Parent and adolescent decisions regarding research genetic sequencing in pediatric cancer

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Abstract

Introduction: In recent years, large-scale genetic sequencing (LSGS) use within pediatric oncology has been growing. LSGS includes sequencing technologies ranging from multi-gene cancer panels to whole genome sequencing (WGS). As use of this technology evolves and its clinical utility is being studied, it is important to assess all stakeholder perspectives, including those of adolescents and parents.

Methods: A scoping review was performed to describe the current landscape of research on adolescent and parent attitudes (motivations and concerns) towards participating in LSGS. A single-centre questionnaire study was then performed to assess adolescent and parent attitudes towards participating in LSGS cancer research programs at the McGill University Health Centre (MUHC).

Results: Fifteen publications were identified via the scoping review. An analysis of these publications provided evidence of gaps in the literature on perspectives from (a) families in Canadian contexts and (b) adolescent patients. The most frequently reported motivations among the publications were altruism and improved treatment. The most frequently reported concern was insurance discrimination.

Seven individuals participated in the MUHC study, including 6 parents and 1 adolescent. All respondents had elected to participate in LSGS. Information seeking and altruism were identified as important motivations in their LSGS decision-making, consistent with the scoping review. No concerns, including insurance discrimination, were reported as important.

Conclusions: Individuals considering LSGS after a pediatric cancer diagnosis may weigh multiple motivations and/or concerns, depending on the context. More research is needed to better understand adolescent and parent attitudes, both at the MUHC and more broadly.

Résumé

Introduction : Récemment, l'utilisation du séquençage génétique à grande échelle (LSGS) en oncologie pédiatrique a augmenté. Le LSGS comprend des applications de séquençage allant des panels multigéniques de cancers au séquençage du génome entier (WGS). Comme notre utilisation et notre compréhension de l'utilité clinique du LSGS évoluent, il est important d'évaluer toutes les perspectives des personnes impliquées, y compris celles des adolescents et des parents.

Méthodes : Une revue de la littérature a été effectuée pour décrire l'état actuel de la recherche sur les attitudes (motivations et préoccupations) des adolescents et des parents à l'égard de la participation au LSGS. Une étude monocentrique par questionnaire a ensuite été réalisée pour évaluer les attitudes des adolescents et des parents à l'égard de la participation aux initiatives de LSGS en oncologie au Centre universitaire de santé McGill (CUSM).

Résultats : Quinze publications ont été identifiées par la revue. Une analyse de ces publications démontre le manque d'études sur les perspectives (a) des familles dans des contextes canadiens et (b) des patients adolescents. Les motivations les plus fréquemment mentionnées dans les publications sont l'altruisme et l'optimisation du traitement. La préoccupation la plus fréquemment signalée était la discrimination en matière d'assurance.

Sept personnes ont participé à l'étude du CUSM, dont 6 parents et 1 adolescent. Tous les répondants ont choisi de participer au LSGS. La recherche d'information et l'altruisme ont été identifiés comme des motivations importantes dans leur prise de décision concernant le LSGS, conformément à la littérature. Aucune préoccupation, y compris la discrimination de l'assurance, n'a été signalée comme importante.

Conclusions : Les personnes qui envisagent le LSGS après un diagnostic de cancer pédiatrique peuvent considérer plusieurs motivations et/ou préoccupations, selon le contexte. D'autre recherche est nécessaire pour mieux comprendre les attitudes des adolescents et des parents, tant au CUSM que de façon plus générale.

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List of abbreviations

CHU – Centre Hospitalier Universitaire (University Hospital Centre)

CPS – Cancer predisposition syndrome

CRA – Clinical research assistant

LSGS – Large-scale genetic sequencing

MUHC – McGill University Health Centre

MCH – Montreal Children's Hospital

WES – Whole exome sequencing

WGS – Whole genome sequencing

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Format of the thesis

This thesis follows the traditional thesis format. Chapter 1 provides a literature review as well as the hypothesis and objectives of this thesis. Chapter 2 describes the methods used. Chapter 3 contains the results. Chapter 4 discusses the results in the context of related research as well as the limitations of this work. Chapter 5 summarizes conclusions and explores future directions. Chapter 6 lists the references used throughout this thesis. Supplementary information may be found in the Appendix.

Contribution of authors

Dr. Catherine Goudie supervised this thesis. Dr. Yann Joly, Dr. Jonathan Kimmelman, Lara Reichman and Evan Weber were supervisory committee members.

Scoping Review

Michelle Carter (MC) wrote the scoping review protocol. Andrea Quaiattini (a McGill University librarian) and MC designed the scoping review search terms. MC performed scoping review searches. MC and Katrina Baldassarre (KB) performed the article screening. MC performed the data extraction and synthesis. KB validated the extracted data.

McGill University Health Centre study

MC designed the study documents with guidance and translation support from Lara Reichman (LR). MC designed the questionnaire with help from the supervisory committee members. Crystal Budd introduced families to the study after LSGS consent sessions and provided consent sessions for individuals who were immediately interested. LR and MC contacted families, provided consent sessions, administered questionnaires and performed chart reviews. MC analyzed the data from the questionnaires and chart review. Melissa Tachdjian was the second coder for the free-text responses from the questionnaire and LR was the third coder.

Chapter 1: Introduction and literature review

1.1. Overview

Cancer is the second leading cause of death among individuals aged 0-15 years in Canada (Statistics Canada, 2022). In 2020, the Cancer in Young People in Canada registry reported 925 new cancer diagnoses among individuals aged 0-15 years in Canada (Public Health Agency of Canada, 2020). The Cancer in Young People in Canada registry has previously estimated that 23% of all Canadian pediatric cancer cases occur in the province of Quebec (Public Health Agency of Canada, 2017). Overall, approximately 300 children are diagnosed with cancer each year in Quebec.

Advances in diagnosis and treatment have led to improvements in pediatric cancer survival rates in high-income countries, including Canada (Kinsey & Picton, 2021; Malvezzi et al., 2021; Rodriguez-Galindo et al., 2015; Ward et al., 2019). In recent years, genetics has become an area of particular interest for improving diagnosis and management of pediatric cancer. An analysis of publications in Web of Science from 2007 to 2016 found that genetics was the most frequently published research domain in pediatric cancer research (Syrimi et al., 2020). Within the domain of genetics, large-scale genetic sequencing (LSGS) has contributed valuable knowledge and has steadily grown in use; LSGS is an umbrella term that includes sequencing applications ranging from multi-gene cancer panels to whole exome sequencing (WES) or whole genome sequencing (WGS). In the context of oncology, LSGS commonly involves paired sequencing of genetic material from somatic (tumor) and germline (normal or non-tumor) tissue samples.

This thesis will focus on attitudes of (1) adolescents with cancer and (2) parents of children with cancer towards LSGS in the setting of a pediatric cancer diagnosis. Throughout this thesis, the terms "child" and "pediatric" will be used to describe individuals from 0-18 years of age, unless otherwise specified, whereas the term "adolescent" will be used when specifically referring to individuals from 12-18 years of age. Additionally, attitudes are operationalized as personally important perceived motivations (sometimes referred to as advantages) and concerns

(sometimes referred to as disadvantages). The subsequent sections in this chapter will present a review of relevant literature followed by the hypotheses and objectives of this thesis project.

1.2. Large-scale genetic sequencing (LSGS) in pediatric cancer populations

1.2.1. Purpose: why is LSGS used?

LSGS has facilitated novel contributions and clinical utility to the ongoing expansion of knowledge in the field of pediatric cancer including (1) improving molecular classification of tumors, (2) identifying potential targeted treatment options and (3) identifying variants related to cancer predisposition (Mody et al., 2017; Sweet-Cordero & Biegel, 2019; Wise, 2019). First, in addition to classic categorization by morphology and immunoprofile, LSGS studies have provided greater insight into the molecular landscape of pediatric tumors which allows for categorization of tumors based on the type of driver mutation(s) present (Cacciotti et al., 2020; Fangusaro & Bandopadhayay, 2021; Suurmeijer et al., 2019). Second, this identification of driver mutations and subsequent molecular classification of tumors allows for the study of treatment efficacy by molecular tumor type, sometimes referred to as targeted treatment (Akhavanfard et al., 2020; Khater et al., 2019; Summers et al., 2022; Wong et al., 2020). LSGS findings with potential treatment implications have been identified in 25-52% of individuals with a primary pediatric cancer diagnosis (Gröbner et al., 2018; Newman et al., 2021) and in 34-61% of individuals with a recurrent or refractory pediatric cancer diagnosis (Forrest et al., 2018). Finally, while the aforementioned improvements in cancer knowledge are primarily based on LSGS findings from somatic (tumor) tissue LSGS, germline LSGS findings have also contributed to the field of pediatric cancer care by improving the ability to identify cancer predisposition syndromes (CPSs) (Fiala et al., 2021; Gröbner et al., 2018; Zhang et al., 2015).

While clinical utility of LSGS is largely cited as a reason for its implementation, the perceived purpose of LSGS may vary depending on the viewpoint of the stakeholders. Stakeholders in the implementation of LSGS among pediatric cancer populations include researchers, physicians, genetic counsellors, ethicists, policy-makers and patients or families offered LSGS. There may be heterogenous perspectives on the utility and value of LSGS across and among these groups; for example, there have been ongoing discussions about the existence of personal utility and/or

disutility for LSGS participants and their families (Bunnik et al., 2015; Halley et al., 2022; Hayeems et al., 2021; Mollison et al., 2020). This thesis will focus on the perspectives of adolescents with cancer and parents of children with cancer as stakeholders.

1.2.2. Setting: research LSGS vs clinical LSGS

Though LSGS use in pediatric cancer populations has largely occurred in research settings, the results may nevertheless have clinical implications for pediatric cancer patients (such as those described in section 1.2.1.). Efforts have been made to distinguish between the concepts of research and clinical interventions (sometimes referred to as clinical treatment). Generally, research is viewed as being in the interest of contributing to generalizable knowledge with the intent of benefitting future patients while clinical treatment is viewed as being in the interest of the patient's needs, with the intent of benefitting the individual patient (Food and Drug Administration, 2019).

Further distinctions between research and clinical testing have been noted, including differences in funding, assessment, access to information by participants/patients, timeframe and release of findings (Food and Drug Administration, 2019). As research applications of LSGS continue to develop cancer knowledge, conversations regarding the clinical implementation of LSGS in adult (Damodaran et al., 2015; Guan et al., 2012; Ku et al., 2013; Pfeifer, 2013; Sabour et al., 2017) and pediatric (Janeway et al., 2013; Ortiz et al., 2016) cancer care have been occurring in tandem. Currently, many countries have initiatives underway to examine "proof-of-principle" and infrastructure needs for clinical LSGS use in cancer care (Simons et al., 2021). A notable example is the nationwide Sequencing Tumor and Germline DNA—Implications for National Guidelines (STAGING) study in Denmark, which offers WGS to children (0-17 years of age) with a newly diagnosed cancer (Byrjalsen, Hansen, et al., 2020). As LSGS use has expanded, the distinction between research and clinical applications has become increasingly complex and blurred (Bertier et al., 2018). In the past five years, clinical LSGS has even become routinely available in certain tertiary/quaternary hospitals.

1.2.3. Population: who has access to LSGS?

LSGS use in pediatric cancer populations has followed behind LSGS use in adult cancer populations, with the slower application timeline being partially due to differences in cancer rates and added ethical concerns around genetic testing of minors (Johnson, Hamilton, et al., 2017; Printz, 2020; Salzer & Hutter, 2021). However, research involving LSGS has shown that pediatric cancers differ molecularly from adult cancers (Bandopadhayay & Meyerson, 2018; Gröbner et al., 2018; Ma et al., 2018). These findings suggest that LSGS use in pediatric cancer contributes valuable knowledge specific to the diagnosis and treatment of pediatric cancer; this knowledge cannot necessarily be translated directly from adult cancer research.

Within pediatric cancer populations, early LSGS programs focused largely on patients with relapsed, refractory or difficult-to-treat cancer diagnoses due to the increased molecular complexity of their tumors, poor prognosis and the potential identification of targeted treatment options (Khater et al., 2019; Mody et al., 2017). Targeted treatment options are of particular benefit to patients with relapsed, refractory or difficult-to-treat cancer as these patients may have exhausted standard treatment options. As knowledge generation and clinical utility has increasingly been demonstrated among pediatric relapsed, refractory or difficult-to-treat cancer populations, more programs have begun offering LSGS to all pediatric patients with newly diagnosed cancers. The STAGING study in Denmark (mentioned in section 1.2.2.), which began in 2016, is one such example and in 2019 England's National Health Service announced that all children with cancer in England would be offered WGS as part of their routine care moving forward (Byrjalsen, Hansen, et al., 2020; National Health Service, 2019; Wise, 2019).

1.2.3.1. Related pediatric populations: Contextual differences

It is important to note two contextual differences between LSGS-applications in pediatric cancer populations and other pediatric populations, particularly children with rare (and/or undiagnosed) diseases. This comparison is especially relevant as LSGS is increasingly used to aid diagnosis in populations of children with rare disease (Bick et al., 2019; Odgis et al., 2021; Rockowitz et al., 2020; Smith et al., 2019).

