogenic variant/whole-gene or intragenic deletion of *GPC3*	embryonal tumours (Wilm's tumour, HB, adrenal NB, gonadoblastoma, hepatocellular carcinoma and MB) [60]
SMARCE1-related meningioma	AD	heterozygous pathogenic variant in *SMARCE1*	spinal and cranial clear cell meningiomas [61]
Sotos syndrome	AD	Heterozygous pathogenic variant in *NSD1*	sacrococcygeal teratoma, NB, presacral ganglioma, acute lymphoblastic leukemia, small-cell lung cancer, and astrocytoma [62, 63]

Tuberous sclerosis complex	AD	heterozygous pathogenic variants in *TSC1* or *TSC2*	subpendymal giant cell astrocytoma, cardiac rhabdomyoma, RCC, chordoma, neuroendocrine tumours [64]
Von Hippel-Lindau syndrome	AD	heterozygous pathogenic variants in *VHL*	hemangioblastomas, RCC, neuroendocrine tumours, PPGL, endolymphatic sac tumours [65]
Weaver syndrome	AD	heterozygous pathogenic variants of *EZH2*	NB [66]
Werner syndrome	AR	biallelic *WRN* pathogenic variants	bone and soft tissue sarcomas, melanoma, and thyroid carcinomas [67]
WT1-related disorders	AD	heterozygous pathogenic variants in *WT1*	Wilm's tumour, gonadoblastoma [68]
X linked acrogigantism (X-LAG)	X-linked	germline or somatic duplication of *GPR101*	pituitary adenoma [69]
Xeroderma pigmentosum	AR	Biallelic pathogenic variants in *DDB2, ERCC1/2/3/4/5, POLH, XPA* and *XPC*	BCC, squamous cell carcinoma, cutaneous melanoma, oral cavity neoplasms [70]

Chapter 3 : Identifying decisional support tools for pediatric cancer predisposition syndromes

3.1 Preface to scoping review

The past 20 years have led to an increase in the development of DSTs for the recognition of both adult and pediatric CPSs. This thesis focuses on the pediatric population given that previous research has synthesized the landscape of DSTs adapted for adult-onset CPSs[1], but also since pediatric CPSs differ from adult CPSs and warrant adapted investigation. To our knowledge, this is the first review to describe and summarize the literature pertaining to DSTs for CPSs presenting in pediatric age.

To begin the review, a preliminary search was conducted to investigate the different terms used in the literature to describe the concept of DSTs. Among many others, terms such as 'risk assessment tool', 'decisional aid', 'questionnaire', and 'scoring system' were often used. As such, it was important to first define a DST in this context and create exclusion criteria that were clear enough to discriminate DSTs from resources that listed the CPSs' genetic testing requirements, official guidelines or offered clinical approaches from experts. Rather, it was important to define DSTs as resources that were intended to be used by clinicians, that allow HCPs to input their patient's features, receive a concrete output (or recommendation) that can contribute to their recognition of CPSs in patients and, ultimately, help the HCP decide whether to refer a child for a CPS genetic evaluation.

In this preliminary search, we also uncovered that the MeSH terms for the concept of a CPS in MEDLINE and EMBASE, the two main databases used for this review, were insufficient and did not capture the literature on many different subtypes of CPSs. Since the review aimed to describe the DSTs applicable to *any* CPS that may affect pediatric patients, we opted instead to create a thorough list of all relevant CPSs, including rare conditions. I consulted with a McGill University Health Centre librarian, who previously worked on CPSs, to inform, review and adapt my search

term strategy. The list of CPSs included each condition's common name, any alternative names, and acronyms in addition to their associated cancer-predisposing genes. For instance, Neurofibromatosis type I was listed along with Von Recklinghausen('s) disease and NF1.

Importantly, the decision to pursue a scoping review rather than a systematic review was discussed at length for this project. We took into consideration the research question and the purpose of the literature review when deciding to commit to a scoping review. Systematic reviews are methodologies aiming to survey the literature, analyzing a smaller number of studies to ultimately answer a specific research question, and often, synthesize the results in a meta-analysis. A scoping review, on the other hand, aims to provide an overview, description and summary of the current literature and tends to address more broad or larger scope questions[2]. Due to the large scope of CPSs, and the heterogeneous nature of decision support tools, a scoping review methodology was followed. I followed the scoping review methodology of Joanna Briggs Institute 2020 guidelines and reported our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3].

3.2 The landscape of decision-support tools identifying pediatric patients likely to have a cancer predisposition syndrome: A scoping review

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3.2.1 Abstract

Background and Aim:

There is increasing recognition of the importance of timely diagnosis of cancer predisposition syndromes (CPSs) in pediatric cancer patients. CPS identification contributes to earlier detection of subsequent cancers and cascade testing of family members. However, many factors can impact CPS recognition, including provider experience and knowledge. A variety of decision-support tools (DSTs) have been developed to aid physicians and other health care professionals (HCPs) in their decision to refer a patient for CPS evaluation. We conducted a scoping review to identify the currently available tools, categorize them, and provide an overview and description of their features.

Methods :
An exhaustive search strategy was developed with a medical librarian to systematically screen MEDLINE and EMBASE, including English and French studies published by February 2021. We searched the grey literature and contacted experts in the field of genetic counselling and oncology. Eligible studies presented and/or validated DSTs that used the patient's profile to determine whether they are likely to benefit from a CPS genetic evaluation.

Results :
A total of 14 DSTs adapted for the pediatric population were identified. Seven of these tools were specific to one CPS, two were specific to one cancer type and five were categorized as general CPS tools, given their applicability to multiple CPSs and/or cancers. Fifty-seven percent (8/14) of the pediatric DSTs have been internally or externally validated for clinical use.

Conclusions:
A large variety of CPS decision-support tools have been developed to help HCPs decipher which patients are likely to benefit from a genetic evaluation. Their utility is largely dependent on the clinician's goals, resources, time constraints and patient population. Importantly, further research is needed on the accuracy and validity of these DSTs in addition to their generalizability to different geographic settings and ethnic populations.

3.2.2 Background

Pediatric cancer predisposition syndromes

Cancer predisposition syndromes (CPSs), estimated to affect at least 1 in 10 pediatric oncology patients, may lead to the development of multiple primary neoplasms throughout a patient's lifetime. Depending on the syndrome, there may be a range of clinical manifestations, patterns of cancer within a family and associated pathogenic germline variants. The growing body of literature establishing the genotype-phenotype correlations of CPSs is accumulating through the use of multiple sequencing approaches, with at least one cancer predisposing gene identified yearly[1]. Clinically, recognizing and diagnosing these CPSs is valuable as it allows for potential

modifications of a patient's oncology treatment plan (e.g. avoiding the use of radiation for those with chromosome instability syndromes[2]); adoption of surveillance measures that may decrease the morbidity and mortality of developing malignancies; and clarity and agency to the affected patients and their at-risk family members.

The recognition of CPSs in clinical settings

Unfortunately, CPSs are not always suspected when a child is diagnosed with cancer, in large part due to the difficulty in recognizing them clinically. CPSs have a diverse phenotypic spectrum (variable expressivity), as one CPS can lead to the development of many types of malignancies and may present with a range of different physical manifestations. In addition, there may be incomplete penetrance of the known cancer-predisposing genes. As such, children harbouring a pathogenic variant may have an unremarkable family history of cancer. These diagnostic challenges may also be compounded by prohibitive systemic barriers.

There is emerging evidence demonstrating gaps in physician knowledge on the topic of cancer genetic risk assessment and interpretation of genetic test results[3,4,5] with many studies reporting underutilization of genetic testing in potential cases of CPSs[6,7,8]. The under-referral practices are influenced by systemic restrictions in clinical settings, including the lack of accessibility and physician awareness of genetic services and/or genetic counsellors in their hospitals or community centres[3,4]. The multidisciplinary team of specialized professionals (medical geneticists, genetic counsellors, pediatric oncologists etc.) necessary for the diagnosis of a CPS has also been shown to be concentrated in metropolitan areas and is often inaccessible or non-existent in many rural settings or low-income countries [9,10].

Decision support tools assisting CPS recognition

Standard of care decision support tools (DSTs) have been developed to facilitate the recognition and diagnosis of CPSs. Earlier tools relied on information about the patient's family history of cancer in order to ascertain the risk of hereditary malignancies[11]. Collecting the patient's family history of cancer[12], noting the early onset of cancer development in relatives[13,14] and detecting the

presence of consanguinity[15] are all valuable predictors of an underlying CPS. Notably, family history can easily be gathered in lower-resource settings, may be self-reported by patients and can be collected by a range of healthcare professionals (HCPs) in a busy clinic. Multiple organizations such as the United States Preventative Task Force (USPSTF)[16] and the American Society of Clinical Oncology[17] have agreeingly recommended that physicians incorporate family history collection tools within their practice.

These earlier tools are less applicable to pediatric hematology-oncology patients for several reasons. In general, the collection of family history in clinical settings is challenging due to time constraints, lack of standardization of intakes, and is limited by the patient's knowledge [48]. In addition, a negative family history does not eliminate the possibility of a CPS, while a positive family history does not ensure a CPS diagnosis. For a pediatric patient, especially, a negative family history may be misleading, as children often come from young families where malignancies may not have manifested yet. More recent evidence has demonstrated that approximately 42% of pediatric patients with a pathogenic or likely pathogenic germline variant had a family history of cancer[18], suggesting that the majority of children with a CPS may have an unremarkable family history of cancer when being evaluated by HCPs. Second, DSTs developed earlier predicted the risk of CPSs predominantly affecting the adult population. Decision support tools for Hereditary Breast and Ovarian Cancer (HBOC)[19,20] and Lynch syndrome, for instance, were popularized. Pediatric patients are affected by a different spectrum of tumours, and as a result, some tumours may not warrant a referral to genetic testing in adults while they are indicated when developed in children.

Decision support tools adapted for pediatrics

Importantly, pediatric hematology-oncology patients require different considerations for CPS risk assessment than their adult counterparts. Importantly, pediatric hematology-oncology patients require different considerations for CPS risk assessment than their adult counterparts. They are affected by CPSs that are not addressed in popularized tools (such as BRCAPRO or the PREMM5 model) and present with different clinical features than adults affected by the same CPS[14]. Individuals with Li-Fraumeni syndrome, for instance, are likely to develop a different range of

malignancies during childhood (soft tissue sarcoma, adrenocortical carcinoma) than in adulthood (breast cancer)[54]. While, similarly, individuals with multiple endocrine neoplasia 1 develop growth hormone-secreting adenomas that lead to gigantism in childhood (abnormal growth) but acromegaly in adulthood (development of coarse facial features and swelling of the extremities)[55]. In addition, with children, cancer may be the first presenting feature of the CPS [51,52]. As a result, more recent DSTs have evolved to enquire beyond family history and incorporate additional predictors of pathogenic germline variants. These tools have also involved CPSs more likely to affect pediatric patients or have included pediatric-specific algorithms. In fact, these tools are valuable for HCPs of different specialties, including oncologists and genetic counsellors. They have been employed when making the decision to refer a child for CPS evaluation, but also, have helped genetic counsellors with the decision to pursue genetic testing. In fact, Ritchie and colleagues have demonstrated that approximately 88.6% of certified genetic counsellors in their cohort used cancer genetic risk assessment tools to calculate hereditary cancer or gene carrier risk[21].

Previous research articles have compared the performance of multiple HBOC detection tools[49,50], but so far, there are no reviews exploring the use of CPS detection and/or prediction tools adapted for the pediatric population. This scoping review will analyze the DSTs available to assist HCPs in their decision to refer patients with pediatric cancers for genetic evaluation. In addition, we will also investigate the features of the DSTs that make them suitable for children in the clinical setting. Our objectives are thus to identify and present a list of publicly-available CPS decision support tools developed for the pediatric population and provide focused descriptions of their different features.

3.2.3 Methods

We conducted a scoping review that adheres to the Joanna Briggs Institute 2020 methodology[43] and that is reported in accordance with the PRISMA Scoping Review guidelines[44].

Study Eligibility Criteria

Peer-reviewed research articles reporting on the development of a new tool, on tool performance and/or tool validation were all included. Both controlled and observational studies were eligible, in addition to any reviews and case reports (or case-series) utilizing a CPS DST. Importantly, studies presenting CPS diagnostic criteria were excluded, as this review focuses on the tools helping HCPs decide whether a child should undergo CPS genetic evaluation rather than the CPS's clinical diagnostic criteria. Only French and English studies were considered. No further restrictions were placed on the study's year of publication or the type of HCPs for whom the DST is intended (physicians, clinical geneticists, and genetic counsellors were all included).

CPS Decision-support Tool Eligibility Criteria

1. The tool is fit and/or intended to be used on people diagnosed with cancer between 0-18 years old
2. The tool can be used on a patient who is already presenting with one or multiple cancers
3. The tool may be specific to one tumour type or may be inclusive of many types of tumours
4. The tool must ultimately use the patient's personal history, cancer history, family history and/or symptoms to either :
    - offer a recommendation to the physician (e.g. "the patient should be referred to genetic testing" or "the patient should not be referred to genetic testing")
    - assess the probability that the patient has a CPS
    - or categorize the patient's risk of a CPS (e.g. high risk, moderate risk, low risk)

Search Strategy

Each database was searched from inception until February 2021. Both MEDLINE, EMBASE (via Ovid) databases were searched, in addition to a survey of the grey literature using Google Scholar. Citation tracking was completed by hand-searching references of relevant studies and experts in our institution (physicians, genetic counsellors, clinical geneticists) were contacted.