First, LSGS in cancer contexts typically involves paired sequencing, where two tissue types, somatic (tumor) and germline (normal or non-tumor) are both sequenced and compared. This comparison of somatic and germline tissue allows for the identification of variants occurring only in the somatic tissue, which facilitates the identification of driver mutations (Kuhlen & Borkhardt, 2015). Driver mutations may have implications for molecular classification or targeted treatments. Though LSGS results of somatic tissue are of primary interest in cancer contexts, results from the germline tissue may lead to the identification of a CPS (via a cancer predisposing variant in the germline) and/or incidental findings, such as carrier status (Kuhlen & Borkhardt, 2015). Identification of individuals with CPS-related variants allows tumor surveillance programs to be implemented and/or cancer treatment plans to be modified (Kesserwan et al., 2016; Reichman & Goudie, 2021). Tumor surveillance programs have been found to improve morbidity and mortality among individuals with certain CPSs (Durno et al., 2021; Villani et al., 2011). The reported rate of CPS-related findings identified via LSGS in pediatric cancer populations ranges from 8.5-12% (Akhavanfard et al., 2020; Chang et al., 2016; Gröbner et al., 2018; Mody et al., 2015; Oberg et al., 2016; Parsons et al., 2016; Zhang et al., 2015).

In contrast to cancer contexts where the tumor (somatic) tissue LSGS analysis is of primary interest, in rare disease contexts the primary indication is diagnosis and there is no tumor tissue to be evaluated. Notably, incidental findings in the germline tissue (including CPS-related variants) may also occur in rare disease contexts. In both cancer and rare disease contexts, positive germline findings may lead to testing of other family members, including parents and siblings (Johnson, Hamilton, et al., 2017; Kuhlen & Borkhardt, 2015).

Second, in children with cancer, LSGS is often performed rapidly after the cancer diagnosis. This is in contrast to children with rare disease, where LSGS is performed in an effort to obtain a diagnosis, often after a prolonged diagnostic odyssey that may involve previous genetic testing, such as single gene tests and/or chromosomal microarray (Bick et al., 2019).

Overall, these contextual differences suggest that families of children with cancer and families of children with rare disease may experience LSGS in different ways and more research is

needed to further explore how these differences may impact LSGS use, preferences and delivery.

1.3. Current landscape of LSGS in Quebec for pediatric cancer populations: Past, present and future access

In the province of Quebec, LSGS access for children with cancer has been expanding through four research programs (Appendix Table 1). In April 2014, the TRICEPS research program began offering molecular profiling, including paired (somatic and germline) WES, to children and adolescents with refractory or recurrent cancer at the Centre Hospitalier Universitaire (CHU) Sainte-Justine in Montreal. Following a two-year feasibility phase which encompassed the first 30 participants, the study was expanded to recruit participants from all four pediatric oncology centers in Quebec (Khater et al., 2019).

Since TRICEPS began, three other programs have begun offering LSGS to children with cancer in Quebec. In April 2016, a Canada-wide program named Precision Oncology For Young People (PROFYLE) began offering molecular profiling, including paired (somatic and germline) WGS, to individuals ≤29 years of age with a hard-to-treat cancer diagnosis (Grover et al., 2020). In April 2017, a biobank named Oncology Repository for Children and Young Adults (ORCYD) began recruiting children and young adults with cancer who were participating in research at the McGill University Health Centre (MUHC) and CHU de Quebec. Research projects using this biobank may then apply LSGS to the collected samples. In December 2019, a program named SIGNATURE began offering paired (somatic and germline) WES for all children (<19 years of age) with a newly diagnosed cancer at CHU Sainte-Justine. In March 2021, SIGNATURE expanded to recruit participants from all four pediatric oncology centers in Quebec. The expansion of research LSGS access from children with relapsed or refractory cancers to all children with a new cancer diagnosis follows the overall research LSGS progression described in section 1.2.3.

The establishment of these research programs has expanded LSGS use in pediatric cancer populations such that almost every child in Quebec with a new cancer diagnosis is currently offered LSGS in a research context. From July 2021 to June 2022, approximately 200 children

with cancer in Quebec participated in LSGS through SIGNATURE, with 34 of those children participating at the MUHC (internal communication).

While all current LSGS programs for pediatric cancer populations in Quebec are provided on a research basis, global discussions around clinical utility and clinical application of LSGS in pediatric cancer populations have been ongoing for more than five years (Kline et al., 2017; Mody et al., 2015; Ortiz et al., 2016; Rusch et al., 2018).

Many genetic professionals believe that LSGS will continue to move into broader clinical use in the future. In a survey of 16 genetic professionals working in clinical leadership roles, participants estimated that by 2030, 48% of cancer patients in Canada would receive tumor LSGS and 32% would receive germline LSGS (Borle et al., 2022). Similarly, in interviews conducted from 2015 to 2017 with pediatric oncology and pediatric rare disease research teams using LSGS in Quebec, six of the seven participants stated that they believed LSGS would be progressively used in clinical settings within the next five years (Bertier & Joly, 2018).

When discussing the implementation of LSGS into clinical cancer care, researchers have noted the need for more research on patient perspectives, equitable access, infrastructure and education (Bertier et al., 2016).

1.4. Current understanding of patient and family stakeholder attitudes towards LSGS use

1.4.1. Value of patient and family perspectives

Health technology assessment (HTA) is an important part of the development and introduction of technologies, such as LSGS, as well as translation from research settings to clinical settings (Rosenkötter et al., 2011). HTA often involves evaluations of clinical effectiveness, cost-effectiveness, technical aspects and social and ethical implications (Gagnon et al., 2014; Simons et al., 2021). With regards to social and ethical implications, many authors have addressed the ethical and practical benefits of including patient and family perspectives in HTA (Callard et al., 2012; Gagnon et al., 2014; Rand et al., 2019). While other relevant components of HTA of LSGS (such as financial-, administrative- and policy-related considerations) will not be discussed in

this thesis, they have been discussed in the literature (Bertier et al., 2016; Chan et al., 2021; Pipitprapat et al., 2021; Tan et al., 2018; Weymann et al., 2018).

In recent years, health research and healthcare have seen a shift from paternalistic approaches to models that value increased patient engagement and autonomy, such as patient- and family-centered care and patient partnerships (Dumez & Pomey, 2019). The importance of patient perspectives has been noted at federal, provincial and organizational levels. At a federal level, in 2011, the Canadian Institutes of Health Research published a strategy for patient-oriented research which defined patient engagement as "meaningful and active collaboration in governance, priority-setting, conducting research and knowledge translation" (Canadian Institutes of Health Research, 2011). At a provincial level, in 2017, Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) published a methodological guide that emphasized the importance of involving stakeholders, including patients and caregivers, in research and healthcare (*INESSS*, 2017). At an organizational level, many hospitals and research centers have incorporated patient-centeredness into their values. For example, the mission of the Research Institute of the MUHC states that the primary objective of research at the centre is to "ensure that the MUHC builds on its strengths as a leader in patient-centered, innovative healthcare research, setting the stage for the transition to patient-centered medicine" (*RI-MUHC: Our Vision and Mission*, n.d.). Patient and family perspectives are integral to implementing patient- and family-centered care and research.

1.4.2. Participation/decline rates

Published decline rates in LSGS in pediatric oncology settings range from 1.2-30% (Table 1). Notably, the reported decline rate for the Quebec-based TRICEPS program is at the lowest end of this range (1.2%), which may reflect higher participation rates among families with relapsed or refractory cancers (Khater et al., 2019). This higher participation rate may be due to population differences, such as children with relapsed or refractory cancers having already exhausted standard treatment options or the extended time since diagnosis. When pediatric cancer populations are compared with other pediatric populations and adult cancer populations, it is unclear if there is a difference in rates of accepting and declining LSGS

participation. However, families of children with cancer may have notably different reasons for declining LSGS than other populations (Amendola et al., 2018).

LSGS program name (reference)	Country	Population	Decline rate
Pediatric cancer populations			
TRICEPS (Khater et al., 2019)	Canada	Children with a relapsed or refractory cancer diagnosis	1.2%
Germline mutations in children with cancer (Brozou et al., 2018)	Germany	Children with newly diagnosed cancers	11.7%
G4K (Howard Sharp et al., 2020)	United States	Children and young adults (0–21 years) with diagnosis of liquid, non-CNS solid, or CNS solid tumor	14.6%
STAGING (Byrjalsen, Hansen, et al., 2020)	United States	Children (0-17 years) with newly diagnosed cancers	15.7%
BASIC3 (Amendola et al., 2018)	United States	Children with newly diagnosed cancers	30%
Other populations			
Australian Genomics Acute Care (Australian Genomics Health Alliance Acute Care Flagship, 2020)	Australia	Critically ill children	4.1%
PediSeq (Amendola et al., 2018)	United States	Children with undiagnosed disorders	12%
NEXT Medicine (Amendola et al., 2018)	United States	Adults with cancer	23-28%

Table 1 *– Published decline rates for LSGS programs.*

1.4.3. Parent and adolescent attitudes towards LSGS use in pediatric oncology

In order to better understand the current body of research assessing parent and adolescent attitudes towards LSGS in pediatric oncology populations, a literature review was conducted.

Parents and adolescents were chosen as the population of interest since in pediatric cancer contexts, they are often the decision-makers regarding LSGS participation. While parents are considered the decision-makers for their minor children, adolescents are considered to be developing skills and abilities related to decision-making (Grootens-Wiegers et al., 2017) Accordingly, adolescents are often involved in medical decision-making, though there are

ongoing discussions around the extent of their participation, their role in decision-making and potential implications for LSGS consent practices (Clayton, 2015; Levenseller et al., 2014; Sisk et al., 2019; Werner-Lin et al., 2016). Research among adolescents considering LSGS for unselected clinical indications and non-cancer disorders shows that adolescents wish to be involved in the decision-making process (Levenseller et al., 2014; Pervola et al., 2019). In practice, children and adolescents are participating in discussions around LSGS decision making: Miller et al (2017) coded audio-recordings of 44 consent sessions for minor participation in research WES for undiagnosed disorders. Almost half (45.5%) of the children and adolescents (8-17 years of age) asked a question or expressed a concern and almost one third (31.8%) expressed an opinion about study participation or secondary findings (Miller et al., 2017). The topic of shared decision-making in other areas of pediatric cancer care, such as treatment decisions, has been explored more broadly in the literature (Boland et al., 2019; Coyne et al., 2016; Lin et al., 2020).

A preliminary evaluation of the literature on adolescent and parent attitudes towards LSGS following a pediatric cancer diagnosis found that small, but seemingly increasing, number of studies have been published on this topic. The majority of these studies were conducted in the United States; no studies conducted in a Canadian context were identified. Additionally, there was an absence of adolescent perspectives towards LSGS use in pediatric cancer settings.

1.5. Hypotheses and objectives

This thesis project is largely exploratory and descriptive in nature, in an effort to describe and contribute to the current body of literature assessing parent and adolescent attitudes towards LSGS following a pediatric cancer diagnosis. The objectives of this project were to describe:

1. the current landscape of research on parent and adolescent perspectives towards LSGS following a pediatric cancer diagnosis

2. motivations and concerns reported by (1) adolescents with cancer and (2) parents of children with cancer regarding research LSGS at the MUHC following a pediatric cancer diagnosis

The first objective was addressed via a scoping review. The decision to perform a scoping review was made in an effort to expand on the initial literature review discussed in section 1.4.3.

The second objective was addressed via a prospective single-centre study, conducted at the MUHC, in an effort to contribute additional perspectives to the literature. I hypothesized that (1) adolescents with cancer and (2) parents of children with cancer who have been offered LSGS participation after a pediatric cancer diagnosis may report multiple motivations and concerns about LSGS participation. Additionally, I hypothesized that families that elect to participate in LSGS may report that their motivations outweigh their concerns.

Chapter 2: Methods

2.1. Overview

As discussed in section 1.4.3., while an initial literature review revealed a small body of research examining the attitudes of parents of children with cancer towards LSGS use, perspectives of families offered LSGS in a Canadian context and perspectives of adolescents with cancer were absent. In an effort to further describe these potential research gaps and contribute additional perspectives to the literature, we implemented a two-step approach to this thesis project: a scoping review and a prospective single-centre study.

First, the scoping review was designed to capture publications reporting the attitudes of (1) adolescents with cancer and/or (2) parents of children with cancer towards LSGS. The scoping review methodology was selected in order to expand on the initial literature review by systematically searching for additional publications on this topic, which allowed for the exploration of these research gaps in greater detail (Lockwood et al., 2019; Munn et al., 2018).

Second, the single-centre study was designed to assess the attitudes of (1) adolescents with cancer and (2) parents of children with cancer towards LSGS for families that were offered LSGS through precision medicine research programs at the MUHC (located in Quebec, Canada). As is standard throughout this thesis, the term “child” is used to describe individuals from 0-18 years of age (unless otherwise specified) and the term “adolescent” is used when specifically referring to individuals from 12-18 years of age.

The attitudes identified via the scoping review were used to design a questionnaire, including quantitative and qualitative items, which was used in the MUHC study. The scoping review allowed motivations and concerns reported in the literature to be collected and selected attitudes were then incorporated into Likert scale items in the questionnaire. Three qualitative items assessing motivations and/or concerns were also included in the questionnaire.

2.2. Scoping review methods

The scoping review was performed in accordance with the methodological framework described by the Joanna Briggs Institute Manual for Evidence Synthesis (Peters et al., 2020) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews (Tricco et al., 2018).

2.2.1. Review questions

The scoping review aimed to explore the following review questions:

- What research has been done on attitudes of adolescents and parents towards LSGS for children and adolescents with cancer diagnoses?
- What are the geographic, contextual (i.e., research or clinical) and participant characteristics of the sources of evidence identified?
- What are the motivations and concerns reported by adolescents and parents within the sources of evidence identified?