The literature search was conducted in two phases. The first phase (the pilot search) aimed to identify the relevant search terms used in the literature to describe CPS decision-support tools

while the second phase used the previously identified index terms and keywords in a fixed search strategy that was developed with the help of a medical librarian and subsequently adapted for both EMBASE and MEDLINE. The fixed search strategy used in MEDLINE may be found in supplementary table 3.1.

Data extraction

One reviewer (C.N.) completed the pilot search and the title and abstract screening of the fixed searches on Medline and Embase. Subsequently, two reviewers (C.G., L.R.) independently screened the title and abstracts of the fixed search strategy. Disagreements were discussed among reviewers until a consensus was reached. A data extraction form was developed prior to starting the literature review and included the following key information: name of the tool, CPS being assessed, the tool's authors, country of origin, year of development, type of input and output parameters, key population, validation methods, sensitivity/specificity/negative predictive and positive predictive values, if reported.

3.2.4 Results

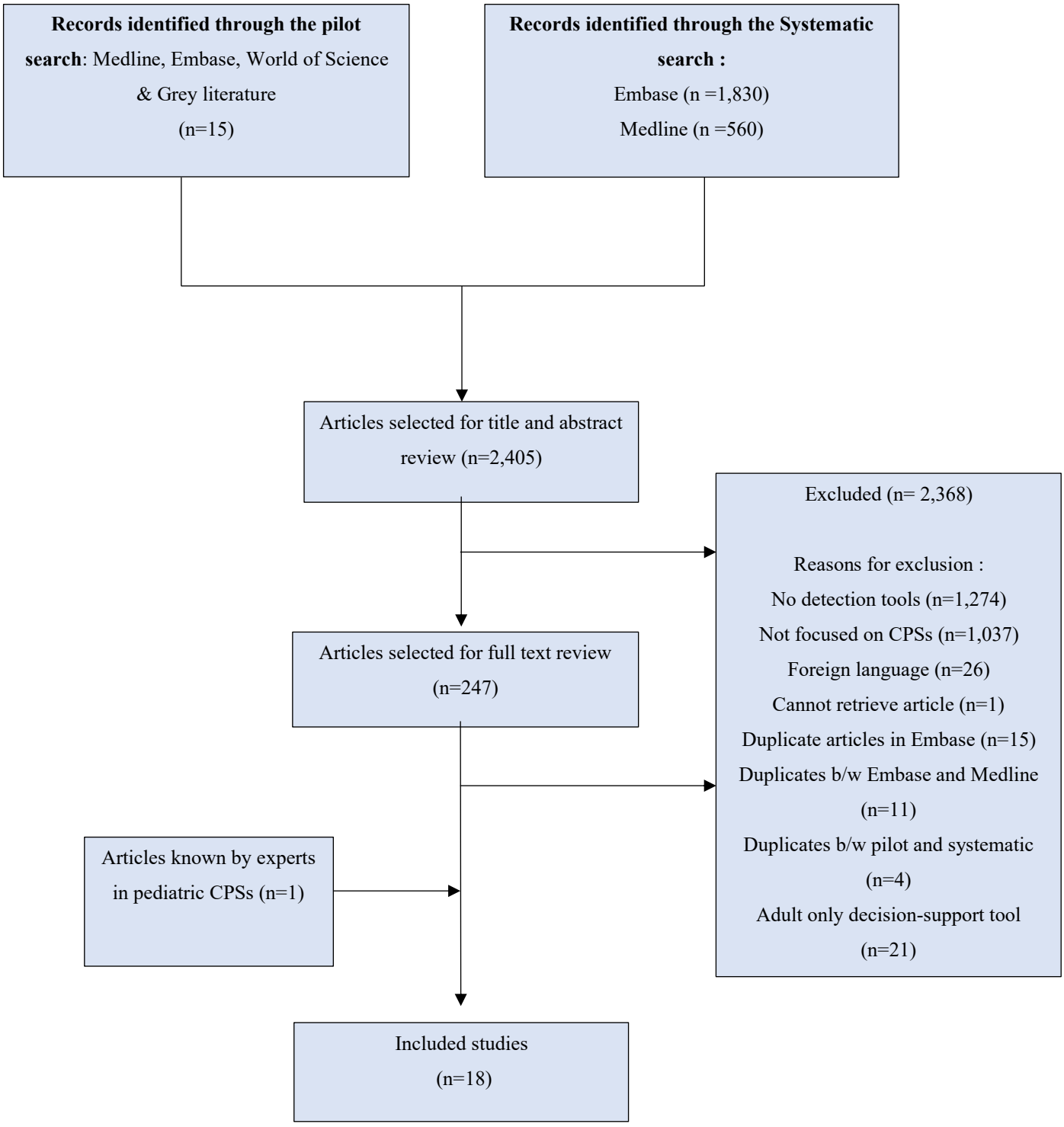

Figure 3.1 : PRISMA diagram

Search findings & general description of included DSTs

Our search identified 560 studies from MEDLINE, of which 84 articles were eligible for full-text review and 14 met our inclusion criteria. In addition, the EMBASE adapted search strategy retrieved 1,830 potentially relevant publications, of which 148 were eligible for full-text review and 23 were included in this study. The results from this systematic search were complemented with 15 publications identified during the pilot search in addition to one publication that was known by a clinician in our team (C.G) but could not be identified with our search strategy. Following the removal of duplicates, this study identified a total of 18 publications presenting 14 unique DSTs. The 14 DSTs[24-37] included in this review, the database and the search terms used to identify them are presented in Supplementary Table 3.2.

All 14 DSTs were published between 2011-2020 but the majority (11/14) were developed after 2016. The countries of origin are limited to those in Western Europe and/or North America and the most common CPSs taken into consideration are Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, constitutional mismatch repair deficiency and *DICER1* syndrome.

Categorization of included CPS decision-support tools

Tools were subsequently categorized according to their targeted age demographic (pediatric or adult population). Six of the fourteen tools (42.9%) addressed pediatric-onset CPSs, while 8/14 (57.1%) addressed CPSs affecting both the adult and pediatric populations. Tools were then categorized according to their scope and whether they addressed (1) one CPS in particular (2) multiple CPSs associated with one tumour type or (3) multiple CPSs and multiple malignancies (i.e. a 'general' DST). Seven of the fourteen tools (50%) were specific to one CPS, 2/14 tools (14.3%) were specific to one cancer type and 5/14 tools (35.7%) addressed multiple CPSs and malignancies. As illustrated in Figure 3.2, pediatric-specific DSTs were either CPS-specific (3/6) or general DSTs (3/6). Tools addressing adult and pediatric populations were more likely to be CPS-specific (4/8), than cancer specific (2/8) or general DSTs (2/8) .

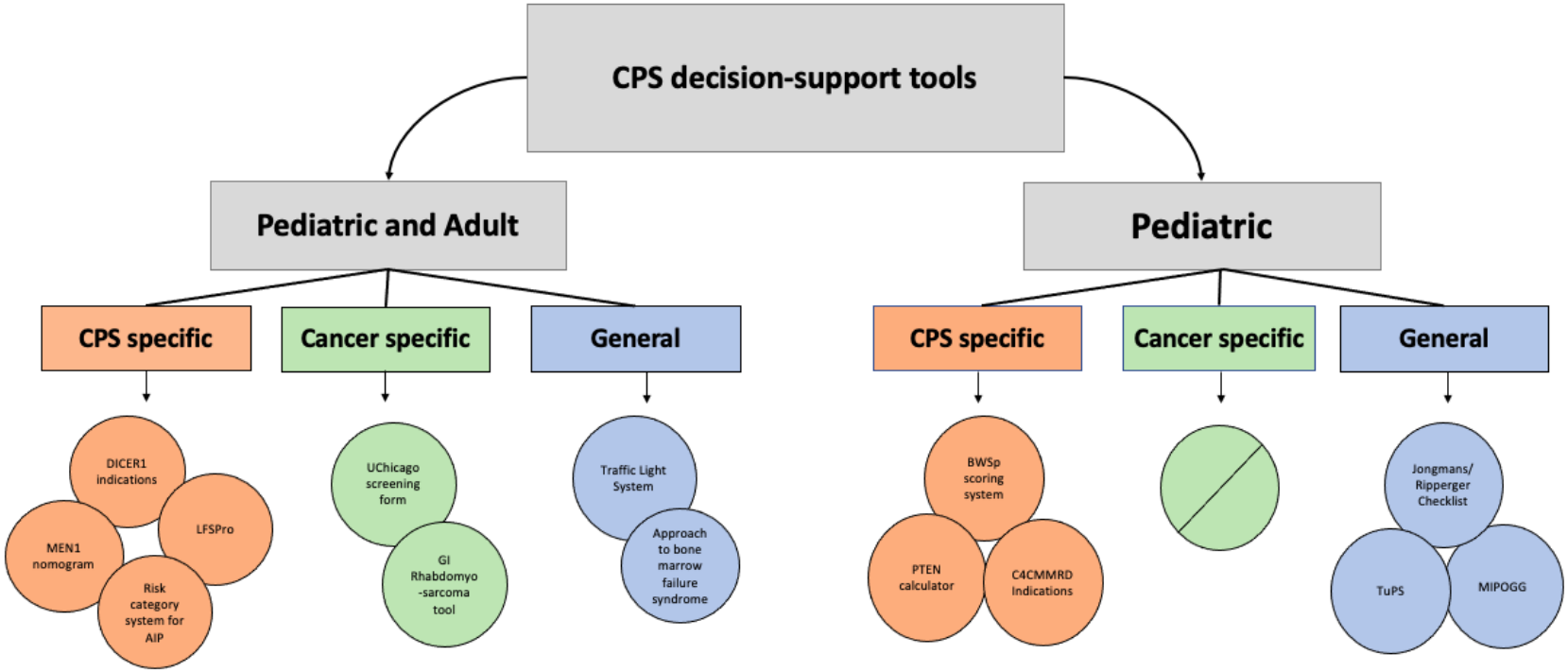

Figure 3.2: Categorization of CPS decision support tools. Tools are first categorized according to their target populations : Pediatric & Adult or Pediatric. Tools are further subcategorized according to their starting point: CPS specific, cancer specific or general. General DSTs refers to tools applicable to multiple types of malignancies and CPSs.

Description of DST features

Detailed description of each tools is presented in Table 3.2 (section A), including the name of the tool, date and country of development, the CPS(s) addressed, tool format, targeted age demographic and its input/output parameters.

Tool format

In regards to the tools' format, 3/14 are accessed electronically while the remaining 11/14 are paper-based tools. The electronic tools are either accessible online (MIPOGG[29], PTEN calculator[31]) or downloaded as a package on the *R* Software (LFSPro[28]). The paper-based tools come in a wider range of formats including indication or criteria lists, flow diagrams, scoring systems, nomograms or risk-stratification systems (Table 3.1)

Tool Format	Description
Indication list, criteria list or checklist	List of clinical features, in which the fulfillment of at least one feature/criteria is sufficient to warrant a CPS genetic evaluation
Flow Diagram	Graphical diagram where clinical variables are sequentially assessed in a yes/no manner and the user is directed towards the recommendation
Scoring system	List of clinical features with assigned point values. The total points must be calculated and the referral to CPS genetic evaluation must be equal to or higher than a predetermined score
Nomogram	A graphic device with a set of *n* scales, one for each clinical feature included in a prognostic model designed to estimate the likelihood of CPS pathogenic variant

Risk stratification system	Clinical variables are categorized in a high/medium/low risk level in relation to the final recommendation

Table 3.1 Paper-based DST formats and their descriptions

Input/Output parameters

When using the DSTs included in this review, the user must input the patient's clinical characteristics to receive a recommendation (output). The input parameters of the 14 DSTs may be classified into one of four broader categories: (1) tumour type (2) family history (3) physical findings and (4) biochemical workup and the patient's medical history. The most commonly requested input parameter is the patient's tumour type and laterality, which is requested by all 14 DSTs. The second most requested input is family history collection (12/14). Family history of cancer includes information about the presence of benign or malignant tumours in first, second or third-degree blood relatives. Further details such as tumour type, localization and age at diagnosis may be requested. In addition, DSTs such as TuPS[33] request familial history of congenital anomalies, and learning and developmental difficulties. The third most requested input has been physical findings (8/14 tools). This includes features observable during the patient's physical examination, such as dermatologic features (e.g. café-au-lait macules, cysts, vascular malformations), anthropometrics (height, weight, head circumference) and neurological features (e.g. ataxia). The final input requested by the CPS risk assessment tools in this review is biochemical findings (5/14 tools) and the patient's medical history.

The output parameters have been classified into three different categories : (1) Dichotomous outcomes (2) probability of having a CPS mutation (3) risk categorization. The majority of tools make their recommendation in the form of a dichotomous outcome (10/14), meaning that the DST directly informs its user on whether a referral to genetics is (or is not) recommended. Tools in the second category (2/14 DSTs) output the probability of a CPS-associated variant in percentages (ex. nomogram indicating that a patient has an 11% risk of having a *MEN1* mutation). The third category includes two tools that output the patient's mutation risk level in a 'low', 'medium' or 'high' category.

Development and validation methods

A small subset of DSTs was developed with algorithms based on the features observed in cohorts of patients with a suspected, clinical diagnosis or a molecularly-confirmed CPS diagnosis (see Table 3.2, Section B). Of the 14 tools included in this review, four were developed using this method [30,31,32,24]. Based on retrospectively obtained medical data, two of these tools (AIP risk category system[32] and the MEN1 nomogram[30]) subsequently developed a logistic regression model to predict the risk of their respective CPS-associated germline pathogenic variants. Four DSTs were developed based on the recurring clinical manifestations identified in a literature review[26,29,33,35]. The remaining 6/14 tools have been developed from expert opinion and consensus alone[25,27,34,35,36]. TuPS, in particular, uses a childhood cancer syndrome checklist which was developed using a two-round Delphi process to reach consensus among a panel of eight experts[41].

Of the 14 tools included in this review, eight (57.1%) have been validated or assessed for their performance (Table 3.2, Section B). In terms of performance assessment, sensitivity and specificity were most commonly reported, often showing high sensitivity rather than specificity. With regards to validity assessment, the two multivariate prediction models included in this review, the MEN1 nomogram and the AIP risk category system, have been internally validated through bootstrap procedures. The MEN1 nomogram was assessed for external validity in a cohort composed of a small proportion of pediatric patients. In contrast, the AIP risk category system has yet to be validated externally, as the cohort of patients included in the development study was too small to be split into a derivation and a validation group.

Table 3.2 Section A

Tool Name (Year; Country)	CPS	Model format	Key population	Input Parameters	Output Parameters
BWSp scoring system (2020; Italy)	Beckwith-Wiedemann Syndrome spectrum (BWS)	Paper-based Scoring System	Prenatal population	Fetal anomalies, gestational complications, family history of BWS, BWS-related tumours, monozygotic twinning, pregnancy from ART, maternal biochemical anomalies	Dichotomous outcome
C4CMMRD indications for genetic testing (2014; EU)	Constitutional Mismatch Repair Deficiency (CMMRD)	Paper-based Scoring System	Pediatric and Young Adult population	Age, type of malignancy/premalignancy, family history of cancer and CPSs, dermatologic features, levels of IgG2/IgA, agenesis of the corpus collosum or presence of cavernomas	Dichotomous outcome

Indications for DICER1 genetic testing (2018; USA)	DICER1 tumour predisposition syndrome	Paper-based Scoring system	Pediatric and Adult Population	Type of malignancy, family history of cancer, and other physical features ▵	Dichotomous outcome
Indications for GU Rhabdomyosarcoma (2020 ; USA)	Multiple※ : DICER1, LFS, CMMRD, Mosaic Variegated aneuploidy syndrome, BWS, NF1, Noonan, Costello and other RASopathies	Paper-based indications for genetic counselling/testing	Pediatric population	location and classification of sarcoma, age, personal or family history of the listed clinical features	Dichotomous outcome
LFSPRO (2017; USA)	Li-Fraumeni syndrome (LFS)	Prediction Algorithm available through the R software	Pediatric and adult populations	family history of cancer , prevalence and penetrance of TP53	Future cancer risk (for asymptomatic patients) + probability of carrying a germline TP53 mutation (low, medium or high risk)
MIPOGG (2018; Canada)	multiple childhood CPSs	Online tool or mobile application	Pediatric population	Type of malignancy, physical features, family history of cancer	dichotomous outcome
Nomogram to predict MEN1 (2012; Netherlands)	MEN1 syndrome	Nomogram	Pediatric and adult populations	Age, personal and family history of endocrine tumors, primary hyperparathyroidism	Risk of MEN1 mutation (%)

PTEN risk calculator (2011; USA)	PTEN hamartoma tumour syndrome (PHTS)	Online tool	Distinct pediatric and adult algorithms	Gender, age, head circumference, neurologic features, dermatologic features, vascular malformations, gastrointestinal polyps, thyroid goiter and early-onset cancers	Dichotomous outcome
Ripperger et al. criteria (2017; Germany)	multiple childhood CPSs	Paper-based criteria list	Pediatric population	Family history of cancer, presence of specific neoplasms, results of genetic tumour analysis, number of malignancies, presence of certain congenital anomalies and excessive toxicity of cancer therapy	Dichotomous outcome
Risk category system for AIP mutations (2018 ; UK/Spain/USA)	Familial isolated pituitary adenoma (FIPA)	Paper-based risk stratification system	Pediatric and adult population	Age, family history of pituitary adenomas, presence of growth hormone excess, and tumour size	Risk of an AIP mutation (%) + Dichotomous outcome

Traffic light classification system (2019 ; UK)	multiple CPSs	Risk stratification system	Pediatric and adult populations	Age and type of cancer	Three-tiered classification
TuPS (2017; Netherlands)	multiple childhood CPSs	Paper-based checklist, photographic series (2D and 3D) & decision support scheme	Pediatric population	Checklist is subdivided in 3 sections : patient characteristics, family history assessment and physical examination	Dichotomous outcome
University of Chicago Screening Form (2017; USA)	Hereditary myeloid malignancy syndromes	Indications for genetic testing & a paper-based screening form	Pediatric and adult populations	Personal and family history of cancer, cytopenias and other specified physical features and medical conditions***	Recommends a list of CPSs to consider depending on the patient's features
West and Churpek's Approach to Bone Marrow Failure Syndromes (2017 ; USA)	Inherited Bone Marrow Failure Syndromes (IBMFs) : Fanconi Anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome	Flow diagram corresponding to tables of physical features, hematologic features and laboratory screening tests	Pediatric and adult populations	Pattern of cytopenia, physical features, type of malignancy, family history of cytopenia/malignancies, results of peripheral blood smear and bone marrow findings	Dichotomous outcome

Table 3.2 Section B

Tool Name (Year; Country)	Model Derivation	Validation methods	1 CPS Type	>1 CPS	1 Tumour Type	>1 Tumor type
BWSp scoring system (2020; Italy)	Retrospective cohort study (n=89)	Internal validation using the cohort's postnatal BWSp score (n=89) No external validation to date	✓ BWS			✓ Adrenal adenoma/carcinoma/ cysts, hepatoblastoma, pancreatoblastoma, pancreatic adenomatous hyperplasia, nephroblastomatosis
C4CMMRD indications for genetic testing (2014; EU)	Expert consensus from the European Consortium "care for CMMRD"	No validation studies to date	✓ CMMRD			✓

Tool Name (Year; Country)	Model Derivation	Validation methods	1 CPS Type	>1 CPS	1 Tumour Type	>1 Tumour Type
Indications for DICER1 genetic testing (2018; USA)	Systematic review, expert consensus -- The International DICER1 symposium	No validation studies to date	✓ DICER1			✓┼
Indications for GU Rhabdomyosarcoma (2020 ; USA)	Expert opinion - Authors (Schneider et al.)	No validation studies to date		✓※	✓ Genitourinary Rhabdomyo-sarcoma	
LFSPRO (2017; USA)	Formula is based on penetrance and prevalence of TP53 inputs	External validation using three different test cohorts : one pediatric cohort (n = 2,553) and two adult cohorts (n= 19,653)	✓ LFS			✓
MIPOGG (2018; Canada)	Literature review	1. External validation of the neuroblastic tumour algorithm (n=209) 2. External validation of MIPOGG (n=636)		✓		✓

Tool Name (Year; Country)	Model Derivation	Validation methods	1 CPS Type	>1 CPS	1 Tumour Type	>1 Tumour type
Nomogram to predict MEN1 (2012; Netherlands)	Retrospective cohort study (n=365)	External validation (n= 144)	✓ MEN1 syndrome			✓ Adrenal tumors, neuroendocrine and pituitary tumors
PTEN risk calculator (2011; USA)	Prospective cohort study (n=92 children)	External Validation (n = 122 children)	✓ PHTS			✓ Thyroid adenoma, renal cell carcinoma and germ cell tumour
Ripperger et al. criteria (2017; Germany)	Literature review	External validation by an independent team (n=102)		✓		✓
Risk category system for AIP mutations (2018 ; UK/Spain/USA)	Retrospective cohort study (n= 1405)	Internal validation, No external validation to date	✓ FIPA		✓ Pituitary adenoma	
Traffic light classification system (2019 ; UK)	Expert Consensus (clinicians at the Drug Development Unit in the Royal Marsden NHS foundation)	No validation studies to date		✓		✓

Tool Name (Year; Country)	Model Derivation	Validation methods	1 CPS Type	>1 CPS	1 Tumour Type	>1 Tumour type
TuPS (2017; Netherlands)	Literature review, expert consensus	Not yet published (protocol available) -- just the Postema checklist is validated by the same group validating the Ripperger et al. checklist		✓		✓
University of Chicago Screening Form (2017; USA)	Expert opinion from the University of Chicago Hematopoietic Malignancies Cancer Risk Team	No validation studies to date		✓		✓ Hereditary hematopoietic malignancies
West and Churpek's Approach to Bone Marrow Failure Syndromes (2017 ; USA)	Expert opinion - author's approach for IBMFS evaluation	No validation studies to date		✓ FA, DBA, SDS		✓ AML, MDS, SCC, Basal cell skin cancer, GI tract malignancies, osteogenic sarcoma

Table 3.2 : **Decision-support tools adapted for the pediatric population**. **(Part A)** For each tool, details are provided about the CPS being assessed, the format of the tool, its population of interest and the input and output parameters. In **Part B**, the derivation and validation methods described in each study are presented, if applicable. Lastly, we describe whether the tool is applicable to one or more CPSs and whether the tool is applicable to one or more tumour types. Tools containing a check in the '>1 tumour' or '>1 CPS' categories, without an enumerated list of syndromes or tumours, contain over 10 different conditions.

A dichotomous outcome indicates whether a tool either recommends or advises against a referral to CPS genetic evaluation i.e. "the patient is at risk/is not at risk" or "the patient should be referred/the patient should not be referred for CPS evaluation"

External validation refers to the evaluation of a tool beyond the cohort of patients used for the development of the model/algorithm.

SDS = Shwachman-Diamond syndrome; DBA = Diamond-Blackfan anemia; FA= Fanconi anemia
MDS = myelodysplastic syndrome, SCC = squamous cell carcinoma

┼ = thoracic embryonal rhabdomyosarcoma, genitourinary sarcomas including undifferentiated sarcoma, ovarian Sertoli–Leydig cell tumors, gynandroblastoma, uterine cervical or ovarian embryonal rhabdomyosarcoma, genitourinary/gynecologic neuroendocrine tumours, thyroid cancer, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, pineoblastoma, pituitary blastoma

**other specified conditions: growth restriction, short stature, intellectual impairment, dermatological features, genital underdevelopment, delayed puberty etc..

▵ other physical features = macrocephaly, goiter, renal/lung cysts

3.2.5 Discussion

This scoping review identified a total of 14 tools that aim to guide HCPs in their decision to refer cancer patients to genetic testing. These tools are defined as decision aids and/or risk assessment algorithms that ultimately offer HCPs guidance on the genetic referral process or likelihood of a CPS. Therefore, their outputs come in the form of recommendations ("the patient should [should not] be referred") or probability of a germline pathogenic variant indicating the need for referral ("the patient has a high [low] risk of having an underlying germline pathogenic variant"). Importantly, these tools do not aim to indicate whether the patient meets the diagnostic criteria of a CPS but rather streamline the decision to refer patients with cancer for CPS genetic evaluation. To our knowledge, this is the first review to systematically synthesize and map out the body of literature pertaining to CPS decision support tools, at large.

In our comprehensive literature search, 14 tools were developed for the pediatric population or included pediatric patients in their target audience. These tools are widely heterogeneous in their conditions for use, format, model development, validation methods, and the range of CPSs and malignancies being considered.

Tool format

The majority of tools included in this review were available in a paper-based format (11/14) rather than a computer or online form (3/14). Electronic tools have the important advantage of being easily accessible internationally, at no cost, to healthcare practitioners (HCPs) who have internet access. Additionally, these online tools can theoretically remain up-to-date more easily with emerging literature pertaining to CPS clinical presentation and genetic testing indications. LFSPro, however, which estimates the probability of a *TP53* germline pathogenic variant associated with Li-Fraumeni syndrome, must be downloaded onto *R* and thus requires the HCP to have prior knowledge of this software and to keep the package updated as newer versions are released.

The paper-based tools come in a wider range of formats including indication lists, flow diagrams and scoring systems. Their ease-of-use depends on the preferences of the HCP and the setting of

their respective clinical practice. However, they are harder to update in real time and the nature of some of these formats may be more conducive to error than others in a busy clinical setting. For instance, the prediction model for *MEN1* variants, which has been transformed into a nomogram for clinical practice, requires HCPs to convert total points into a linear predictor score that is then converted into a risk percentage for a *MEN1* germline pathogenic variant.

Content of Input/Output

Input Parameters

Tumour type and laterality are requested by each tool included in this review, as this input is occasionally sufficient information to warrant a referral [22]. The diagnosis of certain malignancies may be sufficient to warrant a referral if the cancer is known to be strongly associated to a CPS, if it is a rare tumour, if there is an abnormally young age of onset, or if there is an abnormal pattern of cancer presentation[14,23]. In addition, tumours are often the first "sign" of an underlying CPS; however, some tumours have been associated with multiple CPSs, thus it may not be feasible for HCPs to use multiple decision support tools to rule in/out the risk of individual CPSs. Instead, DSTs (MIPOGG[29], Ripperger checklist[33], Traffic light system[34], the University of Chicago form[36]) that use tumours as a "starting point" to evaluate the likelihood of multiple CPSs, simultaneously, may be more advantageous in the clinical setting.

With regards to family history, LFSPro, for instance, requires input from three generations. These tools require more skill from their users and take more time compared to the yes/no questions of the previously mentioned tools. Overall, family history collection forms, themselves, have been shown to increase the rate of referral to genetics; however, the collection of family history of cancer can be subjected to a number of different biases including recall bias[40], unknown family history and input that is subject to change over time, especially in the pediatric settings, where patients have younger parents and families who may develop additional cancers over time.

Input regarding physical findings is only relevant to some CPSs and often requires the evaluation of trained physicians or specialists as dysmorphic features can be subtle. TuPS, in particular, is the

only tool that requires the user to take medical images of the patient during their assessment[35]. The 2D and 3D captured images may then be analyzed by different clinical geneticists and are complemented by a screening form called the childhood cancer syndrome checklist (CCSC). This tiered system has the important advantage of allowing patients to be evaluated remotely but may also be a limiting factor for lower-resource clinical settings unable to capture 3D images, in particular.