2.2.2. Search strategy

Four electronic databases (Medline, EMBASE, PsycINFO and ProQuest Dissertations & Theses Global) were searched. The search strategy was designed with the help of a McGill University librarian (AQ). Each database was searched using two separate search terms: one designed to capture articles related to adolescent perspectives and one designed to capture articles related to parent perspectives. The two search terms each included the same keywords and MeSH headings related to (1) LSGS, (2) cancer and (3) attitudes and differed in keywords and MeSH headings related to either adolescents or parents. Details of the search terms used in each database can be found in Appendix Table 1. The searches of all four databases were performed on June 16, 2021 via Ovid and the results were combined in EndNote 20 (Thomson Reuters).

Results were limited to articles, conference abstracts and theses/dissertations published in English or French between January 1, 2010 and the date the search was performed (June 16, 2021). The initial date limit was applied to remove articles studying early adopters of LSGS, as these results may not be applicable to current attitudes towards the use of LSGS technology

(Lewis et al., 2015). Duplicate records were removed in EndNote 20 and the remaining articles were imported to the Rayyan QCRI web application for screening (Ouzzani et al., 2016).

2.2.3. Selection of sources of evidence

The title/abstract and full-text screenings were completed independently by two reviewers (MC and KB) and a third reviewer (LR) resolved conflicting decisions. Articles were included if they assessed the attitudes of (1) adolescents with cancer or (2) parents of children with cancer towards participating in LSGS. Attitudes were defined as perceived advantages and/or disadvantages of LSGS that factored into their decision-making.

Articles were excluded if they assessed attitudes towards participating in LSGS for newborn screening or for children without a cancer diagnosis. Articles were also excluded if they assessed adolescent or parent attitudes towards participating in non-LSGS forms of genetic testing following a cancer diagnosis. Additionally, articles that assessed the impacts of receiving LSGS results or provider attitudes towards LSGS were excluded.

2.2.4. Data extraction and synthesis

For each included article, relevant study information was compiled in a standardised extraction form adapted from the Johanna Briggs Institute template (Aromataris & Munn, 2020). The following characteristics were extracted for each study: PubMed ID, authors, publication year, study title, study aim(s), participant population, dates of data collection, location of data collection, sample size, type of LSGS offered and attitude-related assessment methods. Attitudes towards LSGS were also extracted from each article, including emergent themes from interviews and focus groups, reasons for declining recorded during LSGS consent processes and questionnaire responses regarding motivations and/or concerns. The corresponding authors of three articles were contacted for further clarification, primarily regarding dates of data collection. Data extraction was performed by one member of the study team (MC) and another member independently validated the data (KB).

To address the review questions, characteristics of the included publications were analyzed using descriptive numerical summary. Reported attitudes were analyzed using inductive thematic methods, allowing similar concepts to be grouped together (Arksey & O'Malley, 2005;

Levac et al., 2010). Tables were created to describe the distribution of studies by: countries of origin, types of participants included, LSGS methods used, tissue type(s) sequenced, attitude assessment methods, context, years of publication and attitudes reported among the studies.

2.3. McGill University Health Centre (MUHC) study methods

2.3.1. Type of study

After the scoping review was completed, a prospective, single-centre study was designed to assess parent and adolescent attitudes towards pediatric cancer LSGS research programs at the MUHC, specifically the Montreal Children's Hospital (MCH), which is within the MUHC. A study questionnaire was designed using the primary motivations and concerns identified in the scoping review (detailed in section 2.3.4. and section 3.1.4.). This study was reviewed and approved by the Research Ethics Board of the MUHC on November 26, 2021 (study ID: 2022-7881) and approved by the members of the division of hematology-oncology at the MCH during a Quality Assurance meeting held virtually on January 5, 2022.

2.3.2. Study population

At the time of this study, four research initiatives were offering LSGS to children diagnosed with cancer at the MUHC: ORCYD, PROFYLE, SIGNATURE and TRICEPS (see section 1.3. for a description of these programs). As this study aimed to assess the perspectives of adolescents and parents who had been offered participation in one of these LSGS studies, the eligibility criteria included*:* families with a child diagnosed with cancer (≤18 years of age at diagnosis) who had been offered the opportunity to participate in oncology-focused research LSGS (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS*)* at the MUHC. Families were excluded if they had received any results from their participation in the LSGS study, as assessing attitudes towards the return of LSGS results is a separate area of study (Fernandez et al., 2014; Vears, Minion, et al., 2021). Families were also excluded if they were not able to read and write English or French. Notably, this includes both families who *accept* or *decline* participation in the LSGS study they are offered. Within families meeting this eligibility criteria, the following members were eligible to participate in the present study: (1) affected adolescents (12-18 years of age) and (2) parent(s) of affected children (0-18 years of age). No limit was placed on the number of

participants per family. Parent(s) and/or affected adolescents from the same family were all eligible to participate. In this context, the term parent is used to encompass both biological parents and legal guardians.

Given that internal reports suggest that less than 50 families are offered LSGS following a pediatric cancer diagnosis at the MUHC each year, we initially aimed to recruit 25-30 families over a 12-month period. Due to the descriptive nature of the study, a minimum sample size was not required.

2.3.3. Recruitment methods

Potential participants were recruited during the consent sessions of LSGS research studies at the MUHC and via posters in the division of pediatric hematology-oncology at the MCH; these methods are summarized in Figure 1.

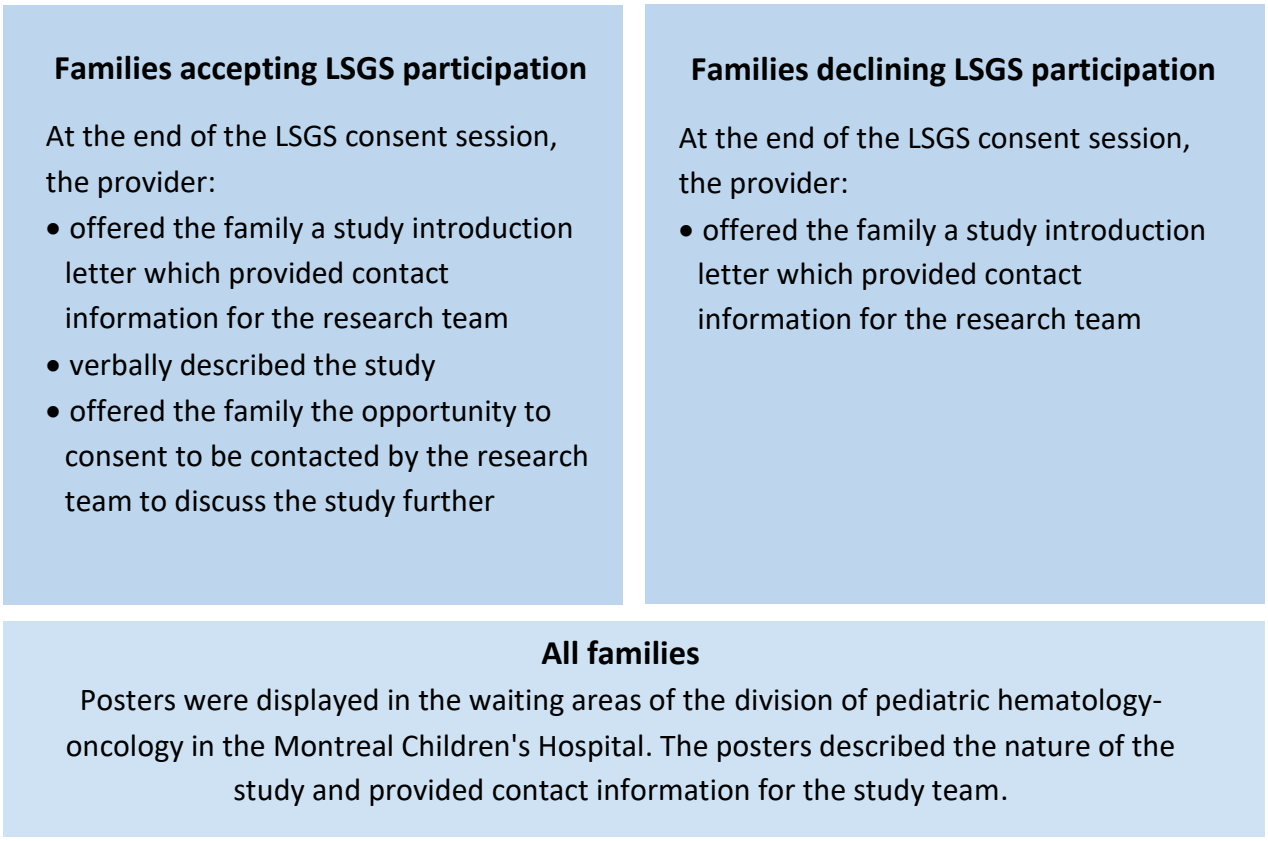

Figure 1 *– Recruitment methods for eligible families in practice. The differential recruitment of families accepting or declining LSGS was a deviation from the initial study protocol.*

A clinical research assistant (CRA; initials CB) in the division of pediatric hematology-oncology at the MCH aided in the recruitment process. The CRA was also a member of the LSGS study teams and was responsible for providing the LSGS consent sessions. At the end of the LSGS consent session, the CRA then briefly introduced eligible families to the present study. The eligibility criteria described in section 2.3.2. were designed to include both families who *accept* or *decline* participation in an LSGS study, as the perspectives of families declining LSGS are underexplored in the literature (discussed further in section 4.1.). However, after the present study began recruitment, the CRA indicated that they were not comfortable introducing the present study to families who declined LSGS. For that reason, recruitment methods were modified such that families declining LSGS were only provided a study introduction letter detailing the study and providing contact information for the study team. For families accepting LSGS, in addition to being provided the study introduction letter, the CRA discussed the present study with them and provided them an opportunity to be contacted within one to eight weeks to discuss the study further.

In addition to the active recruitment process detailed above, posters were displayed in the hematology-oncology waiting area of the MCH describing the study and providing contact information for the study team in both French and English. These posters emphasized that families who accepted or declined LSGS participation were eligible to participate in the present perspectives study, in an effort to recruit declining families.

2.3.4. Questionnaire design and piloting

The questionnaire designed for this study contained 36 items and is included in the appendix of this thesis. At the beginning of the questionnaire, participants were asked to identify which LSGS program they had been offered participation in and whether they had been offered LSGS prior to this program. The questionnaire also included two items that quantitatively assessed participant-perceived risk of a CPS. These items were included as previous LSGS exposure and/or increased perceived risk of a CPS may affect individuals' attitudes towards LSGS participation.

The primary aim of the questionnaire was to assess adolescents' and parents' motivations and concerns towards LSGS participation following a pediatric cancer diagnosis. To address this aim, the questionnaire included items that quantitatively assessed the personal importance of seven possible motivations and eight possible concerns using a 5-point Likert scale. The Likert scale included the following options: extremely unimportant, somewhat unimportant, neither important or unimportant, somewhat important and extremely important. The motivations and concerns assessed in the questionnaire were selected from the results of a scoping review of the literature (see section 2.1. for methods and section 3.1.4. for attitude-related results). Generally, motivations and concerns that were reported in ≥20% of the articles from the scoping review were quantitatively assessed in the questionnaire with three exceptions. First, an item assessing the personal importance of concerns about future insurance or employment discrimination was included. While employment discrimination was mentioned in <20% of the scoping review articles, it is often discussed in conjunction with insurance discrimination so these two potential concerns were assessed in the same item. Second, while the potential emotional impact of negative LSGS results was discussed both in terms of motivations (peace of mind) and concerns (disappointment about not receiving new information), one study reported disappointment in uninformative results as a harm experienced by some individuals after receiving LSGS results (Marron et al., 2016). Additionally, disappointment in uninformative results has been discussed in the context of parents of children with rare disease pursuing LSGS (Donohue et al., 2021; Mollison et al., 2020) and adults pursuing genetic testing for CPS-related reasons (O'Neill et al., 2009; van Dijk et al., 2006). To allow for comparisons with studies assessing attitudes after receiving LSGS results as well comparisons between related populations, the potential emotional impact of negative results was assessed as a concern. Third, concerns about physical invasiveness of LSGS participation were not assessed in the questionnaire. This concern was not considered relevant to the study population as the pediatric cancer LSGS research programs at the MUHC use biopsy samples that have already been collected and collect blood samples during clinically required blood draws.

In addition to these quantitative measures, the questionnaire also included three qualitative items designed to capture additional motivations and concerns that may not have been

reported in the literature thus far. Before beginning the motivations and concerns sections of the questionnaire, participants were asked “What was the main reason you chose to participate or not participate in genetic sequencing through this research program?”, followed by a free-text space to respond. Following each of the Likert scale sections for possible motivations and concerns, a free-text space was provided for participants to add their own personally important motivations or concerns.

One item assessing the balance between participant motivations and concerns was also included with the following response options: my motivations far outweigh my concerns, my motivations slightly outweigh my concerns, my motivations are equal to my concerns, my concerns slightly outweigh my motivations and my concerns far outweigh my motivations.

The secondary aim of the questionnaire was to collect clinical and sociodemographic information of participants. Two items collected clinical and sociodemographic characteristics and additional information was collected through chart review (see section 2.3.6.).

Efforts were made to establish face validity. The questionnaire was piloted with two ethicists, two genetic counsellors, two research assistants and four lay-people to identify any areas of potential confusion as well as approximate the amount of time required to complete it. All individuals involved in the piloting were provided a short summary of the study, similar to a consent session. These individuals were parents and/or individuals within the age range of potential parents from eligible families; individuals with non-medical professions were also included in an effort to mimic typical caregivers. Based on the feedback received during piloting, minor changes were made to emphasize that participants were not required to complete every question and to generally improve the grammar and clarity of items.

The wording of the questionnaire was slightly modified to create two versions, one for parent participants and one for adolescent participants. These modifications involved changes to phrasing (eg: “my child’s cancer” to “my cancer”), however the content of the questionnaire remained the same. Surveys were administered via electronic or paper copies in either French or English, depending on the participant’s preference.

2.3.5. Survey methods

After signing the consent form for this study, all participants were assigned a study identification number. Participants were identified using their study number on all subsequent study-related documents, including the questionnaire, to protect confidentiality.

The questionnaire was administered one time to consenting participants after they made a decision about participation in a LSGS research program at the MUHC and before they received any potential LSGS results. Questionnaire responses were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the Research Institute of the MUHC. REDCap is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009, 2019). Questionnaires that were completed in a paper format were entered into REDCap by study team members (MC and LR) and stored as a scanned PDF file, in addition to securely storing the paper copy, for data integrity.

Individuals who had not completed the questionnaire were sent two email reminders via REDCap after two and four weeks, respectively. Additionally, individuals who had not completed the questionnaire six weeks after receiving it were contacted by phone to follow up.

2.3.6. Chart review methods

For each participating patient or family, the following measures were collected from the affected child's electronic medical records: age, sex, citizenship, cancer diagnosis and time since diagnosis. Pedigrees, often collected during the LSGS consent session, were used to obtain: family history of related cancers, patient ethnicity and the number of biological siblings. As the LSGS studies are research initiatives, no reasons for participating in/declining LSGS are documented in patients' clinical charts.

2.3.7. Data analysis methods

Responses to questionnaire items were summarized using descriptive statistics due to the small number of respondents and exploratory nature of this study. Frequency distributions were used to describe responses to (1) Likert scale items evaluating personal importance of individual motivations and concerns, (2) items assessing balance of motivations and concerns and (3)

items assessing perceived likely causes of their/their child's cancer (MacFarlane et al., 2014). Sample mean and standard deviation were used to describe numerical values, including the child's age and the respondent's perceived likelihood of the cancer being related to a CPS. Mean and standard deviation were selected instead of median and range to avoid identification of exact patient ages within such a small sample population.

Free-text responses to qualitative items were individually coded by two reviewers (MC and MT) using content analysis and the frequency of each motivation or concern is reported (Krippendorff, 2019; Vaismoradi et al., 2013). Any conflicts in coding were discussed by the reviewers and, if no consensus was reached, resolved by a third reviewer (LR). Excel was used to code the responses since the number of participants was low and responses ranged from a few words to one sentence in length. Free-text responses were received in both French and English. All responses were assessed in their original language and assigned English codes by bilingual coders to reduce the possibility of translation as a source of error (Scholz et al., 2022).

Chapter 3: Results

3.1. Scoping review results

3.1.1. Selection of sources of evidence

The process of selection of sources of evidence is described in Figure 2 (Page et al., 2021). Searches of the four included databases yielded 2009 articles. Following the review of titles and abstracts for eligibility, 26 articles were identified for full-text screening.

During the full-text screening, articles were excluded for not assessing parent or adolescent attitudes (n = 7), assessing attitudes towards LSGS in adult cancer populations (n = 1), assessing attitudes towards LSGS in pediatric non-cancer populations (n = 1), assessing attitudes towards the return of LSGS results (n = 1) and assessing attitudes towards the use of non-LSGS genetic testing (n = 1). This resulted in 15 articles meeting the inclusion criteria of this review. The reference lists of these 15 articles were then reviewed, which resulted in the identification of two additional articles meeting inclusion criteria (Amendola et al., 2018; Howard Sharp et al., 2020).

The 17 articles identified via database searches and reference list review included two conference abstracts (Johnson et al., 2017; Ruiz et al., 2014) that reported on data sets which were later published in journal articles, already included in the 17 articles (Howard Sharp et al., 2020; Oberg et al., 2015). For this reason, these conference abstracts were each collated with the corresponding journal article and reported together as one unit, as per Cochrane systematic review guidelines (Higgins et al., 2022).

In sum, the database searches and review of reference lists yielded a total of 15 individual articles meeting inclusion criteria. Table 2 describes the characteristics of the included articles. Appendix Table 3 provides citations for the included articles and additional information, including attitude-related study aims, populations and methods.

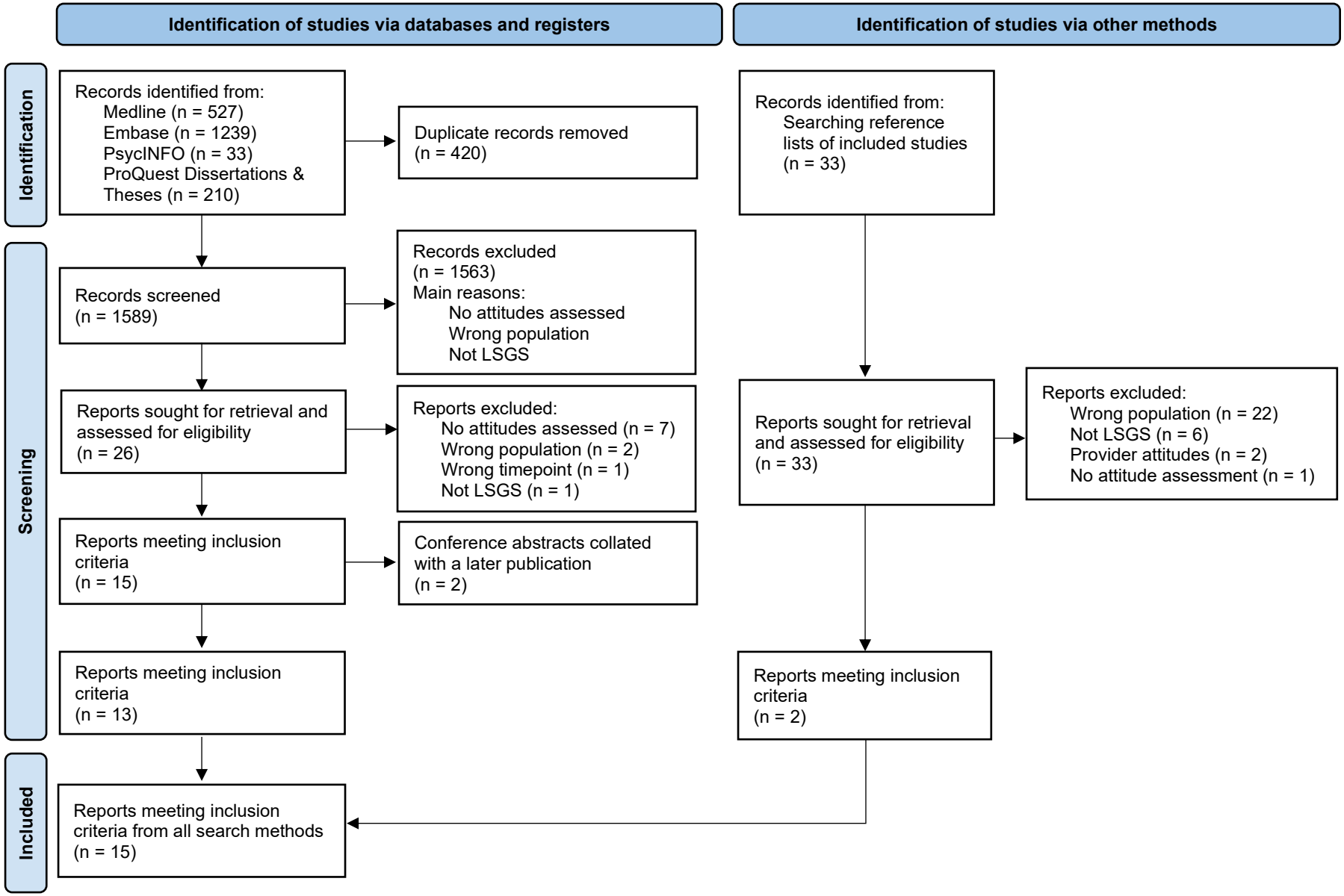

Figure 2 *– PRISMA flow diagram of the sources of evidence screening for the scoping review (Page et al., 2021).*

Characteristic	n (%)
Country of study	
United States	12 (80.0)
Australia	1 (6.7)
Denmark	1 (6.7)
Germany	1 (6.7)
Participants	
Parents of children with cancer	10 (66.7)
Parents of children with cancer and young adults with cancer	3 (20.0)
Families of children with cancer	2 (13.3)
LSGS decision of participants	
Participating in LSGS	8 (53.3)
Declining LSGS	4 (26.7)
Considering hypothetical LSGS	2 (13.3)
Participating in or declining LSGS	1 (6.7)
LSGS method	
Whole exome sequencing	6 (40.0)
Whole genome sequencing	7 (46.7)
Not specified	2 (13.3)
Tissue type(s) sequenced	
Tumor and germline tissue	9 (60.0)
Tumor tissue only	2 (13.3)
Germline tissue only	2 (13.3)
Unspecified, hypothetical scenarios of sequencing	2 (13.3)
Attitude assessment methods	
Interviews	6 (40.0)
Recorded main reason for declining during consent processes	4 (26.7)
Questionnaires	3 (20.0)
Focus groups	1 (6.7)
Mixed-methods	1 (6.7)
Context	
Clinical sequencing through a research program	7 (46.7)
Research program	5 (33.3)
Clinical trial	2 (13.3)
Clinical program	1 (6.7)
Year of publication	
2014-2015	2 (13.3)
2016-2017	4 (26.7)
2018-2019	6 (40.0)
2020-2021	3 (20.0)

Table 2 *– Characteristics of articles meeting the inclusion criteria of the scoping review (total n = 15 articles).*

3.1.2. What research has been done on attitudes of parents and adolescents towards LSGS for children and adolescents with cancer diagnoses?

The methods most frequently used to assess participant attitudes in the fifteen studies included in this review were interviews and recording individuals' main reason for declining LSGS during the consent process. Other methods used included questionnaires, focus groups and mixed-methods (observations of genetic counselling sessions and interviews). The majority of the studies included individuals that participated in LSGS, while the remaining studies included individuals that declined LSGS, were asked to consider a hypothetical LSGS program and a mixed cohort of individuals that participated in or declined LSGS.

3.1.3. What are the geographic, contextual (i.e. research or clinical) and participant characteristics of the sources of evidence identified?

The majority of the studies were conducted in the United States, with remaining studies conducted in Australia, Denmark and Germany. Together, two LSGS programs in the United States accounted for the majority of the publications: BASIC3 from Baylor College located in Texas and G4K from St. Jude Children's Research Hospital located in Tennessee.

Overall, the authors described the context in which participants were offered LSGS in a variety of ways including: clinical sequencing through a research program, research, clinical trial and clinical.

Of the fifteen publications, the majority included only parents as participants, while the remaining studies describe their participants as parents and young adults (young adults defined as 18-30 years of age) or families. The publications that included both parents and young adults as participants reported the attitudes of these groups in aggregate. None of the studies included in this review explicitly included adolescent participants.

3.1.4. What are the motivations and concerns reported by parents and adolescents within the sources of evidence identified?

As none of the studies included in this review explicitly included adolescent participants, this review will primarily summarize the parent perspectives reported in the included studies. However, adolescent attitudes towards LSGS were indirectly mentioned in the two studies that described their participants as families (Brozou et al., 2018; Howard Sharp et al., 2020). Both of these studies assessed main reasons for declining LSGS and reported families who declined LSGS due to the child, adolescent or young adult not wanting to participate. The G4K cohort reported six children/young adults who declined participation in LSGS, which accounted for 17.1% of the families that provided a reason for declining LSGS participation in their study (Howard Sharp et al., 2020). Similarly, Brozou and colleagues (2018) described eleven families' reasons for declining LSGS and reported one family where both parents wished to participate in LSGS but the adolescent patient declined. Due to the fact that children, adolescents and young adults that declined LSGS were reported separately from other attitudes summarized in these two studies, the remaining attitudes reported are presumed to be collected from parents.

A summary of the motivations and concerns reported in the included articles can be found in Table 3. An expanded version of this table can be found in the appendix (Appendix Table 5) with articles grouped by the LSGS participation decision of the study participants (ie: accepting LSGS, declining LSGS or considering hypothetical LSGS). For additional context, Appendix Table 6 describes motivations and concerns reported by studies of adolescent and parent attitudes towards LSGS in non-cancer pediatric populations.

Motivations		
Motivation	**Subcategory**	**Number of studies (%)**
Altruism	*Help other children, contribute to research*	8 (53.3)
Treatment	*Potential for improved treatment*	8 (53.3)
Information seeking	*Child's cancer genetics/CPS information*	7 (46.7)
	General information, not specified	5 (33.3)
	Other health information, secondary findings	4 (26.7)
	Family members' cancer risk	3 (20.0)
	Information for reproductive decisions	3 (20.0)
	About parent(s)	2 (13.3)
	About child/adolescent	1 (6.7)
Meaning making	*Wanting to know why*	5 (33.3)
Ability to prepare for the future	*Surveillance methods/prevention*	3 (20.0)
	Avoid being blindsided	2 (13.3)
	Additional genetic tests	1 (6.7)
Potential emotional impact	*Peace of mind, negative result*	3 (20.0)
	Relief from guilt, exculpatory	2 (13.3)
Parental responsibility	*Doing everything possible*	2 (13.3)
Concerns		
Concern	**Subcategory**	**Number of studies (%)**
Privacy	*Insurance discrimination*	5 (33.3)
	General privacy	4 (26.7)
	Employment discrimination	2 (13.3)
Feeling overwhelmed	*By cancer diagnosis and decisions*	4 (26.7)
Potential emotional impact	*General, not specified*	4 (26.7)
	Positive CPS results	2 (13.3)
	Guilt/blame	2 (13.3)
	Secondary findings	1 (6.7)
	Worse prognosis	1 (6.7)
	Disappointment, no new information	1 (6.7)
Invasiveness	*Tumor biopsy, skin biopsy, blood sample*	4 (26.7)
Conflict with beliefs	*Religious or cultural*	3 (20.0)
Child or young adult declined	*Child, adolescent or young adult declined LSGS*	2 (13.3)
No concerns	*General, not specified*	3 (20.0)
	About potential emotional impact	2 (13.3)

Table 3 *– Summary of the attitudes reported by articles included in the scoping review (total n = 15 articles).*

In terms of reported motivations, both altruism and the potential for improved treatment were reported in more than half of the included studies (n = 8 for each, 53.3%). Additionally, a preference for information, particularly information about the child/adolescents' cancer, was reported in seven of the included studies (n = 7, 46.7%). However, these motivations were largely reported by individuals who were participating in LSGS or considering hypothetical LSGS participation. The only two motivations reported among individuals who declined LSGS were altruism and the ability to prepare for the future by implementing prevention or surveillance methods (Mandrell et al., 2021).