Output Parameters

The direct nature of tools with dichotomous outcomes makes them valuable in clinical settings as it provides HCPs with unambiguous recommendations to consider in their decision-making process. In particular, CPS-specific decision support tools with dichotomous outcomes will explicitly recommend the evaluation of certain CPSs, which may be more helpful to providers than recommendations from cancer-specific tools that are providing little information on which type of CPSs to evaluate further.

Two tools have outputs in the form of "% of mutation risk" [30,32] . This format allows for greater discrepancy between the patients that are recommended for genetic referral. Clinicians may want to differentiate between patients who are referred, for instance, with a 21% risk of a germline pathogenic variant in a cancer predisposing gene compared to those referred with a 56% risk of the same germline pathogenic variant. In lower resource settings, where only a small portion of patients may be sent to genetic testing, this output style would allow patients with higher risks of germline pathogenic variants to be prioritized. The risk category system for *AIP* germline pathogenic variants which accompanies the risk of a variant with a clinical recommendation presents both output styles which can be clinically advantageous.

Two tools output their recommendations in a Low/Medium/High pathogenic variant risk style [28,34.] The cancers in the "medium" pathogenic variant risk, or in the "orange" category, of the Traffic Light System are moderately associated with CPSs, thus the tool invites the HCP to consider additional criteria (such as a positive family history of cancer) in order for the patient to be eligible for a referral to genetic testing. LFSPro does not offer additional guidance for patients who are at

"medium risk" of having a *TP53* germline pathogenic variant. The "medium" risk category does not provide HCPs with much guidance unless it is accompanied with additional considerations that will help with the decision-making process.

Methods of development

The development of DST based on cohorts is often necessary in the context of rare CPSs. However, they run a higher risk of selection bias, as many of the participants were recruited from consortiums of patients with more prominent phenotypes. With regards to tools developed based on literature reviews, the search strategies are reported at different extents. PubMed was the only database reported to be used and English and French studies were the only languages reported to be included. Bias in the selection of studies is thus a possible and important limitation for these DSTs. The features identified in the literature review were subsequently reviewed by the experts developing the tool [29,33] or by international CPS symposiums [26], helping to mitigate the previously mentioned selection bias. Literature reviews and expert consensus as methods of tool development have the advantage of aggregating more heterogeneous patient data, originating from different countries and incorporating different time points. Lastly, DSTs developed based on expert opinion are particularly sensitive to the heterogeneity and composition of its expert panel members[42] in addition to the methods used to arrive at a consensus.

Validation methods

In clinical settings, sensitivity may be more valuable, as clinicians want to ensure a minimal risk that patients with a CPS be missed. However, in low-resource settings, lack of access to genetic counsellors/testing would render tools of high negative predictive value with maximized specificity to be more valuable. In all, a considerable number of studies reporting the development of CPS decision support tools has not included or has yet to publish a validation study of their tools. It is important for future research to address this gap for HCPs to understand the generalizability of these tools, their predictive abilities and their indications for use.

Demographic diversity

Further research is needed on the generalizability of CPS decision support tools for patients of diverse racial and ethnic backgrounds because they may present with a different array or frequency of clinical features. A recent study by Duffy *et al.*[46] has demonstrated the frequency of different clinical features in children from different ethnic/racial groups affected by Beckwith-Wiedemann syndrome (BWS). Cardinal features of BWS, such as macroglossia and the presence of BWS-related tumours, remained consistent among Caucasian, mixed and non-Caucasian groups. In contrast, the incidence of other cardinal features such as omphalocele was significantly lower in non-Caucasian and mixed groups compared to Caucasian children, while other features such as hyperinsulinism were twice as likely to be present in non-Caucasian groups compared to Caucasians. As such, tools developed based on cohorts lacking ethnic diversity may be overestimating, or more importantly, underestimating the presentation of certain CPS manifestations in different patient populations.

In this review, 4/14 tools are developed based on the features observed in retrospective cohorts originating mostly from North American and/or Western European countries. Therefore, the tools are modelled after features frequently observed in these populations, making their generalizability to patients of non-Caucasian descent unknown. In addition, despite the country of origin being reported in their demographic data, ethnicity and race are not reported in any of these four studies.

Although tools developed through literature review and expert consensus statements are more likely to involve ethnically diverse patients, their validation on cohorts of diverse ethnicities should not be overlooked. An independent study validating multiple CPS decision support tools (Ripperger checklist, TuPS and MIPOGG) on children of Asian descent[47] demonstrated that the combination of multiple checklists increased the specificity of their recommendations, indicating that these tools, independently, may not be sufficient to detect CPSs in children of Asian descent diagnosed with cancer.

Limitations of the study

There are important limitations to consider for this scoping review. First, the search was limited to publications in English and French. Second, despite the development of a thorough search strategy, developed with the expertise of a medical librarian, the wide range of CPSs that exist (>100) and the ambiguity of the terms used to describe "decision support tools" may have led to the exclusion of some tools from this review. In addition, important factors may contribute to some tools easily being retrieved in our search while making others hard to find. For instance, studies briefly using CPS decision support tools, without expanding on its derivation or validation methods, could have been excluded from the results of our search. Conversely, those that have been validated or have their performance evaluated are more likely to be found as there is often more than one publication about the same tool. Third, "in-house" tools used by individual institutions may not be published, and thus could not be included in this review. Last, tools known by the experts on our team and those used in Western academic centres are more likely to be included in this study.

3.2.6 Conclusion

The increasing number of CPS DSTs emerging in the past decade is important to mitigate the alarming under-referral rates of individuals with a high probability of a CPS[39]. DSTs have also been developed as a response to the undeniable difficulty of recognizing CPSs clinically and deciding which patients would benefit from a genetic evaluation. As the number of CPS DSTs increases over the years, it is important to categorize and compare them in order for clinicians to become aware of their applicability and understand which tools are best suited for their patients' unique circumstances. This scoping review is the first to present the current landscape of decision support tools currently available to help HCPs in their decision to refer pediatric patients for CPS evaluation and may be used in the future to build an online registry that can be accessed by HCPs to find the most appropriate tool for their clinical scenario.

Overall, our results have demonstrated the wide variety of formats, methods of development and the extent of the tools' validation methods. The majority of CPS decision support tools has been developed based on literature reviews and expert opinions, primarily used the patient's tumour type and family history of cancer as input and often outputted recommendations in a dichotomous outcome. Importantly, approximately half of the tools have been both internally

and externally validated, which is a critical avenue of future research. Validation of these tools is important, as it may allow more appropriate integration into clinical practice and would further our understanding of each tool's strengths and limitations. Lastly, future research comparing the performance of these tools in different populations is important to further our understanding of their applicability to different ethnicities and other subgroups of the pediatric population.

3.2.7 Appendix

Supplementary Table 3.1 : Search strategy –Medline (Ovid) in November 2020

(((heredit* or inherit* or famil* or germline* or predispos* or constitution* or syndrome* or mutat* or susceptib* or congenital) adj5 (cancer)) or Aicardi or Ataxia-Telangiectasia or Beckwith-Wiedemann or Birt-Hogg-Dube or Cartilage-Hair Hypoplasia or Congenital Amegakaryoctic Thrombocytopenia or Denys-Drash or Diamond-Blackfan Anemia or Dyskeratosis Congenita or Fanconi Anemia or LZTR1 germline mutations or Multiple Endocrine Neoplasia or Multiple Hereditary Exostoses or MUTYH-associated Polypos* or Neurofibromatosis or Polymerase Proofreading-associated Polypos* or RASopathy or Severe Congenital Neutropenia or SMARCE1 germline mutations or X-linked acrogigantism or Xeroderma Pigmentosum or (trisonom* adj2 ("18" or "21")) or ((syndrome* or disorder* or disease*) adj2 (((Bloom or Cardio-Facio-Cutaneous or Congenital Central Hypoventilation or Constitutional Mismatch Repair Deficiency or cowden or PTEN hamartoma tumor or Costello or DICER1 or Frasier or GATA2 or Gorlin or Noonan or Juvenile Polyposis or Klinefelter or Li-Fraumeni or Immunodeficiencies) and lymphoproliferative) or Lynch or Maffucci or Mosaic Variegated Aneuploidy or Ollier or Nijmegen Breakage or Perlman or Peutz-Jeghers or Rothmund-Thomson or Rubinstein-Taybi or Schwachman-Diamond or Turner or Von Hippel-Lindau or WAGR or Weaver or Werner or Wiskott-Aldrich or Down* or Edwards or Sotos or Simpson-Golabi-Behmel or Bannayan-Riley-Ruvalcaba or Proteus*)) or ((familial or predispos* or hereditary) adj2 ((((ALK-related adj5 neuroblastoma) or (CEBPA-Associated adj3 (Acute Myeloid Leukemia or AML)) or (ETV6-related adj3 Leukemia) or Melanoma* or (platelet disorder adj5 (AML or acute myeloid leukemia)) or (breast adj4 (cancer or neoplasm* or tumo?r)) or Leiomyomatosis) and Renal Cell Carcinoma*) or Papillary Renal Cell Carcinoma* or paraganglioma-pheochromocytoma or Familial Adenomatous Polyposis or BAP1-tumo?r or isolated hyperparathyroidism or Retinoblastoma or Rhabdoid tumo?r or (ovarian adj4 (cancer or neoplasm* or tumo?r)))) or (pathogenic variants adj2 (KIT or NOTCH3 or PDGFRA or PDGFRB)) or (familial adj4 syndrome* adj2 (Isolated Pituitary Adenoma or AML or MDS or acute myeloid leukemia or Hyperparathyroidism-jaw tumo?r or Familial Atypical Multiple Mole Melanoma)) or (complex* adj2 (Carney or Tuberous Sclerosis))).tw,kf. [cancer predisposition syndromes]
exp *Algorithms/ or *Decision making, Computer-assisted/ or *Forecasting/ or *Logistic Models/ or *Medical History Taking/ or *Models, Genetic/ or *Predictive Value of Tests/ or *Reproducibility of Results/ or *Risk Assessment/ or *Risk Factors/ or exp *"Sensitivity and Specificity"/

((algorithm* or carrier* or model* or tool* or assess* or guideline* or approach* or technol* or modalit* or metric* or test or refer* or checklist* or system* or instrument* or evaluat*) adj3 (predict* or probab* or risk* or decision support or diagnos* or detect* or screen* or score or scores or scoring or select*)).ti,kf. or ((algorithm* or carrier* or model* or tool* or assess* or guideline* or approach* or technol* or modalit* or metric* or test or refer* or checklist* or system* or instrument* or evaluat*) adj3 (predict* or probab* or risk* or decision support or diagnos* or detect* or screen* or score or scores or scoring or select*)).ab. /freq=2
2 or 3 [risk assessment tools]
(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or preadolesc* or prepubesc* or preteen or tween).tw,kf. or (pediatr* or paediatr*).jw. [pediatric filter]
1 and 4 and 5 [risk assessment tools for CPSs in the pediatric population]

Tool Name	Pilot Search		Systematic Approach to literature search			
	Source	Search terms ; Database	Identified in Medline	Medline Source	Identified in Embase	Embase Source
Approach to Bone marrow failure syndrome	x	x	✓	West and Churpek 2017	✓	West and Churpek 2017
BWSp Scoring system	x	x	x	x	✓	Carli, D et al. 2020
CMMRD Scoring System	x	x	✓	Wimmer et al. 2014	✓	Wimmer et al. 2014 Tabori et al. 2017
DICER1 Indications	x	x	x	x	✓	Schultz et al. 2018
GI Rhabdomyosarc-oma tool	x	x	x	x	✓	Schneider, K. et al. 2020
Ripperger & Jongmans checklist	Jongmans et al. 2016 Ripperger et al. 2017	Cancer predisposition syndrome AND "screening tool" in **web of Science** ; Cancer predisposition syndrome AND "screening tool" in **web of Science** + referenced in Kuhlen et al. 2019	✓	Jongmans et al. 2016 Chan et al. 2018	✓	Jongmans et al. 2016 Chan et al 2018
LFSPro	Peng G et al. 2017	Li-Fraumeni syndrome/ AND [Risk assessment/ or Risk factors/ or Decision making, Computer-assisted/ or Diagnosis, computer assisted/ or Decision support systems, clinical/ or artificial intelligence/ or decision support techniques/ or "surveys ad questionnaires/ or models, statistical/ ; **Medline**	✓	Peng et al. 2017	✓	Peng et al. 2017 Shin et al. 2020

MEN1 Nomogram	Calmari et al. 2018	Multiple endocrine neoplasia type 1 AND [Risk assessment/ or Risk factors/ or Decision making, Computer-assisted/ or Decision support systems, clinical/ or artificial intelligence/ or decision support techniques/ or "surveys ad questionnaires/ or models, statistical/] ; **Medline**	x	x	x	x
MIPOGG	Goudie et al. 2017	Genetic Predisposition to Disease/ AND Neoplasm/ AND Risk Assessment ; **Medline**	✓	Cullinan et al. 2020 Goudie et al. 2018 Goudie et al. 2017	✓	Cullinan et al. 2020 Goudie et al. 2018 Goudie et al. 2017
PTEN Calculator	Lu et al. 2014	Genetic Predisposition to Disease/ AND Neoplasm/ AND Risk Assessment ; **Medline**	✓	Tan et al. 2011	✓	Tan et al. 2011
Risk Category System for AIP mutations	De Laat et al. 2012	Pituitary Neoplasms/ AND Risk assessment/ ; **Medline**	x	x	x	x
Traffic Light System	Moss et al. 2019	Known by contacting experts (C.G)	x	x	x	x
TUPS	Postema et al. 2017	decision support system/ and hereditary tumor syndrome/ or childhood cancer/ or cancer susceptibility/ ; **Embase**	✓	Postema et al. 2017	✓	Postema et al. 2017
University of Chicago Screening Form	x	x	✓	The University of Chicago Hematopoietic Malignancies Cancer Risk Team, 2016	x	x