In terms of reported concerns, insurance discrimination was reported in the highest number of articles (n = 5, 33.3%), followed by feeling overwhelmed at the time of LSGS recruitment, general privacy concerns, potential emotional impact (general, not specified) and physical invasiveness of the procedure (each n = 4, 26.7%). Notably, concerns about feeling overwhelmed and concerns about the potential emotional impact of receiving LSGS results (general, not specified) were reported only by individuals declining LSGS. Concerns about insurance discrimination and general privacy concerns were reported both by individuals participating in LSGS and individuals declining LSGS, in studies published between 2015 and 2021. The dates of these publications are notable as these studies were conducted in the United States after the 2008 implementation of the Genetic Information Nondiscrimination Act which offers protections against insurance and employment discrimination (Joly et al., 2013). Concerns about invasiveness as well as concerns about the potential emotional impact of results were reported by individuals from all decision categories (participating in LSGS, declining LSGS and considering hypothetical LSGS participation).

3.2. Study results

3.2.1. Recruitment results

Recruitment is summarized in Figure 3. Families were recruited between January 5, 2022 and August 12, 2022. While initial plans included a 12-month recruitment period, the Research Ethics Board approval process required more time than anticipated, leading to a delayed recruitment timeline. During the recruitment period, eighteen families were eligible to participate in this study. Five families declined LSGS and were therefore not actively recruited by the CRA (see section 2.3.3.). The remaining thirteen families consented to LSGS and were subsequently introduced to the present study by the CRA. Among these thirteen families, two consented to participate immediately and eleven provided consent to be contacted by the research team within one to eight weeks to discuss participation further. Of the eleven families that provided consent to be contacted at a later date, one ultimately did not meet inclusion criteria (non-cancer diagnosis) and one was considered inappropriate to recontact due to family circumstances. Of the remaining nine families that were recontacted at a later date, six families consented to participate and three families passively declined participation by not consenting in the required timeframe prior to receiving LSGS results. These six families, in addition to the two that consented upon first presentation, lead to a total of thirteen individuals from eight families that consented to participate. Families that passively declined frequently cited that they had not yet had time to consider participation or consult the consent form further. No families contacted the study team as a result of the posters displayed in the hematology-oncology waiting area of the MCH nor the study introduction letters provided to families declining LSGS.

Seven participants (53.9% of consented individuals) from five families (62.5% of consented families) completed the questionnaire within the required timeframe, before receiving any potential LSGS results. Notably, while four adolescents consented to participate, only one (25.0% of consented adolescents) completed the questionnaire. Participants included one parent-parent dyad (two parents from the same family) and one adolescent-parent dyad (an adolescent and a parent from the same family). Five participants (71.4%) completed the questionnaire in French, while two participants (28.6%) completed it in English.

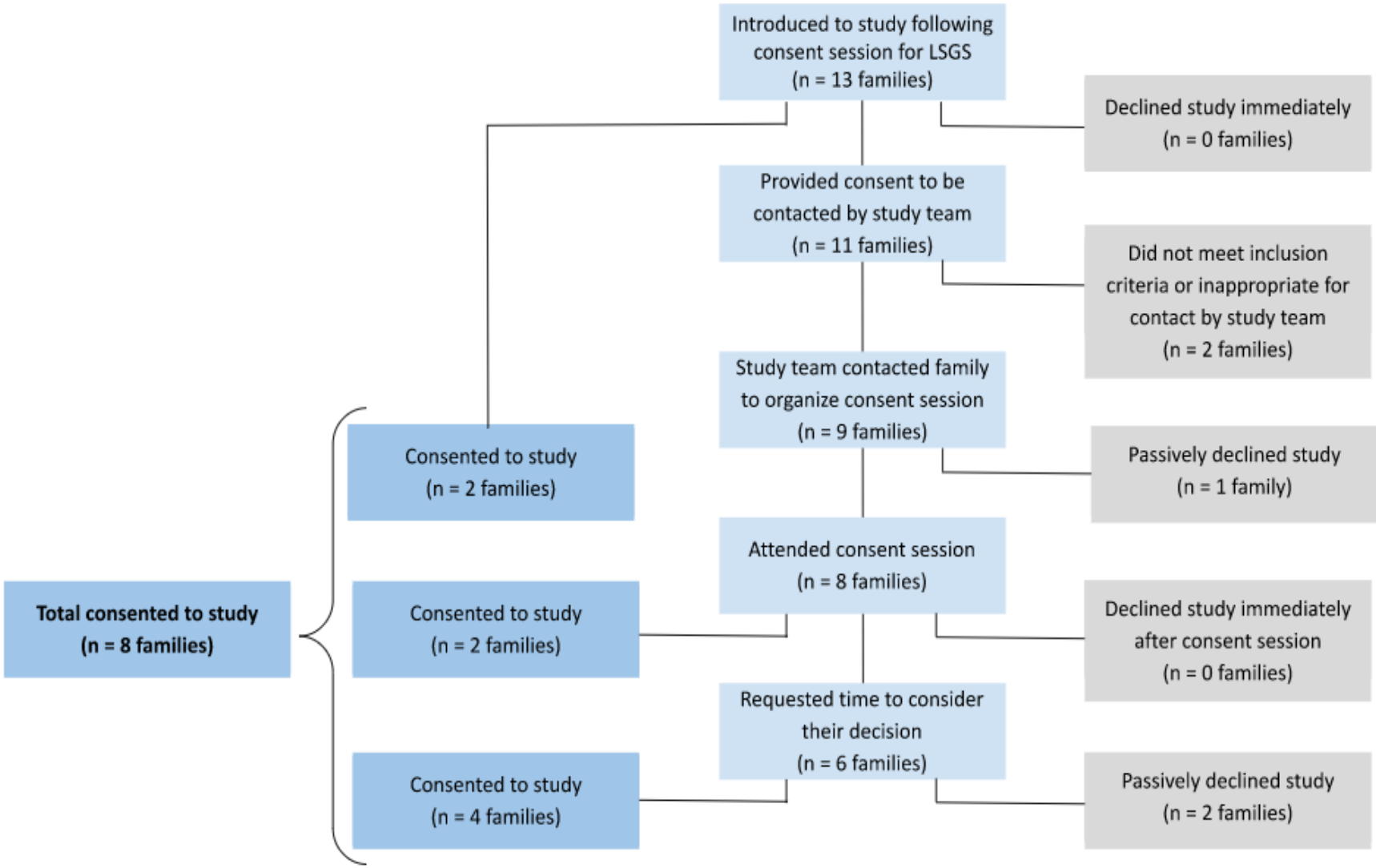

Figure 3 *– Summary of recruitment from the MUHC study. Recruitment was open from January 5, 2022 to August 12, 2022.*

3.2.2. Participant characteristics

Results reported in this section will be presented in aggregate to avoid identifying any participants. Participant characteristics are summarized in Table 4. All participants in this study had elected to participate in LSGS. Only one participant (14.3%) was an adolescent, the remaining participants were parents. The affected children from participating families spanned a broad range of ages with a mean age of 9.7 years (standard deviation: 6.3 years). Participants returned the study questionnaire a mean of 65.4 days after confirmation of diagnosis via pathology report (standard deviation: 30.9 days; date of most recent diagnosis was used for individuals with relapsed cancer), 50.9 days after consenting to an LSGS study (standard deviation: 14.9 days) and 33.0 days after initial contact by the study team for the present study (standard deviation: 14.2 days). Ethnicity was only reported in the electronic medical record of one of the five participating families and will therefore not be reported.

3.2.3. Questionnaire results

3.2.3.1. General questionnaire results

When presented with a multiple-choice item asking the respondent to identify the name of the LSGS program they had been offered participation in, the majority of participants (n = 5, 71.4%) responded that they did not remember the name of the program. Similarly, when asked if they had been offered LSGS prior to this program, over half of participants (n = 4, 57.1%) responded that they did not remember. Only one participant reported that they had been offered LSGS in the past.

3.2.3.2. Participant-perceived likelihood of a cancer predisposition syndrome

When asked about the likelihood that their/their child's cancer was genetic (hereditary) on a scale of 0 to 100, the mean response was 26.4 (standard deviation: 14.6), with responses ranging from 0 to 50. Four participants (57.2%) reported that they felt genetics was a likely cause of their/their child's cancer while two felt that it was an unlikely cause and one was uncertain about the contribution of genetics.

Characteristic		
Participant characteristics (total n = 7)		**n (%)**
Participant		
Parent		6 (85.7)
Adolescent		1 (14.3)
LSGS decision		
Participating		7 (100.0)
Declining		0 (0.0)
Child characteristics (total n = 5)		**n (%)**
Diagnosis		
Solid tumor		3 (60.0)
Brain tumor		1 (20.0)
Leukemia or lymphoma		1 (20.0)
Primary cancer or relapse		
Primary cancer		3 (60.0)
Relapse		2 (40.0)
Sex		
Female		2 (40.0)
Male		3 (60.0)
	mean (median)	**standard deviation (range)**
Age (years)		
	9.7	6.3
Time since diagnosis* (days)		
	65.4 (56.0)	30.9 (40 – 115)
Time since LSGS decision (days)		
	50.9 (42.0)	14.9 (41 – 75)

Table 4 *– Characteristics of participants from the MUHC study, including 7 participants from 5 families. *Time since diagnosis was calculated as the number of days between the date of a pathology report in the child's chart confirming a cancer diagnosis and the date of questionnaire completion.*

3.2.3.3. Qualitative questionnaire results: main reason for participating in LSGS

Six participants (85.7%) responded to the qualitative, open-ended item asking about their main reason for deciding to participate or not in LSGS. Some of the six respondents reported more than one reason. Altruism was mentioned by five (83.3%) respondents, often expressed as wanting to contribute to research and/or help future children diagnosed with cancer. Information seeking, particularly regarding the child's cancer and/or genetics, was mentioned by two respondents. Meaning making was also mentioned by two respondents.

The remaining two qualitative, open-ended items, which prompted respondents to write in additional motivations and concerns that were not addressed in the Likert scale items (see section 3.2.3.4.), received no responses.

3.2.3.4. Quantitative questionnaire results: motivations and concerns

All participants completed the Likert scale items assessing the personal importance of seven motivation-related and eight concern-related statements regarding their decision to participate in or decline LSGS. The frequency of Likert scale responses to these motivation- and concern-related items are summarized in Figure 4 and Figure 5.

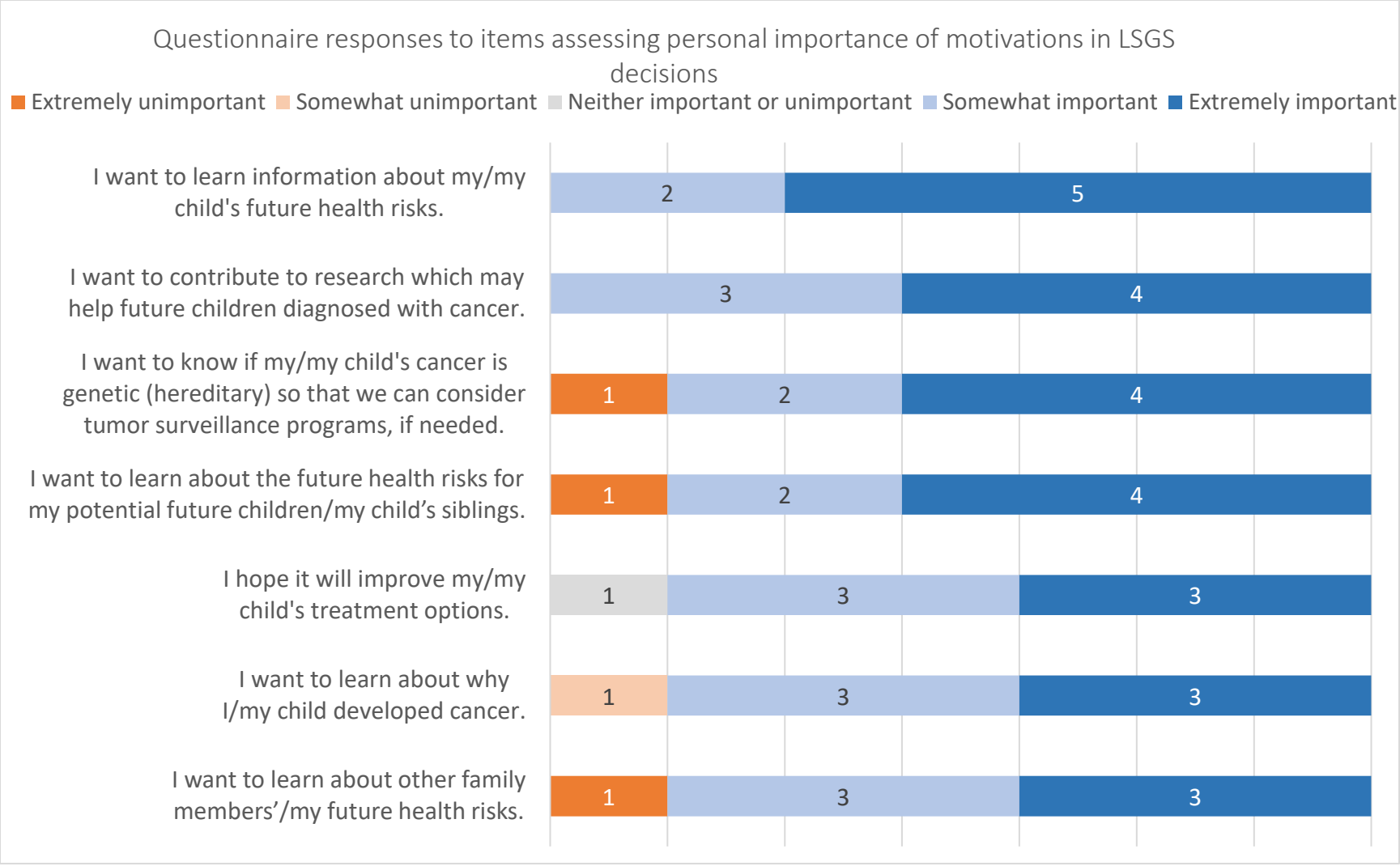

Figure 4 *– Frequency of Likert scale responses to motivation-related items. To account for differences in the language of adolescent and parent questionnaires, both phrasings have been included with the adolescent phrasing always appearing first (eg: I want to learn about my [adolescent]/my child's [parent] future health risks).*