Supplementary Table 3.2 : Summary of decision-support tools, their associated publications and database. The 14 CPS decision-support tools identified in this review are listed in Table 1. Only five tools were identified in all three parts of the literature search (Jongmans/Ripperger checklist, LFSPro[33], MIPOGG[29], PTEN calculator[31] and TuPS[35]). Seven tools were identified in a single database, and two tools were uncovered by contacting experts in our team (Traffic Light System[34] and the Muir-Torre variant of Lynch syndrome scoring system[45]). The first column lists the DST's official name and the following two columns (in blue) represent the DSTs identified during the pilot search. If the tool was identified during the pilot search, the tool's associated publication is listed (author, date of publication) followed by the search terms and database used for its identification. DSTs with an 'x' in the blue columns were not identified during the pilot search but were during the systematic search. The last four columns (yellow) represent the results of the systematic approach to the literature search. DSTs identified in the MEDLINE database contain a '✓' in this box and have the MEDLINE-associated publication listed, while those not identified in this database contain an 'x'. Similarly, articles identifiable in the EMBASE

3.2.8 References

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Chapter 4 : Assessment of decision support tool use among Canadian pediatric hematologists-oncologists

4.1 Preface to the Canadian survey

Once the scoping review established the landscape of DSTs available for the recognition of pediatric CPSs, it remains to be known whether these tools are familiar to practicing pediatric hematologists-oncologists (PHOs) and whether they are being used in real time. Given the variety of tools, different levels of accessibility, and the large scope of their applicability, some tools may be well integrated in Canadian physicians' practices, while others may not be known at all. There is also a paucity of data regarding the clinician's attitude towards such tools. Rather than improving physician workflow, previous studies have demonstrated physician fatigue with the use of certain electronic tools during clinical practice[1]. Therefore it is not always evident that tools made for HCPs directly translate into helpful clinical aids. The following survey aims to assess whether these tools have been made accessible to Canadian PHOs and whether they find these tools to be well adapted for clinical use.

4.2 The use of decision support tools among Canadian pediatric hematologists-oncologists for the recognition of cancer predisposition syndromes: A nationwide survey

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4.2.1 Abstract

Background

The recognition of cancer predisposition syndromes (CPSs) has important clinical implications for pediatric patients. Due to the challenges of recognizing CPSs, there has been the development of multiple decision support tools (DSTs) to help clinicians decipher whether a child would benefit from a CPS genetic evaluation. However, little is known about the use of DSTs by pediatric hematologists-oncologists (PHOs) in clinical settings. This study aims to identify whether PHOs are familiar with DSTs and whether they find such tools to have been adequately adapted for clinical use.

Methods

An electronic questionnaire was distributed to PHOs practicing in the 16 largest pediatric hematology, oncology, and stem cell transplant programs across Canada. The survey inquired about the clinical applicability of DSTs in the context of CPS recognition. We aimed to explore whether Canadian PHOs have previously used a DST, which DST they were familiar with, in which clinical scenarios they employed DSTs, and which DST feature they found most useful during their clinical practice. Responses were analyzed using descriptive statistics.

Results

A total of 36 responses were received from 153 PHOs, leading to a response rate of 23.5%. Half of the respondents (18/36) have previously used a DST in their practice, while 44.4% (16/36) have not and 5.6% (2/36) were unsure. Features reported to be most valuable during clinical practice include the DST's ease-of-use, its accessibility and its promotion by academic institutions/hospitals. Among those who have previously used a DST, the tool's recommendation is considered as an important part of their decision-making process (61.1% of DST users). Among those who have not previously used DSTs, 50% report not knowing these tools existed, while 38.9% report not knowing where to access them. The majority of non-DST users (72.2%) report that, despite not using these tools, their adoption would be useful in their practice.

Conclusion

This study is the first to describe the use of DST for the recognition of pediatric CPSs within Canadian institutions. Overall, these tools have been previously used by half of surveyed PHOs. To improve their adoption in clinical settings, features such as ease-of-use, accessibility and recognition by Canadian institutions/hospitals should be prioritized. Future studies should address the utility of such tools within different geographical and socio-economic contexts.

4.2.2 Introduction

Cancer predisposition syndromes (CPSs) are genetic conditions estimated to affect 10% of children with cancer[21–23,88,89]. For families of pediatric oncology patients, identifying a CPS can provide some understanding as to why a malignancy has developed, since it can be more difficult to identify environmental exposures for cancers in children compared to adults[69,85]. Importantly, recognizing an underlying CPS may have consequential clinical implications. For instance, it allows for the modification of treatment plans: recognizing CPSs such as DNA repair disorders (e.g ataxia-telangiectasia, Fanconi anemia etc.) in a patient with acute lymphoblastic leukemia might guide a clinician to decrease chemotherapy doses and/or avoid radiation therapy. [39,71]. Recognition of CPSs also informs cancer surveillance measures, risk reduction strategies (prophylactic colectomies in APC-associated polyposis conditions) and may also have important consequences for their family members if the CPS is inherited [64,90].

Currently, the best approach to identify children affected by CPSs continues to be investigated by different research groups. The clinical recognition of CPSs remains difficult despite the development of published guidelines, as evidenced by incidental cases uncovered during patients' involvement in research-based sequencing studies [74,90]. For one, due to incomplete presentation of the CPS phenotype or to variable expressivity, patients may present some features of the CPS but not enough to meet the diagnostic criteria, which may prevent clinicians from investigating CPSs any further. Second, many non-oncological symptoms such as ear pitting (as in Beckwith-Wiedemann syndrome) and skin changes (as in the café-au-lait macules associated with Neurofibromatosis 1) may be subtle upon presentation and remain unnoticed until the development of more apparent or pathognomonic features. Importantly, a family history of cancer, a common criterion for the referral to CPS genetic evaluations, is often misleadingly negative due to genetic factors (*de novo* variants, incomplete penetrance, variable expressivity). In fact, about 50% of children who have developed optic pathway tumours associated with Neurofibromatosis Type 1, for instance, have *de novo* pathogenic variants resulting in a non-informative family history of cancer [91].

Non-genetic factors may also contribute to the misleading nature of family history collection (family members of a child with cancer may be young, parents may lack knowledge of family history, etc.) [92]. Beyond clinical recognition of CPSs, the treating physician's decision-making process is further complicated by the increasing CPS genetic testing options and the rapid

evolution of cancer genetics knowledge. As such, the decision to offer CPS genetic testing to pediatric oncology patients (and which testing option to choose from) has become increasingly complex and multifactorial.

An emerging strategy to mitigate these challenges has been the development of decision support tools (DSTs) that aim to assist health care practitioners in their recognition of underlying CPSs. In the past 10 years, these tools have evaluated both pediatric and adult CPSs and generally request input about the patient's symptoms, tumour type, family history of cancer and other CPS-specific features. These DSTs vary widely; while some are specific to one CPS, others address all known CPSs associated with a particular malignancy. Ongoing research is being conducted to validate some of these tools, with some recent evidence demonstrating high sensitivity for the detection of common CPSs [93,94]. As such, these tools may be an important avenue for improved clinical recognition of CPSs. However, it remains unclear how often these tools are being used in real-time by pediatric hematologists-oncologists (PHOs) and whether they have been well adapted for clinical use.

To form a better understanding of the clinical use and applicability of DSTs for the recognition of CPSs, we designed a questionnaire to be distributed to the 16 pediatric hematology-oncology academic hospitals in Canada. Our primary objective is to assess the PHOs' familiarity with DSTs. Our secondary objective is to establish whether the tools are adequately adapted for clinical use, by ascertaining which features DST users find most helpful during practice and, conversely, which features are lacking.

4.2.3 Methods

A 25-item cross-sectional questionnaire was designed to explore pediatric CPS evaluations and diagnoses in clinical settings. Questions were designed and reviewed by different clinicians including a pediatric hematologist-oncologist and a genetic counsellor. The online questionnaire, distributed through *Google Forms*, contained a mixture of multiple-choice questions, requiring the selection of either a single response or multiple responses, in situations where more than one was applicable. The questionnaire was subdivided into four sections. The first section addresses

relevant demographic characteristics (e.g. institution and years of practice, completion of graduate genetics training). The second section inquires about the physician's genetic evaluation practices (e.g. how CPSs are typically evaluated, what proportion of children is sent for genetic testing, etc.). Prior to starting the third section of the questionnaire, respondents were provided with a working definition of a DST (as written below).

The third section of the survey aims to assess the respondent's familiarity with DSTs and the respondent's opinions on given DSTs' utility during clinical practice. Those who previously used DSTs had to identify which DST they had previously used, which were familiar, and which DST feature they found most beneficial to their clinical practice. In contrast, non-DST users were directed to a section of the survey that assessed their familiarity with pediatric DSTs and answered questions aiming to identify why DSTs have not been used, and which features they wish to see implemented in these tools.

Working definition of a decision-support tool

A clinical decision-support tool (DST) is referring to any paper-based or online reference requiring the input of your patient's unique clinical profile to ultimately provide:

- A recommendation for testing (your patient should [or should not] be evaluated for a CPS);
- The risk of harbouring a known CPS genetic variant (e.g. your patient has a 63% risk of having a MEN1 mutation);
- And/or general references that guide your decision to refer a patient for CPS evaluation

Examples of DSTs often used in the adult oncology population includes BRCAPro and the Tyrer-Cuzick model that predict the probability of harbouring a Hereditary Breast and Ovarian Cancer-associated variant. Please note that a DST is not referring to any tool that lists the diagnostic criteria of a CPS (e.g. Chompret criteria for LF1, Bethesda guidelines, NIH consensus diagnostic criteria for Neurofibromatosis 2 etc.)

A list of 14 DSTs identified in the previously conducted scoping review was provided (Supplementary Table 4.1) , with links to the DST's research publication or official website. The respondent's familiarity with each tool was assessed by selecting whether they "have used this tool", "have heard of this tool but never used it" or "have never heard of this tool". Further multiple choice and free text questions evaluated which features of the DSTs are useful, or could potentially be useful to the respondent. Respondents were provided with the opportunity to add additional DSTs that were not mentioned in Supplementary Table 4.1. The final section addresses the

different genetic sequencing methods and protocols available at their institution. Implied consent was obtained by all participating physicians before the start of the questionnaire. Respondents remained anonymous through the completion of the questionnaire and were free to skip any questions.

The questionnaire was distributed to members of the C^{17} Council, an organization uniting all "sixteen heads of the pediatric hematology, oncology and stem cell transplant programs across Canada"[B], through their online Q&A posting board (*Sosido*). An invitation to complete the questionnaire was also emailed to the heads of the pediatric hematology-oncology departments of the 16 centres involved in the C^{17} Council and their administrative assistants in order to reach the rest of their respective staff. The questionnaire could be completed in French or English by PHOs, and remained open from December 2021 until February 2022. Two reminders to fill out the questionnaire were emailed to the department heads and posted on the *Sosido* website. Survey questions relevant to DST use were analyzed using Excel. This study has been approved and authorized by the McGill University Health Centre Ethics Board (REB # 2022-8172).

4.2.4 Results

Demographics

A total of 153 PHOs across the 16 hospitals in the C^{17} Council organization received an invitation to complete our questionnaire. Within this population, 36 responses were recorded, leading to a response rate of 23.53% (36/153). Responses were received from all 16 hospitals taking part of the C^{17} Council, which spans 8 of the 10 Canadian provinces (not including Prince Edward Island and Newfoundland & Labrador). One to four responses were received from each institution. Following training, responding physicians were most commonly practicing pediatric hematology-oncology for less than 5 years (47.2%) or greater than 20 years (19.4%). Overall,

[B] https://c17.ca/

surveyed respondents had not completed any specialized training in cancer genetics (75.0%) and described their patient populations most often as 'general hematology-oncology' (41.7%) or 'brain or solid tumours' (30.6%) (Table 4.1).

Table 4.1 Demographics of survey respondents

	n (%)
Years Of Practice (Not Including Training)	
<5	17 (47.2)
5-9	5 (13.9)
10-14	4 (11.1)
15-19	3 (8.33)
≥20	7 (19.4)
Specialized Training Completed in Cancer Genetics (e.g, Fellowship Or Graduate Studies (MSc Or PhD))?	
No	27 (75.0)
Yes	9 (25.0)
Focused Population Of Physicians' Practice	
General Hematology-Oncology	15 (41.7)
Brain Tumour Or Solid Tumours	11 (30.6)
Benign Hematology	3 (8.33)
Stem Cell Transplant	2 (5.56)
Leukemia/Lymphoma	3 (8.33)
No Response	2 (5.56)

Physicians' familiarity with decision support tools in clinical settings

DSTs for the evaluation of CPSs in pediatric patients are used among half of the surveyed respondents. Specifically, half (18/36) of respondents have reported that they previously used a DST to evaluate the likelihood of an underlying CPS, while 41.7% (15/36) have reported never having used a DST for this purpose, and 8.33% (3/36) indicated they are unsure. Comparison of PHOs who have previously used a DST with those who have not (or are unsure), reveals that the majority of DST users have been practicing for less than 5 years (after training), while, among

those who have not previously used DSTs, the majority have been practicing for 5 years or more (Figure 4.1A).

In addition, of those who have not completed additional genetics training, the majority are non-DST users, while the majority of those who have trained in genetics have previously used a DST (Figure 4.1B).