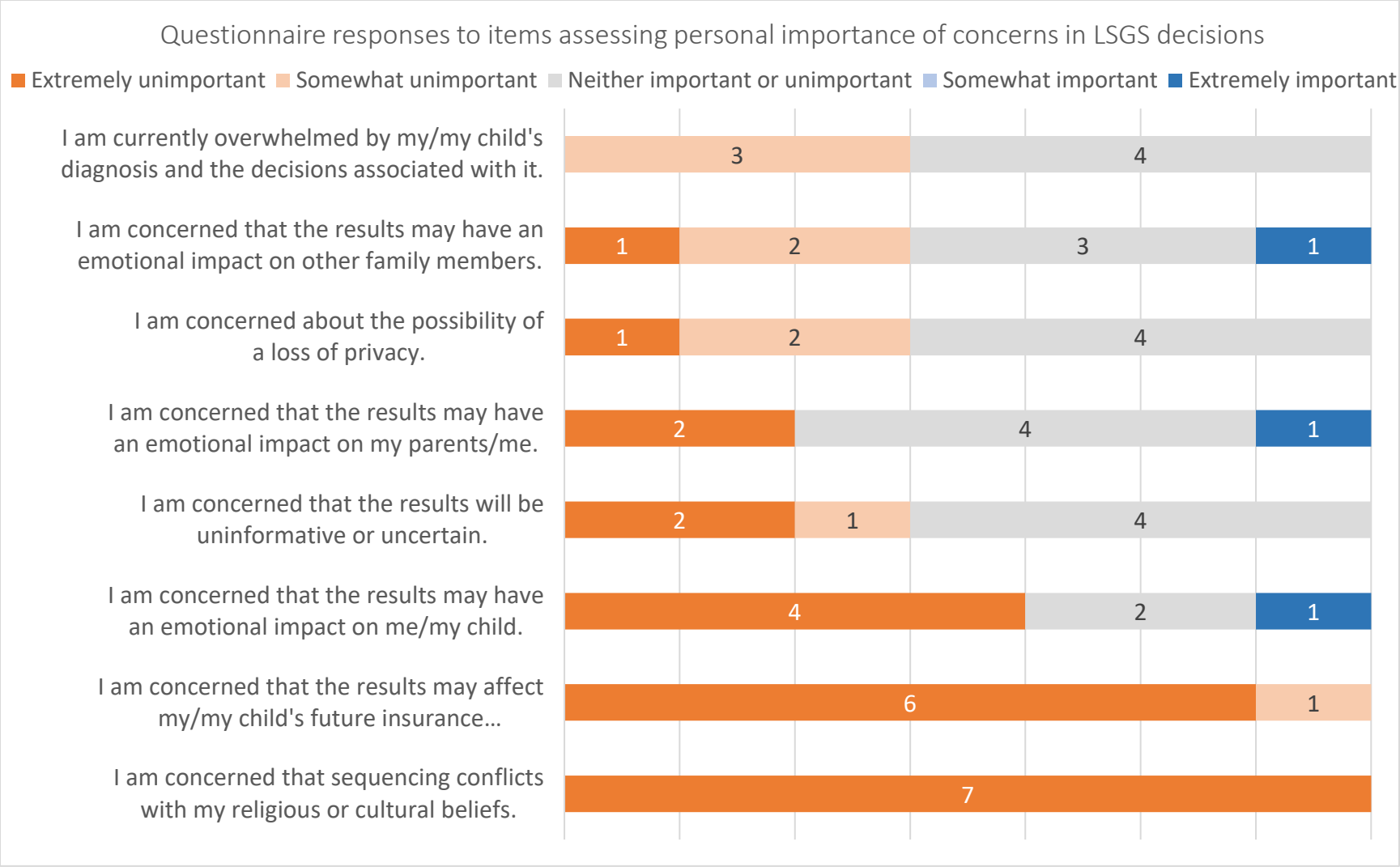

Figure 5 *– Frequency of Likert scale responses to concern-related items. To account for differences in the language of adolescent and parent questionnaires, both phrasings have been included with the adolescent phrasing always appearing first (eg: I am currently overwhelmed by my [adolescent]/my child's [parent] diagnosis).*

Overall, the most frequently selected responses for all motivations assessed were either "somewhat important" or "extremely important". "Extremely important" was the most frequently selected response for wanting to learn more about the affected child's future health risks (n = 5, 71.4%), wanting to contribute to research that may help future children (altruism), wanting to know if the child's cancer was related to a CPS and wanting to learn about the future health risks of the child's siblings (each n = 4, 57.1%). Notably, wanting to learn more about the affected child's future health risks and altruism were the only two statements selected by all participants as personally important (either "somewhat important" or "extremely important") in their decision-making. Additionally, when asked how personally important the potential that LSGS would improve the child's treatment options was in their decision, participants Likert scale responses ranged from "neither important or unimportant" to "extremely important". All other potential motivations assessed received a mixture of personally important and personally unimportant Likert-responses. Out of the seven motivations assessed, respondents reported that a mean of 6.3 (range 3 to 7) motivations were important (either "somewhat important" or "extremely important") when making their decision about LSGS.

In contrast, out of the eight possible concerns assessed, respondents reported that a mean of 0.4 (range 0 to 3) concerns were important (either "somewhat important" or "extremely important") when making their decision about LSGS. Six of the seven (85.7%) respondents reported that none of the eight concerns assessed were important (either "somewhat important" or "extremely important") when making their decision about LSGS; the remaining participant indicated that three of the concerns were "extremely important" in their decision (concerns about the potential emotional impact of LSGS results on the child, the parent and other family members). Overall, the most frequent responses for all concerns assessed ranged from "extremely unimportant" to "neither important or unimportant". All participants responded that the item regarding LSGS participation conflicting with religious or cultural beliefs was "extremely unimportant" in their decision-making. Similarly, all participants reported that concerns about LSGS results affecting the child's future insurance or employment opportunities were personally unimportant (either "somewhat unimportant" or "extremely unimportant") in their decision-making.

All participants (100.0%) responded that the statement “Overall, I have no concerns about participating in sequencing through a research program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS)” was true for them. When asked to select the answer that best described the balance between their motivations and concerns on a Likert scale ranging from “my concerns far outweigh my motivations” to “my motivations far outweigh my concerns”, six respondents (85.7%) reported that their motivations far outweighed their concerns while one respondent reported that their motivations and their concerns were equal (Figure 6).

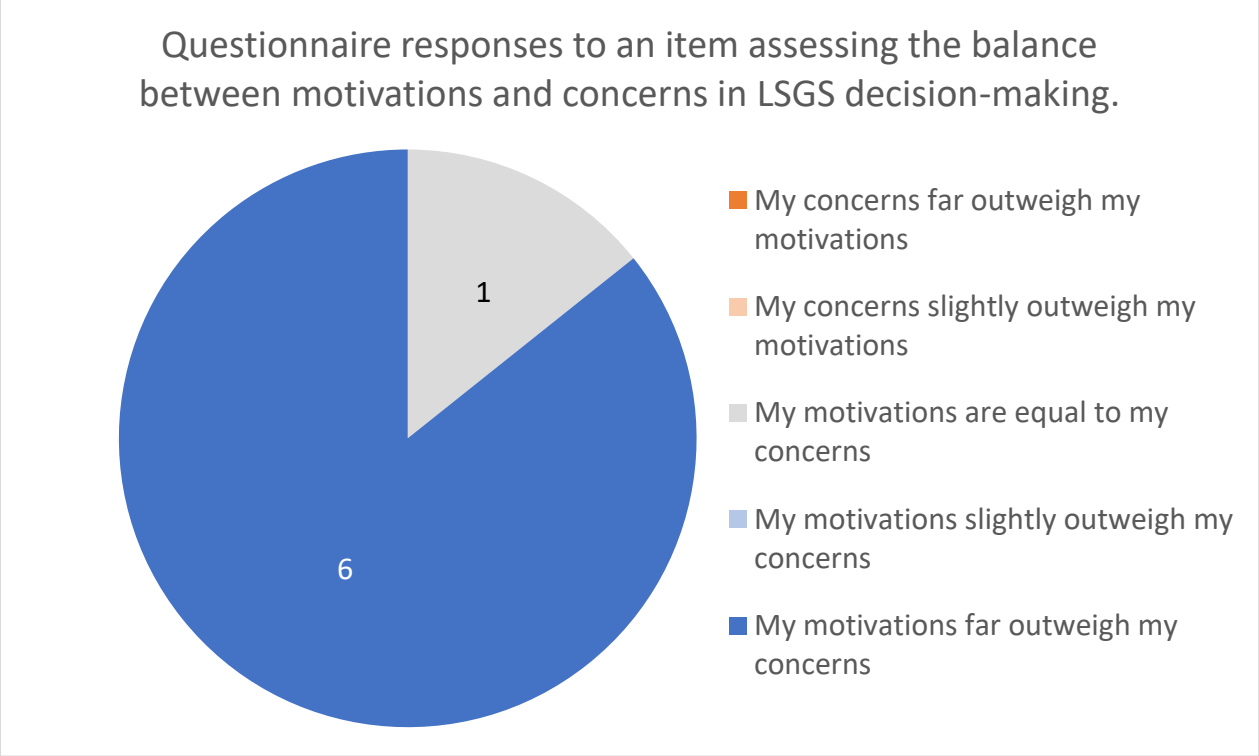

Figure 6 *– Frequency of responses to an item assessing participants’ balance between motivations and concerns.*

Chapter 4: Discussion

The combined use of a scoping review and a single site study allowed for motivations and concerns to be collected from the literature and assessed among individuals participating in LSGS at the MUHC following a pediatric cancer diagnosis.

4.1. Scoping review discussion

The scoping review aimed to describe the current landscape of research on adolescent and parent attitudes towards participating in or declining LSGS following a pediatric cancer diagnosis. The review was able to identify articles assessing the motivations and concerns of parents of children with cancer who participated in or declined LSGS, thereby allowing the identification of themes which were then included in the questionnaire design for the MUHC study. However, this review revealed that there was very little data on perspectives from adolescents with cancer. The review also found that attitudes from families offered LSGS in a Canadian context were absent and the motivations and concerns of decliners were underexplored.

Adolescents were not the primary population of any of the publications included in the review, however, two publications noted child, adolescent and/or young adults patients who declined participation in LSGS (see section 3.1.4.; Brozou et al., 2018; Howard Sharp et al., 2020). Adolescents and young adults (often defined as 18-30 years) with cancer are generally understood to have low participation rates in clinical trials as well as research involving patient reported outcomes (M. E. Burke et al., 2007; Keegan & Parsons, 2018; Vlooswijk et al., 2022). A study involving 16 adolescents and young adults (12-22 years of age) with cancer who declined non-LSGS health research participation in Canada and the US found that the most frequently reported reasons for not participating were concerns that the study would take too much time (45%) and having too much to think about at the time of enrollment (36%) (Read et al., 2009). Similarly, among 765 young adult cancer survivors who provided a reason for declining participation in a patient-reported outcomes study in the Netherlands, the most frequently reported reasons included: not interested in the research, not wanting to think about cancer, too busy, questionnaire is too long/too personal/difficult and not considering themselves a

young adult cancer patient (Vlooswijk et al., 2022). These reasons may also relate to the low participation rates among adolescents with cancer in attitude-related studies and the absence of adolescent participants in this scoping review.

None of the publications included in the scoping review explored motivations or concerns of parents or adolescents offered LSGS in a Canadian context. The vast majority of publications identified in this review were conducted in the United States with a high proportion of the publications resulting from two LSGS programs in the southern United States (BASIC3 and G4K). For this reason, the results of this review may be heavily influenced by the healthcare and social contexts of the United States as well as by the specific structure of the two prominent LSGS programs. In particular, LSGS research programs in the United States may provide participants access to LSGS free of cost, which may hold additional incentive in the context of their private healthcare system (Pace et al., 2003). It is notable, however, that this effect may also be present in mixed private-public healthcare systems, as Lynch and colleagues (2021) reported that parents in Australia who had been offered LSGS for their critically ill child free of cost through a research initiative perceived that they were receiving special access to a technology they otherwise may not have been able to afford.