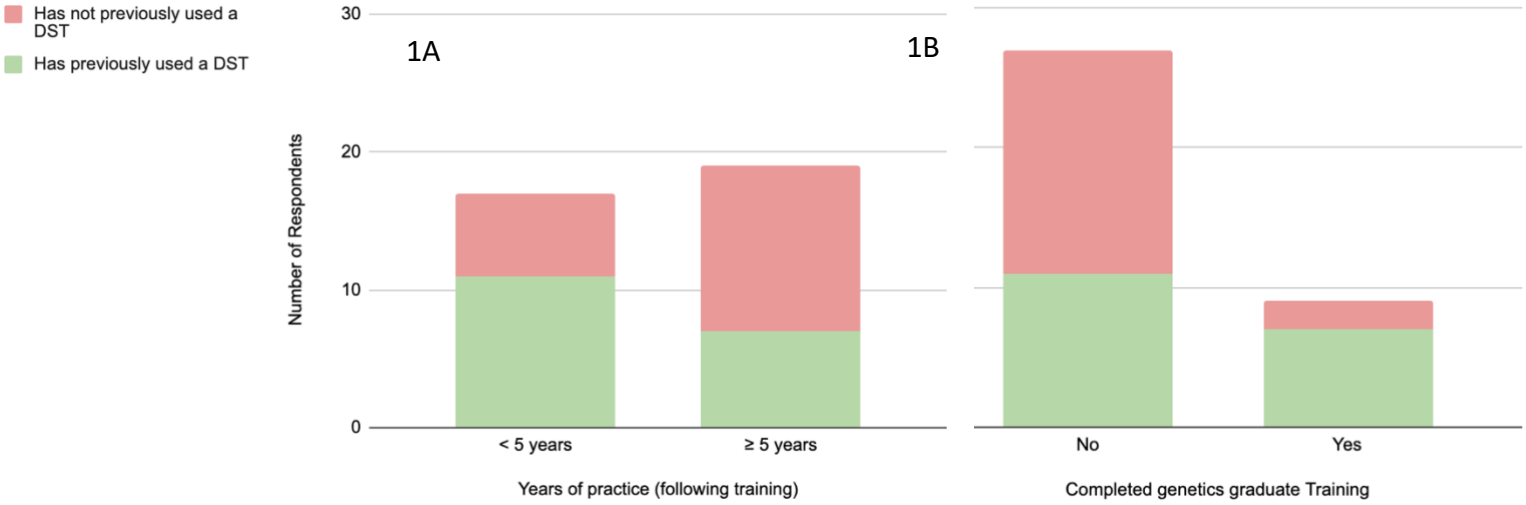

Figure 4.1: Use of decision support tools. 1A Previous use of decision support tools according to years of practice as a pediatric hematologist-oncologists (after training). 1B Previous use of decision support tools according to completion of specialized training in cancer genetics

When assessing which DST, in particular, the physician had previously used, all respondents were able to indicate whether a tool was previously used by them, familiar but never used, or completely unfamiliar (Figure 4.2). Assessment of the respondents' familiarity with pediatric DSTs revealed that the most utilized DST was the McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG), which has been previously used by 47% of respondents; the DICER1 form, previously used by 17% of respondents, the Bone Marrow Failure (BMF) syndrome form and the C4CMMRD form, which were each previously used by 11% of respondents. Decision support tools that were most familiar to respondents, but never used in the clinic, were MIPOGG (recognized by 22% of respondents), the DICER1 form (22%), the BMF syndrome form (22%), the C4CMMRD form (19%) and the MEN1 nomogram (19%). Overall, tools were unknown by the respondents and, as

illustrated in figure 4.2, the average DST was likely to be unknown by 74% of respondents. Beyond the 14 DSTs listed in figure 4.2, no additional tools were suggested by the respondents.

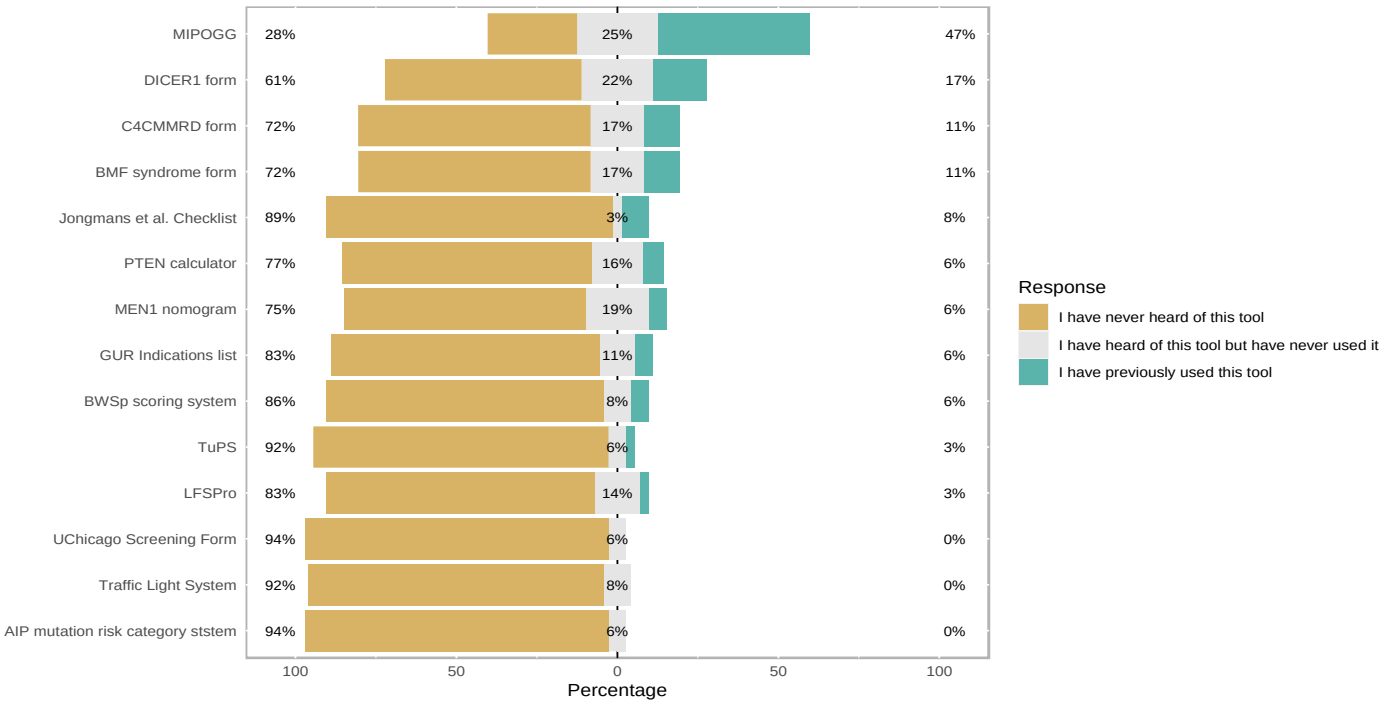

***Figure 4.2 : Familiarity of decision-support tools among Canadian pediatric hematologists-oncologists. MIPOGG** = McGill Interactive Pediatric OncoGenetic Guidelines. **C4CMMRD** form = Care 4 Constitutional mismatch repair deficiency syndrome ; **BMF** = Bone Marrow Failure ; **GUR** = genitourinary rhabdomyosarcoma ; **BWSp** = Beckwith-Wiedemann syndrome spectrum ; **TuPS** = clinical screening instrument for Tumour predisposition syndromes in patients with childhood cancer ; **LFSPro** = Li-Fraumeni Syndrome*

Physicians who have previously used a decision-support tool

Among users of DSTs (18/36 surveyed respondents), tools are most often discovered through a colleague's recommendation (66.7%), a research article (61.1%), the physician's hospital setting (38.9%) or through the physician's involvement in the validation of a DST (MIPOGG) (11.1%) (2/18).

When asked which circumstances prompted the respondents to resort to DSTs during clinical practice, they reported that DSTs were most often used with patients who have had multiple primary tumours (77.8%), have a family history of cancer (77.8%), have physical manifestations of a CPS (66.7%) or abnormal toxicity to medications (66.7%) (multiple choices were allowed). Respondents were likely to employ DSTs in cases of hard-to-treat cancers (38.9%), with their

entire patient population (chosen by 27.8% of DST users), and/or in cases of early tumour onset (11.1%), or due to the presentation of tumours commonly associated with a hereditary CPS (5.56%).

With regards to the tool's features, DST users select the tool's accessibility (cost, language), its ease-of-use (format, simple yes/no questions) and its applicability to multiple CPSs as the most valuable features of a DST during clinical practice. The less commonly chosen option was the tool's specificity to a particular CPS (chosen by 22.2% of DST users).

Finally, when the DST provides its recommendation, 61.1% of DST users do not always rely on the recommendation but consider it as an important factor in their decision-making process. Thirty-three percent of DST users selected that they rely on the DST's final recommendation "always", while one DST user did not respond to the question.

Respondents who have *not* previously used a decision-support tool or are unsure of it

A total of 18/36 respondents have not previously used a DST or reported they are unsure. Among them, the most commonly cited explanation is that they 'have never heard of these tools before' (selected by 50% of non-DST users). Second to that, 38.9% of non-DST users reported that they do not know how to find or access these tools. There are also concerns that the use of such DSTs would be time-consuming in a clinical setting (16.7%), concerns that they are unreliable or in need of further validation (5.6%), the impression that DSTs would be unnecessary given the straightforward nature of CPS diagnoses (5.6%), and the need for more mobile tools such that it can be adapted to a handheld device (5.6%) (multiple answers could be selected).

Factors selected by respondents as most likely to incite the adoption of DSTs include increasing their simplicity or ease-of-use (61.1%), knowing the DST is being promoted by their academic program/hospital (44.4%), increasing its accessibility, including cost and language (44.4%) and increasing research on validity and applicability of the tools (33.3%) (multiple answers could be selected).

A total of 72.2% of non-DST users reported that, despite not using such tools, their adoption would be useful in their practice. The remainder of non-DST users reported that they are unsure about the clinical benefits of such tools, and none responded that DSTs would not be useful.

Decision-Making: How do PHOs decide which children to send for CPS genetic evaluation?

Irrespective of DST usage, physicians were subsequently prompted on their decision-making processes for the evaluation of CPSs in their patient populations. The multiple-choice question revealed that the majority of surveyed physicians (67% or 24/36), evaluate the possibility of CPS on a case-by-case basis, relying on their clinical judgment and expertise. Among them, 5/24 depend solely on clinical judgment, without using online references (e.g *GeneReviews*) or scientific publications. The remaining 19/24 depend on their clinical judgment in addition to seeking out additional resources (online references, published guidelines, or scientific publications). Thirty percent (12/36) of PHOs report that they do not evaluate the probability of CPSs based on clinical judgment, but rather, defer to additional resources (i.e DSTs, scientific publications, published guidelines or online references).

Following different decision-making practices, the majority (88%) of respondents refer less than 25% of their patient population to genetics. More specifically, 44% (16/36) of PHOs refer less than 10% of their patient population to genetics. Forty-four percent of PHOs refer between 10-24% of their patient population, 8.3% refer between 25-49% and 2.7% refer between 50-75%. No PHOs refer greater than 75% of their patient population to genetics (Figure 4.3). Non-DST users, as seen in figure 4.4, tend to refer less of their patient population compared to DSTs users.

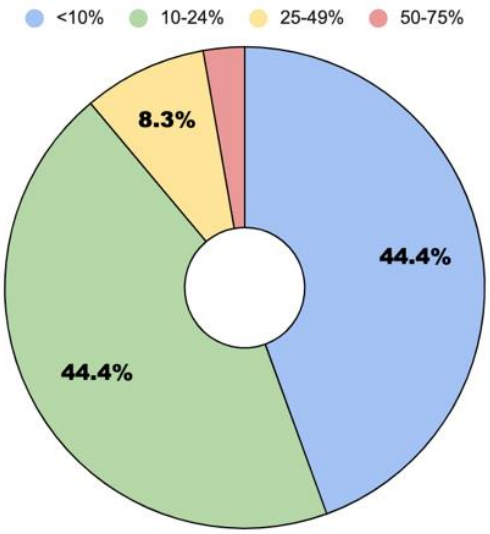

Figure 4.3 : Percentage of hematology-oncology population referred to genetics.

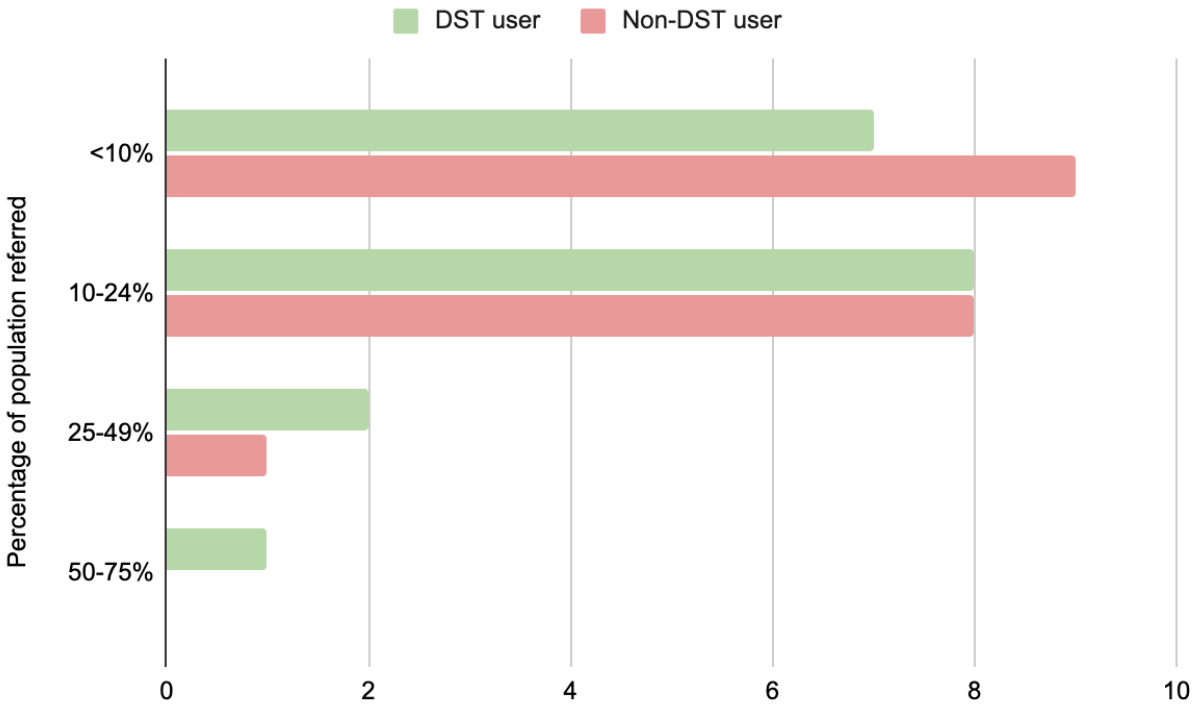

Figure 4.4: Percentage of the patient population referred to genetics according to the PHO's use of DSTs. Y axis represents the percentage of the PHO's patient population referred for a CPS genetic evaluation. X axis represents the number of PHOs. Red-coloured bars represent PHOs who have not previously used DSTs, while green bar represent those who have previously used a DST

4.2.5 Discussion

In this study, we have investigated whether Canadian PHOs are familiar with DSTs developed for the recognition of CPSs and whether they find such tools to be adequately adapted for clinical settings. Our results show that, despite half of surveyed PHOs having previously used DSTs, most of the 14 DSTs presented remain unknown or unused by clinicians. In addition, most tools are found to be challenging to adapt to clinical settings due to their low ease-of-use, lack of accessibility and low acknowledgement rate by Canadian hematology-oncology hospital departments.

Our first finding assesses the proportion of DST-users among surveyed Canadian PHOs, which reveals that half have utilized such tools. Despite the divided level of use of DSTs, both users and non-users find such tools to be clinically valuable in terms of informing decision-making. This demonstrates a desire for appropriate resources to assess the probability of an underlying CPS in children with cancer. This need is echoed by the majority of respondents who seek out additional resources (online references, published guidelines, scientific publications) to inform their decision to genetically test for CPSs.

Our second finding assesses the PHOs' familiarity with 14 DSTs that aim to help physicians recognize and refer children likely to be affected by CPSs. We have found that these tools are, in large part, unknown to the respondents. In fact, 50% of non-DST users indicate they have never heard of such tools before and 39% indicate that, although some DSTs are familiar, they do not know how to access or find them. This indicates an important need for resources to inform PHOs of the tools developed for them, which may become more important as the number of DSTs increases over the years.

Of the DSTs that are most commonly used by Canadian PHOs (MIPOGG, the DICER1 form, the C4CMMRD indications, the BMF form and the Jongmans *et al.* Checklist), MIPOGG is the most used (47%) by surveyed physicians. There may be a bias in respondents who completed the survey as some of these physicians may have participated in the development of MIPOGG.

When asked which tools are known, without necessarily having previously been used in the clinic, a similar selection of DSTs was chosen (MIPOGG, DICER1 form, BMF form, C4CMMRD indications and the MEN1 nomogram). Interestingly, when comparing each tool's rate of familiarity ("I have heard of this tool but never used it") versus the rate of usage ("I have previously used this tool"), DSTs tend to have a higher rate of familiarity than usage, with the exception of MIPOGG and the Jongmans *et al.* checklist. This may suggest that, among the tools that are known to PHOs, few are chosen to be adopted into the physician's clinical practice. It is probable that these MIPOGG and the Jongmans et *al.* checklist were often used due to their applicability to multiple tumour types and CPSs. Both DSTs have also been externally validated and assessed for their performance, increasing their prevalence in the literature in recent years[26,93,94].

Our third finding addresses whether pediatric DSTs are well adapted for clinical use. To investigate this question further, we began by asking DST users to select the features that are most helpful in practice. The DST's ease-of-use, accessibility and application to multiple CPSs were the most commonly selected options. The importance of a tool's ease-of-use, in particular, has been widely reported in the literature. Although defined in many ways, it is generally regarded as "the degree to which a person believes that using a particular system would be free of effort"[95]. Within the context of clinician-oriented DSTs, ease-of-use refers to the tool's capacity to be easily integrated to the physician's workflow and includes aspects such as formatting (if paper-based), user interface (if computer-based), simplicity of questions and time commitment. The improvement of a DST's ease-of-use has been demonstrated to lead to improved clinical practice[96–98]. In a meta-analysis, Kawamoto et al. demonstrate that (1) providing decision support at the time and location of decision making, (2) using a computer to generate the decision support and (3) automatically providing decision support as part of the workflow are all independent predictors of a DST's ability to lead to improved clinical practice[96]. The results of our study confirm that these features are also sought out by PHOs in the context of CPS recognition.

Accessibility has also been selected as an important feature for clinical practice. This indicates that features such as cost (access to these tools free of charge) and language (availability in English and French) are valued by PHOs in Canada. Lastly, the DST's capacity to be applicable to multiple CPSs is preferred over a DST's specificity to one CPS. We can stipulate that this is likely due to the nature of one malignancy leading to the possibility of multiple CPSs or the need to investigate the likelihood of different CPSs simultaneously.

To investigate whether DSTs are adequately clinically adapted, we also asked non-DST users to indicate which features would incite them to adopt DSTs into their respective clinical practices. Features most commonly selected include, once again, the DST's ease-of-use (selected by 61% of non-DTS users) and accessibility (selected by 44% of non-DST users). Improvement on the aforementioned aspects of ease-of-use (time consumption, online format, simplicity of input/output parameters) may be necessary for greater adoption of these tools into clinical settings. Respondents also indicated that they are more likely to implement these tools into clinical practice if they are promoted by their hospital setting (or endorsed by their academic institution) and if further research is conducted to provide evidence of the DSTs' validity and generalizability. This

may allow for the integration of these tools into the physician's electronic health records and may permit such DSTs to become a standardized and systemic implementation in pediatric oncology practice. Further promotion could come from discussions at grand rounds or journal clubs.

Limitations

One limitation of our study is the low response rate (23.5%), which is slightly below the pediatrics response rate reported by other research groups. Cunningham *et al.,* for instance, reported a 29.2% pediatrician response rate in their analysis of Canadian physician specialists' response rates to web-based surveys[99]. Nevertheless, survey respondents represent each of the 16 institutions and major Canadian cities, in addition to a wide representation of hematology-oncology sub-specialities and years of practice, suggesting all C^{17} Council sites had some team members aware of the survey.

Approximately 10% of respondents are unsure of whether they have previously used a DST. A formal definition for DSTs was provided, in addition to examples of DSTs adapted for adult CPSs; however, the definition of a DST may have remained unclear to certain respondents. When given the opportunity to add a DST which was not already listed, no propositions were made, suggesting it may be safe and conservative to assume that the "unsure" users have not previously used a DST and can be analyzed along with the non-DST users.

Another limitation is that knowledge of tools may be biased by the tool's development in Canada or by Canadian researchers (MIPOGG and the DICER1 form). This is especially relevant since respondents have reported that they most often become aware of a DST through another physician's recommendation. This, however, reinforces the need for databases allowing PHOs to access tools developed worldwide.

4.2.6 Conclusions

This study has revealed that there is significant heterogeneity in PHOs knowledge and usage of DSTs in Canadian hospitals. This survey suggests that the currently available DSTs are difficult to access and remain unknown by many PHOs, despite their recommendations being deemed valuable by our respondents. Features such as ease-of-use, accessibility, and the promotion of DSTs by academic institutions are reported as important factors for their integration into the physician's practice. Resources for physicians to identify validated DSTs applicable to their patient populations is an important avenue for future research. Given that most PHOs work in concert with genetic counsellors, geneticists, multidisciplinary tumor boards and/or research sequencing initiatives, it may be advantageous for DSTs to integrate or promote the collaboration between treating physicians and the genetics and research teams.

4.2.7 Supplementary Information

Supplementary figure 1 : English version of the REB approved survey. Uploaded on Google Forms

Survey title

Exploring the genetic evaluation and sequencing practices among pediatric hematologist-oncologists in tertiary Canadian hospitals

1. Demographics

1. Please select your institution
    - Alberta's Children's Hospital
    - British Columbia Children's Hospital
    - CancerCare Manitoba
    - Children's Hospital of Eastern Ontario
    - Children's Hospital at London Health Sciences Centre
    - CHU Sainte-Justine
    - CHU de Sherbrooke
    - CHU De Quebec-Université Laval
    - Hospital for Sick Children (SickKids)
    - IWK Health Centre
    - Janeway Children's Health & Rehabilitation
    - Kingston General Hospital
    - McMaster Children's Hospital - Hamilton Health Sciences
    - Montreal Children's Hospital

- Saskatoon Cancer Centre
- Stollery Children's Hospital
- Other

2. How many years have you been practicing as a pediatric hematologist/oncologist (not including training) ?
    a. <5
    b. 5-9
    c. 10-14
    d. 15-19
    e. >20

3. Have you completed any specialized training in cancer genetics (e.g. fellowship or graduate studies (MSc or PhD))?
    a. Yes
    b. No

4. Is there a focused population to your hematology-oncology practice?
    a. Benign hematology
    b. Brain tumors or solid tumors
    c. General hematology-oncology
    d. Stem cell transplant
    e. Thrombosis
    f. Other : _____

2. Genetic evaluation and sequencing practices in hematology-oncology (for assessment of a cancer predisposition syndrome)

1. How do you typically evaluate the probability of a cancer predisposition syndrome in your patients? Select all that apply

a) Case-by-case basis without the use of any references or decision-support tools
b) Use of published guidelines
c) Use of online references (e.g GeneReviews)
d) Following the approach proposed by scientific publications
e) Non-applicable to my practice
f) I don't evaluate the probability as all my patients undergo genetic sequencing (germline)
g) Other : _____

2. What percentage of your hematology-oncology patients do you refer to genetics (approximately) ?

a) None.
b) <10%
c) 10-24%
d) 25-49%
e) 50-75%
f) >75%

3. Referring a child with cancer for cancer predisposition syndrome evaluation to clinical/cancer genetics is done:

a) With all pediatric patients at our institution
b) With some pediatric patients at our institution depending on certain factors (tumor type, family history of cancer, etc.)
c) Based on the treating physicians' clinical judgment
d) With additional consultation from a geneticist/genetic counsellor
e) Other : _____

3. Use of cancer predisposition syndrome decision-support tools

The second portion of this questionnaire is intended to better understand the use of clinical decision-support tools among physicians during their evaluation of a pediatric oncology patient with a potential cancer predisposition syndrome (CPS).

Throughout this survey, a clinical "decision-support tool" (DST) is referring to any paper-based or online reference requiring the input of your patient's unique clinical profile to ultimately provide:

• A recommendation for testing (your patient should [or should not] be evaluated for a CPS);

• The risk of harbouring a known CPS genetic variant (e.g. your patient has a 63% risk of having a MEN1 mutation);

• And/or general references that guide your decision to refer a patient for CPS evaluation

Examples of DSTs often used in the adult oncology population includes BRCAPro and the Tyrer-Cuzick model that predict the probability of harbouring a Hereditary Breast and Ovarian Cancer-associated variant. Please note that a DST is not referring to any tool that lists the diagnostic criteria of a CPS (e.g. Chompret criteria for LF1, Bethesda guidelines, NIH consensus diagnostic criteria for Neurofibromatosis 2 etc.)