The scoping review also found that the attitudes of families declining LSGS were underexplored. Among the five publications included in this review that assessed attitudes of families who declined sequencing, four of these publications only recorded the families' *main reason* for declining during the LSGS consent process. Recording only the main concern does not account for the fact that individuals may have multi-faceted motivations and/or concerns when considering LSGS participation. In contrast, all of the included articles that assessed attitudes of families that accepted LSGS allowed participants to identify multiple motivations and/or concerns and demonstrated that participants weighed more than one motivation and/or concern while deciding about LSGS participation. When an individual declines participation in a LSGS program, some research recruitment protocols dictate that the study team ask why they decided to decline and record the response (Howard Sharp et al., 2020; Scollon et al., 2014). Recruitment of families declining LSGS to attitude-related studies may be difficult; individuals that decline LSGS may be more likely to also decline research on patient and family

perspectives. If recruitment of LSGS decliners for attitude-focused studies is low, researchers may retrospectively review the reasons for declining recorded by the study team during LSGS recruitment, as this provides some insight without requiring any additional time input from the family (Sanderson et al., 2022). While this method provides some insight into declining individuals attitudes towards LSGS, it also limits knowledge to their main reason for declining as determined by a third-party, without exploring their other possible motivations and concerns.

4.1.1. Continued screening of the literature

The scoping review includes articles that were published as of the date the search was performed (June 16, 2021), however, in an effort to be thorough, the literature has been intermittently screened for relevant articles published between June 2021 and September 2022. In that timeframe, two additional articles have been published that assessed adolescent and/or parent attitudes towards participating in or declining LSGS following a pediatric cancer diagnosis. The first of these publications included a sample of adolescents with cancer and parents of children with cancer who were participating in LSGS in the United States; the authors reported questionnaire responses to items assessing their motivations for LSGS participation, collected between 2015 and 2017 (Sedig et al., 2022). The second publication included parents of children with cancer who had either accepted or declined LSGS participation in the Netherlands and were interviewed between 2019 and 2021 (Bon et al., 2022). Both publications reported altruism and the potential for improved treatment to be relevant motivations among their participants, which is congruent with the findings of the scoping review. Sedig and colleagues (2022) reported that adolescents considered their doctor's recommendation to participate and their family's wishes for them to participate to also be motivations. Additionally, Bon and colleagues (2022) assessed concerns; they reported that parents who had elected to participate in LSGS rarely mentioned concerns. Individuals who had declined LSGS each cited different reasons, including feeling overwhelmed, concerns about the psychological impact, conflict with religious beliefs and concerns about privacy (Bon et al., 2022). These findings are also consistent with the scoping review results.

4.1.2. The role of LSGS consent processes

The aim of informed consent processes in genetic testing, including LSGS, is to inform potential participants (or their parents) of relevant information about the test including procedure, purpose, potential results as well as potential risks and benefits so they may make a voluntary, autonomous decision about participation (Burke & Clarke, 2016; McGuire & Beskow, 2010; Ormond et al., 2021). While individuals may decline LSGS at multiple timepoints (at initial introduction, during consent sessions, post-consent sessions or withdrawal of consent), consent sessions involve in-depth discussion of LSGS and are often an opportunity for providers to observe individuals' attitudes towards LSGS.

Aspects of the consent process may affect individual's attitudes towards LSGS, including the format, timing and setting of the consent session as well as the identity of the provider leading the consent session. These aspects are addressed in the appendix, within the section titled "Relevant aspects of LSGS consent processes". It is important to note that variation in consent processes across the publications included in the scoping review may have affected individuals' attitudes towards LSGS.

4.1.3. Scoping review limitations

In an effort to compare the included articles, this review focused on parent and adolescent decisions regarding LSGS participation as having two possible outcomes: participating or declining. The use of these binary outcomes may be a limitation of this review as they do not represent the full reality of LSGS decisions; in practice, LSGS participation has a nuanced range of options in terms of participation and return of results. For example, some programs allow participants to select which tissues types are sequenced (germline and/or tumor) and which specific categories of results they wish to receive, including medically actionable non-cancer findings and carrier status for recessive disorders (Byrjalsen et al., 2018; Henderson et al., 2014; Mandrell et al., 2021; Scollon et al., 2014). However, nuanced information about LSGS decisions was reported to varying degrees among the articles included in the scoping review, and was therefore not included in this analysis.

Additionally, decisions regarding LSGS participation may not be made within the same timeframe for all individuals. Interviews with 33 adults who declined genetic testing for cancer predisposition 1-10 years previously (mean 2.9 years) found that, while the interviewees had been labeled “decliners” by the researchers, some individuals reported that they had not yet made their decision (Keogh et al., 2017). Some individuals who were reported as declining among the review articles may have been taking additional time to consider their decision.

4.2. Study discussion

This study aimed to describe the motivations and concerns that were considered important to parents and adolescents when making a decision regarding research LSGS at the MUHC following a pediatric cancer diagnosis. This study also aimed to describe the clinical and sociodemographic characteristics of families currently offered research LSGS at the MUHC following a pediatric cancer diagnosis. Although the study had a small number of participants, responses were analyzed in a descriptive manner to provide what may be among the first reports of attitudes of families in a Canadian context towards participating in research LSGS after a pediatric cancer diagnosis.

This work complements that of Fernandez et al. (2014), who previously reported on attitudes of parents of children with rare disease or cancer towards the return of LSGS results in a Canadian context. Their study focused on parental attitudes related to the right to participate in LSGS, the right to receive results and result types of interest. The authors explored reasons the respondents believed research programs should offer to return LSGS results to families as well as issues respondents felt families should consider when making a decision about whether or not to receive LSGS results. As these questions were all framed in a hypothetical, population-level manner, the results of their study contributed valuable information on parents’ broader views of LSGS access. The study presented in this thesis contributes complementary information on motivations and concerns that were *personally* important to parents when they were making the decision about their own child’s LSGS participation.

I hypothesized that parents and adolescents who have been offered LSGS participation after a pediatric cancer diagnosis may express both motivations and concerns about LSGS

participation. In response to an open-ended item assessing respondents' main reason for participating in LSGS, altruism, information seeking and meaning making were all reported as motivations. Authors Snell and Helén (2020) describe the concept of "meaning-making" as the use of health information to construct a personal narrative of health or illness; responses in this category referred to wanting to understand the cause of the cancer. Additionally, in response to Likert scale items in our study, respondents most frequently reported all of the motivations assessed as personally important (either "somewhat important" or "extremely important") in their decision to participate in LSGS. Information seeking about the child's future health risks and the future health risks of the child's sibling, altruism and wanting to know if the child's cancer was related to a CPS were most frequently reported as being "extremely important" motivations. These findings closely reflect those of the scoping review also described in this thesis, which found that the most frequently cited motivations were altruism, the potential for improved treatment and information seeking, particularly regarding information about the child's cancer genetics or CPS-related information (see section 3.1.4.).

Regarding concerns, only one respondent indicated that any of the concerns assessed were personally important in their LSGS decision-making. All respondents reported that concerns about LSGS conflicting with their religious or cultural beliefs were extremely unimportant in their LSGS decision-making. This finding is consistent with the results of the scoping review which found no publications reporting these concerns among families participating in LSGS (Appendix Table 5). All respondents reported that concerns related to insurance or employment discrimination were personally unimportant (either "somewhat unimportant" or "extremely unimportant") in their LSGS decision-making. This finding is discordant with the findings from the scoping review, where insurance discrimination was the most frequently reported concern across the included studies. However, this finding is concordant with recent work by Sedig and colleagues (2022; discussed in section 4.1.1.) who found that parents of children with cancer who had elected to participate in LSGS in the United States reported that any potential concerns about insurability had not influenced their LSGS decision-making.

All participants responded that the statement "Overall, I have no concerns about participating in sequencing through a research program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS)"

was true for them. This finding is consistent with the results of the scoping review, where having no concerns about LSGS was one of the most frequently reported concern categories among studies that included individuals participating in LSGS (Appendix Table 5).

While feeling overwhelmed was among the most frequently reported concern categories in the scoping review, none of the participants in this study reported it as important in their decision-making regarding LSGS. This, as well as the overall lack of personal importance of concerns in respondents' decision-making, may be related to the fact that all of the respondents in this study had elected to participate in LSGS. Respondents may have been less overwhelmed and/or held more positive views of LSGS than individuals that declined LSGS, declined participation in this study or consented to this study but did not complete the questionnaire.

I hypothesized that individuals that elect to participate in LSGS may report that their motivations outweigh their concerns. When reporting the balance between their motivations and concerns, the majority of respondents indicated that their motivations far outweighed their concerns. This is consistent with findings from other studies assessing the attitudes of parents of children with cancer who elected to participate in LSGS. McCarthy and colleagues' (2020) reported that all individuals interviewed described their decision to participate as an "easy decision to make". Similarly, Oberg and colleagues' (2018) found that the majority of questionnaire respondents felt that even a small chance that their child would benefit from LSGS "outweigh[ed] all the other risks of participating" and Sedig et al (2022) reported that some interviewees mentioned that potential benefits outweighed any potential drawbacks.

Notably, this study had a low adolescent participation rate: four adolescents consented to participate, however only one ultimately completed the questionnaire. As discussed in section 4.1., adolescents with cancer generally have lower participation rates in research than parents of children with cancer (Read et al., 2009). All adolescents in this study were still in active treatment, with varying side effects from treatment. Additionally, while the eligibility criteria of this study were purposefully designed to allow multiple members of the same family (eg: affected adolescent and/or multiple parents) to participate in an effort to explore intrafamilial

differences in attitudes, the sample size of this study was not sufficient to explore any potential intrafamilial differences.

4.2.1. Study limitations

4.2.1.1. Recruitment limitations

This study was limited in its ability to recruit families who declined LSGS. Specifically, the differential recruitment of families participating in or declining LSGS (described in section 2.3.3.) was a limitation, as individuals participating in LSGS were actively recruited while individuals declining LSGS were passively recruited. This placed the burden of contact on individuals declining LSGS. During the recruitment period for this study, five families declined participation in LSGS programs at the MUHC after attending a LSGS consent session.

It is important to note that since the introduction for this study occurred after families attended a LSGS consent session, families who declined LSGS participation before attending a consent session were not approached for recruitment. Posters were placed in waiting areas in an effort to recruit families that declined LSGS before attending a consent session; however, no families contacted the study team as a result of the recruitment posters. In light of the fact that the majority of respondents were unable to recall whether they had previously been offered LSGS and the name of the LSGS study they were currently participating in (see section 3.2.3.1.), it is possible that potential participants saw the study posters but were unaware that they had been offered participation in LSGS, especially for families who had declined LSGS participation. Additionally, individuals who declined LSGS had the added burden of contacting the study team.

4.2.1.2. Results limitations

Most notably, the results of this study are limited by the small number of respondents and the fact that no responses were from participants who declined LSGS. Additionally, participation and questionnaire completion were potentially biased towards families who were less overwhelmed at the time of contact. Families who passively declined this study stated that they simply had not had time to consider participation. There were also six consented individuals who did not complete the questionnaire, suggesting there was an interest to participate but

ultimately the study requirements were not completed. Families were recruited for participation in this study during what is understandably a busy and emotionally-sensitive time; non-therapeutic research may not have been their main priority. The importance of the individual motivations and concerns assessed in the questionnaire may therefore be different in families who are more overwhelmed at the time they are approached about LSGS participation.

Similarly, the interpretation of adolescent attitudes was limited by the fact that only one adolescent completed the questionnaire. For this reason, adolescent attitudes were not reported separately from the aggregate responses. Efforts were made to collect additional adolescent perspectives however, as discussed in section 4.1., adolescents with cancer are generally understood to have low research participation rates. It is also notable that adolescents who were eligible to participate in this study were often actively receiving cancer treatment, which may further reduce the time and energy they have available to complete a questionnaire.

Finally, with respect to timepoints, the study only measured attitudes at one timepoint which may be a limitation as decisions (and their related motivations and concerns) may change over time (Bartley et al., 2020; Mallinger et al., 2006; Schupmann et al., 2021). Since the questionnaires were completed on average 50.9 days after consenting to an LSGS study, the responses are retrospective in nature and therefore subject to recall bias (Althubaiti, 2016). These responses may represent participants' motivations and concerns at the time of completing the questionnaire rather than at the time of LSGS decision. The delay in questionnaire completion/return was due to the time required to contact, consent and enroll families in a manner that was sensitive to their recent cancer diagnosis and associated life circumstances. Additionally, some families completed paper copies of the questionnaire at home; the return of paper questionnaires required further coordination and additional time.

Chapter 5: Conclusions and future directions

Adolescent and parent attitudes towards LSGS should be considered when performing health technology assessments, developing policies and designing LSGS programs in research and clinical settings. Understanding adolescent and parent perspectives is an essential step towards ensuring LSGS is offered in a patient- and family-centered manner.

This thesis combined the results of a scoping review and single centre study at the MUHC on adolescent and parent attitudes towards LSGS following a pediatric cancer diagnosis. By combining a scoping review and a single centre study, this thesis was able to describe the current body of literature on adolescent and parent attitudes towards LSGS following a pediatric cancer diagnosis, including the attitudes reported thus far, and assess the level of personal importance of those attitudes among seven individuals participating in LSGS at the MUHC following a pediatric cancer diagnosis.