1. Have you ever used a decision-support tool to guide your evaluation of a child with a potential cancer predisposition syndrome?

a) Yes
b) No
c) I don't know

3A. If you use a decision-support tool

1. Which pediatric decision-support tool have you previously used and/or heard of?

If needed, the following link provides additional information about the tools referenced below : https://docs.google.com/spreadsheets/d/e/2PACX-

Risk assessment tool	I have used this tool	I have heard of this tool but not used it	I have never heard of this tool
Bone Marrow Failure Syndromes form			
BWSp scoring system			
C4CMMRD form			
DICER1 form			
GU Rhabdomyosarcoma Indications for genetic referral			
Jongmans/Ripperger checklist			
LFSPro			
MEN1 nomogram			
MIPOGG			
PTEN calculator			
Risk category system for AIP mutations			
TuPS (Postema et al. checklist)			
Traffic Light System			
The University of Chicago Hereditary Hematopoietic Malignancies Screening Form			

2. Are there any tools known to you that have not been mentioned in the previous question?

3. How did you hear about the tool(s) you are using ? Select all that apply

a) The tool is commonly used at my hospital
b) Through another physician's recommendation
c) From an academic conference
d) From a journal/academic article
e) Other : _____

4. When do you decide to use the decision-support tool? Select all that apply

a) I use it with every pediatric hematology-oncology patient

b) I use it with patients with recurrences or hard-to-treat cancers
c) I use it with patient who have had multiple primary tumors
d) I use it with patients having a family history of cancer
e) I use it with patients having physical manifestations of a cancer predisposition syndrome or abnormal toxicity to medications
f) Other : _____

5. With regards to the decision-support tool(s) that you have previously used, which feature(s) do you find most valuable during clinical practice? Select all that apply

a) Its ease-of-use (format, simple yes/no questions)
b) Its accessibility (free of charge, language, etc.)
c) Its specificity to one cancer predisposition syndrome
d) Its applicability to multiple types of cancer predisposition syndromes
e) Other : _____

6. How often do you rely on the final recommendation/answer provided by the tool?

a) Always
b) Not always, but it is an important factor in my decision-making process
c) Occasionally. It is sometimes an important factor in my decision-making process but other times, not
d) Rarely

3B. If you have never used a decision-support tool

Or are unsure of whether you have previously used a decision-support tool

1. Please select all of the decision-support tools that you have previously heard of

If needed, the following link provides additional information about the tools referenced below : https://docs.google.com/spreadsheets/d/e/2PACX-1vSPgPV_ntWeM912xJwwWGrlpkG3NgJD8FgGGWyFHmTvQ3TSVkdTdtOoW9sZlm03VD6ufotXz_2td9sg/pub?output=pdf

Bone Marrow Failure Syndromes form
BWSp scoring system
C4CMMRD form
DICER1 form
GU Rhabdomyosarcoma Indications for genetic referral
Jongmans/Ripperger checklist
LFSPro
MEN1 nomogram
MIPOGG
PTEN calculator
Risk category system for AIP mutations
TuPS (Postema et al. checklist)
Traffic Light System
The University of Chicago Hereditary Hematopoietic Malignancies Screening Form
I have never heard of the cancer predisposition syndrome decision-support tools listed above
Other : _____

2. Which factor(s) prevent you from using a decision-support tool? Select all that apply

a) I don't find these tools helpful
b) I find these tools to be unreliable
c) I have never heard of these decision-support tools
d) I am unsure how to find or access these tools
e) The use of decision-support tools would be too time consuming
f) Other : ____

3. Which factor(s) would incite you to use a decision-support tool? Select all that apply

a) Increasing its ease-of-use (format, output recommendation, etc)
b) Increasing its accessibility (charge, language, etc.)
c) Additional research on the validity and applicability of these tools

d) Waitlist time for genetic testing at my institution is reduced
e) If it is promoted by my academic program/hospital
f) Other : _____

4. Do you think the use of a cancer predisposition syndrome decision-support tool would be helpful in your practice?

a) Yes, please provide a brief explanation
b) No, please provide a brief explanation
c) Unsure, please provide a brief explanation

4. Options for genetic sequencing in your institution

The final portion of this questionnaire would like to assess the sequencing options available to the pediatric oncology patients at your institution

1. Paired tumor and germline testing at your centre is done (select all that apply):

a) Through research initiatives
b) Clinically (via oncology)
c) Clinically (via genetics service)
d) Through a combination of research and clinical test options

2. Who makes a decision about offering/enrolling a patient for paired tumor and germline testing?

a) All patients are offered paired tumor/germline testing
b) Treating physician
c) Research committee linked to a cancer sequencing study
d) Interdisciplinary meeting decision (tumor board)
e) Other : _____

3. Are all cancer patients offered paired tumor and germline testing? Select all that apply

a) No, only tumor testing is completed
b) Patients always undergo paired tumor/germline testing
c) Patients undergo paired tumor/germline testing due to refractory or multiple primary malignancies
d) Patients undergo paired tumor/germline testing due to certain types of malignancies
e) Other : _____

4. If a child is enrolled on a cancer sequencing study (through research), when is a referral to genetics made for a cancer predisposition syndrome evaluation (if indicated)?

a) After the sequencing results are received
b) Before the sequencing results are received, if suspicious of a cancer predisposition syndrome
c) Before the sequencing results are received, independent of the suspicion of a cancer predisposition syndrome
d) Depends on the patient/family. Some get referred before, some after.
e) Other : ____

5. Are you comfortable ordering genetic tests (germline) for your patient population? Select all that apply.

a) Yes, most or all of the time
b) No, I refer to a genetic counsellor or MD geneticist
c) No, I do not know when ordering a test would be appropriate
d) No, I do not know which test(s) would be most appropriate
e) No, I do not know from where to order genetic testing
f) Other : ___

6. What is the type of germline sequencing you offer most often to patients at your institution? Select all that apply

a) Whole genome sequencing
b) Whole exome sequencing
c) Cancer panel (hereditary cancer panel) – customizable gene list
d) Cancer panel (hereditary cancer panel) – fixed gene list
e) Single gene (or few gene) sequencing based on tumor type or family history
f) Other : _____

7. What proportion of patients get genetic tests ordered by their physician compared to the genetics team?

a) The majority is ordered by physicians
b) The majority is ordered by genetics
c) It is approximately equal
d) I don't know
e) Other : _____

Supplementary Table 4.1 : Fourteen decision-support tools (DSTs) provided to survey respondents prior to answering questions in section 3

Tool Name	Country, Year
Bone marrow failure syndrome form	USA, 2017
BWSp scoring system	Italy, 2020
C4CMMRD indications for genetic testing	EU, 2014
DICER1 form	USA, 2018
Indications for GU Rhabdomyosarcoma	USA, 2020
LFSPRO	USA, 2017
MIPOGG	Canada, 2018
Nomogram to predict MEN1	Netherlands, 2016
PTEN risk calculator	USA, 2011
Ripperger/Jongmans checklist	Germany, 2017
Risk category system for AIP mutations	UK/Spain/USA, 2018
Traffic light classification system	UK, 2019
TuPS (Postema et al. checklist)	Netherlands, 2017
University of Chicago Screening Form	USA, 2016

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Chapter 5 : Discussion

5.1 Summary

My thesis investigates the DSTs that help clinicians recognize the possibility of CPSs in pediatric patients. To investigate these tools, I began by conducting a scoping review, in which I systematically reviewed the existing literature using multiple databases and consulted experts in the field of pediatric oncology and clinical genetics. I used the DSTs identified in the scoping review to design a survey that assessed whether Canadian pediatric hematologists-oncologists were familiar with and/or found DSTs useful to their clinical practice. The scoping review revealed a total of 14 DSTs that fit our inclusion criteria. I explored these DSTs with a clinical lens, focusing on the ways in which their features could be beneficial or burdensome for clinical practice. In contrast, previous studies have utilized pediatric DSTs for research purposes. Wagener *et al.* provided germline analysis in cancer predisposing genes of an unselected cohort of 160 children with cancer, and correlated the results with the recommendations provided by the Jongmans *et al.* checklist and the TuPS tool, in order to have a better understanding of the correlation between clinical suspicion of CPSs and carrying pathogenic variants in cancer-predisposing genes[97]. Similarly, Byrjalsen *et al.* used MIPOGG and the Jongmans *et al.* screening tools to explore this same relationship, and see whether carriers of pathogenic CPS gene variants would raise clinical suspicion[98]. Therefore, the tools also have an important role in answering research questions and may be used beyond clinical settings.

For clinical purposes, however, I investigated whether the tools were simple to integrate into busy physician workflows, by looking at their format, how questions were formatted, the input and output parameters, and whether they were adequately validated or generalizable to different populations. The scoping review revealed that most tools were paper-based, were often in the form of scoring systems or questionnaires, outputted their recommendation in a dichotomous format, and that only half of them were validated. Some DST features (e.g. paper-based) may not be preferred in electronic health record-dependent practices, for instance, while they may be preferred in a setting that is less dependent on computers. For this reason, the second manuscript of this thesis analyzed the Canadian PHOs' perspective. We aimed to assess with which tools Canadian

PHOs were familiar and which DST features they appreciated or found challenging to implement into their practice. With that, we can build on the knowledge of DST utility in clinical practices, such that these tools can optimize CPS recognition and diagnosis in patients.

5.2 Accessibility of pediatric DSTs

The survey established that the DSTs identified in the scoping review were predominantly unfamiliar to Canadian PHOs. The accessibility of these tools was an important and significant barrier to their use. In fact, most tools were discovered through another physician's recommendation rather than being discovered in published articles. This suggests that the DSTs are not easily accessible through literature searches, which is an important pillar of science communication among clinicians and researchers. We encountered this challenge when first conducting the scoping review. First, there are many alternatives terms that encapsulate the concept of DSTs. For instance, in Medline, the MEN1 nomogram is captured under the subject headings 'Algorithms' and 'Risk Factors', while the TuPS tool is captured under the subject heading 'checklist' and the keyword 'screening instrument'. The "Traffic light" classification system, in particular, was known to us prior to starting the scoping review but was not captured with our search strategy. This is because it is not classified under any MeSH or keyword headings for DSTs, despite being a potentially beneficial instrument for the detection of CPS and instead, is classified under the much broader heading of 'referral and consultation'. In fact, this DST contains features deemed clinically useful by our surveyed PHOs (such as its generalizability to multiple CPSs) but was unheard of by 92% of PHOs and 'familiar but unused' by 8%, likely due to its hidden accessibility.

Secondly, there is currently no MeSH term for CPSs, at large. Instead, 'genetic predisposition to disease' and 'neoplasm' must be searched concomitantly, or the specific CPS must be searched. Therefore, due to these barriers to accessing DST articles in the literature, it is likely that other DSTs are published but classified in inaccessible ways, or that DSTs are used within institutions and inaccessible to clinicians. The scoping review conducted in this thesis may serve as a resource for PHOs to become familiar with the DSTs available for their patient population in addition to providing an overview of their characteristics, features and performance.

5.3 DST features and their compatibility with clinical practice

It is not enough for a tool to be accessible, but it must also feature characteristics that make it compatible and feasible to use in clinical practice. Our survey established that ease-of-use was the most valued feature of DSTs among respondents. Interestingly, the C[17] council surveyed Canadian PHOs 10 years ago and established that they spend most of their time doing clinical work (median 60%, range 40-75%) compared to administrative, teaching and research work. The study also discusses that this exceeds the 55% clinical workload recommended by the Pediatric Oncology Group of Ontario (POGO) and the C[17] HR committee[100]. Therefore, tools that are time-consuming and/or are cumbersome to adapt to clinical practice would not be optimal for PHOs.

Our survey also revealed that it is important for DSTs to address multiple CPSs, rather than focusing on one. Among the 14 DSTs included in our scoping review, half address more than one CPS, while 4 tools are considered 'general' and address all CPSs affecting the pediatric population. Given that PHOs are often faced with cancer patients first, it is likely that they prefer tools that address the many CPSs associated with the patient's tumour type.

An important finding in the scoping review was that 7/14 tools have not published any validation studies as of February 2022[C]. When looking at whether this was an important limiting factor for PHOs, one third of non-DST users reported that increasing the evidence of the DSTs' validity and generalizability was an important factor for them to adopt these tools to their practice. Similarly, 44% of non-DST users claimed that the promotion of DSTs by their academic program/hospital would incite them to adopt DSTs, which is generally dependent on evidence of the tool's validity and performance. As such, for tools to be systematically used by Canadian PHOs, it is first important for future research to address the tools' performance and validity and subsequently, to assess whether the implementation of these tools in oncology departments would lead to increased detection of CPSs in pediatric patients.

[C] Two validation studies have been published since the scoping review was conducted in February 2021. TuPS has been validated and assessed for its performance in a prospective, observational, multi-centre study published in October 2021[101]. An additional study assessing MIPOGG's performance and diagnostic accuracy was published in October 2021[94]

Chapter 6: Conclusion

The early recognition of CPSs in pediatric patients has become an increasingly relevant aspect of their global management and outcome. The development of DSTs for the recognition of CPSs in pediatric patients is both an emerging and potentially beneficial avenue to increase clinicians' ability to identify CPSs. Through a scoping review process, pediatric-onset CPS-focused DSTs were identified. They were subsequently categorized according to their features, revealing that the tools address a wide range of CPSs, are heterogeneous in their formats, developmental methods and levels of validation. The real-world application of these tools is also underexplored in the literature. Through the second part of the thesis, we established Canadian PHOs' low familiarity with these DSTs but, also, their inclination for resources that can assist decision-making.

My thesis contributes to the field of CPS identification in pediatric patients. To our knowledge, the scoping review serves as the first resource for PHOs and other clinicians to familiarize themselves with DSTs that may increase their screening methodology of CPSs in children. In addition, our survey contributes to a broader discussion of the use of tools to inform clinical decision-making and the translation of cancer genetics into routine practice. Future research should aim to add any DSTs that were not captured in our scoping review and to assess DST use in diverse clinical settings. Clinicians, hospitals settings and academic programs should be aware of the potential advantage of incorporating DSTs systematically in order to optimize the identification of CPSs in pediatric patients.

6.1 Future directions

Future research should aim to replicate the Canadian survey and allot more time for PHOs to participate in hopes of increasing the response rates. It is also important to reproduce the survey in other countries to expand our understanding of how DSTs are used in different hospital settings and how they may be optimized for differing populations. In particular, it would be important to assess their relevance in lower resource settings and in areas where genetic testing and experts in genetics (clinical geneticists, genetic counsellors) are less accessible.

Second, since these tools are not only useful to hematologists-oncologists, further studies should be conducted on the utility of DSTs among other pediatric specialties. General pediatricians, for instance, may benefit from the systematic use of DSTs in patients with an underlying CPS whose early symptoms are non-oncological (e.g. café-au-lait macules as the first indication of NF1 or mucocutaneous pigmented lesions as the first indication of Peutz-Jeghers syndrome)[20,102]. However, in specialties outside of oncology, only the subset of DSTs in which tumour type is not compulsory for the tool's functioning can be utilized.

Third, given that accessibility has been established as an important barrier to DST use by Canadian PHOs, the development of an online resource or registry listing all pediatric DSTs should be publicized. Lastly, it is important to continuously assess whether the tools ultimately lead to a greater recognition of CPSs compared to the current CPS identification methods used in our hospital settings, as has been done with MIPOGG and the Jongmans *et al*. checklist [94,103].

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7.3 Discussion and Conclusion References

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