More research is needed to understand the perspectives of adolescents with cancer and parents of children with cancer towards LSGS in a Canadian context. The findings presented in this thesis suggest that individuals participating in LSGS at the MUHC after a pediatric cancer diagnosis generally experience multiple motivations and may also experience concerns, however their motivations ultimately outweigh their concerns. Collecting responses from additional individuals would increase the reliability of this research and assess whether these findings are generalizable to the larger population of adolescents with cancer and parents of children with cancer participating in LSGS at the MUHC. A larger number of respondents may allow for the identification of attitudes that are associated with clinical or sociodemographic factors, such as participant age, race/ethnicity or cancer diagnosis. For example, previous research has shown that race/ethnicity may be related to differing participation rates in LSGS and other types of genetic testing (Borges et al., 2016; Howard Sharp et al., 2020). Consideration should be given to possible intra-familial differences in attitudes towards LSGS, in order to better understand the role of adolescents in shared decision-making. Additionally, the effects of consent processes on individuals' attitudes towards LSGS should also be considered,

in order to complement research exploring the impact of consent processes on LSGS-related knowledge (Johnson et al., 2019).

Future research, at the MUHC and more broadly, should aim to engage groups whose perspectives are currently underrepresented in the literature, especially individuals that decline LSGS and adolescents, in a manner that is suitable and sensitive to their situations. This may include approaching individuals that decline LSGS and/or adolescents after a longer period of time, especially if they are feeling overwhelmed at the time of approach for LSGS. Including individuals that decline LSGS and/or adolescents into study design processes may provide insight on ways to more effectively and appropriately engage these communities in research related to their perspectives (MacLeod et al., 2017; Teela et al., 2022). Including patients in health research planning and design may result in increased enrollment and decreased attrition (Domecq et al., 2014).

Chapter 6: References

Akhavanfard, S., Padmanabhan, R., Yehia, L., Cheng, F., & Eng, C. (2020). Comprehensive germline genomic profiles of children, adolescents and young adults with solid tumors. *Nature Communications*. https://doi.org/10.1038/s41467-020-16067-1

Althubaiti, A. (2016). Information bias in health research: Definition, pitfalls, and adjustment methods. *Journal of Multidisciplinary Healthcare*, *9*, 211–217. https://doi.org/10.2147/JMDH.S104807

Amendola, L. M., Robinson, J. O., Hart, R., Biswas, S., Lee, K., Bernhardt, B. A., East, K., Gilmore, M. J., Kauffman, T. L., Lewis, K. L., Roche, M., Scollon, S., Wynn, J., & Blout, C. (2018). Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. *Journal of Genetic Counseling*, *27*(5), 1220–1227. https://doi.org/10.1007/s10897-018-0243-7

Anderson, J. A., Meyn, M. S., Shuman, C., Zlotnik Shaul, R., Mantella, L. E., Szego, M. J., Bowdin, S., Monfared, N., & Hayeems, R. Z. (2017). Parents perspectives on whole genome sequencing for their children: Qualified enthusiasm? *Journal of Medical Ethics*, *43*(8), 535–539. https://doi.org/10.1136/medethics-2016-103564

Arksey, H., & O'Malley, L. (2005). Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology*, *8*(1), 19–32. https://doi.org/10.1080/1364557032000119616

Aromataris, E., & Munn, Z. (Eds.). (2020). *JBI Manual for Evidence Synthesis*. JBI. https://doi.org/10.46658/JBIMES-20-01

Australian Genomics Health Alliance Acute Care Flagship. (2020). Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System. *JAMA*, *323*(24), 2503–2511. https://doi.org/10.1001/jama.2020.7671

Bandopadhayay, P., & Meyerson, M. (2018). Landscapes of childhood tumours. *Nature*, *555*(7696), 316–317. https://doi.org/10.1038/d41586-018-01648-4

Bartley, N., Best, M., Jacobs, C., Juraskova, I., Newson, A. J., Savard, J., Meiser, B., Ballinger, M. L., Thomas, D. M., Biesecker, B., & Butow, P. (2020). Cancer patients' views and understanding of genome sequencing: A qualitative study. *Journal of Medical Genetics*, *57*(10), 671–676. https://doi.org/10.1136/jmedgenet-2019-106410

Berrios, C., James, C. A., Raraigh, K., Bollinger, J., Murray, B., Tichnell, C., Applegate, C. D., & Bergner, A. L. (2018). Enrolling Genomics Research Participants through a Clinical Setting: The Impact of Existing Clinical Relationships on Informed Consent and Expectations for Return of Research Results. *Journal of Genetic Counseling*, *27*(1), 263–273. https://doi.org/10.1007/s10897-017-0143-2

Bertier, G., Cambon-Thomsen, A., & Joly, Y. (2018). Is it research or is it clinical? Revisiting an old frontier through the lens of next-generation sequencing technologies. *European Journal of Medical Genetics*, *61*(10), 634–641. https://doi.org/10.1016/j.ejmg.2018.04.009

Bertier, G., Carrot-Zhang, J., Ragoussis, V., & Joly, Y. (2016). Integrating precision cancer medicine into healthcare-policy, practice, and research challenges. *Genome Medicine*, *8*(1), 108. https://doi.org/10.1186/s13073-016-0362-4

Bertier, G., & Joly, Y. (2018). Clinical exome sequencing in France and Quebec: What are the challenges? What does the future hold? *Life Sciences, Society and Policy*, *14*(1), 17. https://doi.org/10.1186/s40504-018-0081-2

Bick, D., Jones, M., Taylor, S. L., Taft, R. J., & Belmont, J. (2019). Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. *Journal of Medical Genetics*, *56*(12), 783–791. https://doi.org/10.1136/jmedgenet-2019-106111

Boland, L., Graham, I. D., Légaré, F., Lewis, K., Jull, J., Shephard, A., Lawson, M. L., Davis, A., Yameogo, A., & Stacey, D. (2019). Barriers and facilitators of pediatric shared decision-making: A systematic review. *Implementation Science: IS*, *14*(1), 7. https://doi.org/10.1186/s13012-018-0851-5

Bon, S. B. B., Wouters, R. H. P., Hol, J. A., Jongmans, M. C. J., van den Heuvel-Eibrink, M. M., & Grootenhuis, M. A. (2022). Parents' experiences with large-scale sequencing for genetic predisposition in pediatric renal cancer: A qualitative study. *Psycho-Oncology*, *n/a*(n/a). https://doi.org/10.1002/pon.6016

Borle, K., Kopac, N., Dragojlovic, N., Rodriguez Llorian, E., Friedman, J. M., Elliott, A. M., & Lynd, L. D. (2022). Where is genetic medicine headed? Exploring the perspectives of Canadian genetic professionals on future trends using the Delphi method. *European Journal of Human Genetics*, 1–9. https://doi.org/10.1038/s41431-021-01017-2

Bos, W., & Bunnik, E. M. (2022). Informed consent practices for exome sequencing: An interview study with clinical geneticists in the Netherlands. *Molecular Genetics & Genomic Medicine*, *10*(3), e1882. https://doi.org/10.1002/mgg3.1882

Brozou, T., Taeubner, J., Velleuer, E., Dugas, M., Wieczorek, D., Borkhardt, A., & Kuhlen, M. (2018). Genetic predisposition in children with cancer – affected families' acceptance of Trio-WES. *European Journal of Pediatrics*, *177*(1), 53–60. https://doi.org/10.1007/s00431-017-2997-6

Budin-Ljøsne, I., Bentzen, H. B., Solbakk, J. H., & Myklebost, O. (2015). Genome sequencing in research requires a new approach to consent. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke*, *135*(22), 2031–2032. https://doi.org/10.4045/tidsskr.15.0944

Bunnik, E. M., Janssens, A. C. J. W., & Schermer, M. H. N. (2015). Personal utility in genomic testing: Is there such a thing? *Journal of Medical Ethics*, *41*(4), 322–326. https://doi.org/10.1136/medethics-2013-101887

Burke, K., & Clarke, A. (2016). The challenge of consent in clinical genome-wide testing. *Archives of Disease in Childhood*, *101*(11), 1048–1052. https://doi.org/10.1136/archdischild-2013-304109

Burke, M. E., Albritton, K., & Marina, N. (2007). Challenges in the recruitment of adolescents and young adults to cancer clinical trials. *Cancer*, *110*(11), 2385–2393. https://doi.org/10.1002/cncr.23060

Byrjalsen, A., Hansen, T. V. O., Stoltze, U. K., Mehrjouy, M. M., Barnkob, N. M., Hjalgrim, L. L., Mathiasen, R., Lautrup, C. K., Gregersen, P. A., Hasle, H., Wehner, P. S., Tuckuviene, R., Sackett, P. W., Laspiur, A. O., Rossing, M., Marvig, R. L., Tommerup, N., Olsen, T. E., Scheie, D., … Wadt, K. (2020). Nationwide germline whole genome sequencing of 198 consecutive pediatric cancer patients reveals a high incidence of cancer prone

syndromes. *PLOS Genetics*, *16*(12), e1009231. https://doi.org/10.1371/journal.pgen.1009231

Byrjalsen, A., Stoltze, U. K., Castor, A., & Wahlberg, A. (2020). Germline whole genome sequencing in pediatric oncology in Denmark-Practitioner perspectives. *Molecular Genetics & Genomic Medicine*, *8*(8), e1276. https://doi.org/10.1002/mgg3.1276

Byrjalsen, A., Stoltze, U., Wadt, K., Hjalgrim, L. L., Gerdes, A.-M., Schmiegelow, K., & Wahlberg, A. (2018). Pediatric cancer families' participation in whole-genome sequencing research in Denmark: Parent perspectives. *European Journal of Cancer Care*, *27*(6), e12877. https://doi.org/10.1111/ecc.12877

Cacciotti, C., Fleming, A., & Ramaswamy, V. (2020). Advances in the molecular classification of pediatric brain tumors: A guide to the galaxy. *The Journal of Pathology*, *251*(3), 249–261. https://doi.org/10.1002/path.5457

Callard, F., Rose, D., & Wykes, T. (2012). Close to the bench as well as at the bedside: Involving service users in all phases of translational research. *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy*, *15*(4), 389–400. https://doi.org/10.1111/j.1369-7625.2011.00681.x

Canadian Institutes of Health Research. (2011). *Canada's Strategy for Patient-Oriented Research—CIHR*. https://cihr-irsc.gc.ca/e/44000.html#a1.1

Chan, K. K. W., Cheung, M. C., Regier, D. A., Hay, A., Louie, A. V., Cheung, W. Y., Tarride, J.-E., Udayakumar, S., & Mittmann, N. (2021). The Past, Present, and Future of Economic Evaluations of Precision Medicine at the Committee for Economic Analyses of the

Canadian Cancer Trials Group. *Current Oncology (Toronto, Ont.)*, *28*(5), 3649–3658. https://doi.org/10.3390/curroncol28050311

Chang, W., Brohl, A. S., Patidar, R., Sindiri, S., Shern, J. F., Wei, J. S., Song, Y. K., Yohe, M. E., Gryder, B., Zhang, S., Calzone, K. A., Shivaprasad, N., Wen, X., Badgett, T. C., Miettinen, M., Hartman, K. R., League-Pascual, J. C., Trahair, T. N., Widemann, B. C., … Khan, J. (2016). MultiDimensional ClinOmics for Precision Therapy of Children and Adolescent Young Adults with Relapsed and Refractory Cancer: A Report from the Center for Cancer Research. *Clinical Cancer Research*, *22*(15), 3810–3820. https://doi.org/10.1158/1078-0432.CCR-15-2717

Clayton, E. W. (2015). How much control do children and adolescents have over genomic testing, parental access to their results, and parental communication of those results to others? *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics*, *43*(3), 538. https://doi.org/10.1111/jlme.12296

Coyne, I., O'Mathúna, D. P., Gibson, F., Shields, L., Leclercq, E., & Sheaf, G. (2016). Interventions for promoting participation in shared decision-making for children with cancer. *The Cochrane Database of Systematic Reviews*, *11*, CD008970. https://doi.org/10.1002/14651858.CD008970.pub3

Damodaran, S., Berger, M. F., & Roychowdhury, S. (2015). Clinical tumor sequencing: Opportunities and challenges for precision cancer medicine. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting*, e175-182. https://doi.org/10.14694/EdBook_AM.2015.35.e175

Donohue, K. E., Dolan, S. M., Watnick, D., Gallagher, K. M., Odgis, J. A., Suckiel, S. A., Teitelman, N., Gelb, B. D., Kenny, E. E., Wasserstein, M. P., Horowitz, C. R., & Bauman, L. J. (2021). Hope versus reality: Parent expectations of genomic testing. *Patient Education and Counseling*, *104*(8), 2073–2079. https://doi.org/10.1016/j.pec.2021.01.030

Dumez, V., & Pomey, M.-P. (2019). From Medical Paternalism to Care Partnerships: A Logical Evolution Over Several Decades. In M.-P. Pomey, J.-L. Denis, & V. Dumez (Eds.), *Patient Engagement: How Patient-provider Partnerships Transform Healthcare Organizations* (pp. 9–16). Springer International Publishing. https://doi.org/10.1007/978-3-030-14101-1_2

Durno, C., Ercan, A. B., Bianchi, V., Edwards, M., Aronson, M., Galati, M., Atenafu, E. G., Abebe-Campino, G., Al-Battashi, A., Alharbi, M., Azad, V. F., Baris, H. N., Basel, D., Bedgood, R., Bendel, A., Ben-Shachar, S., Blumenthal, D. T., Blundell, M., Bornhorst, M., … Tabori, U. (2021). Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *39*(25), 2779–2790. https://doi.org/10.1200/JCO.20.02636

Fangusaro, J., & Bandopadhayay, P. (2021). Advances in the classification and treatment of pediatric brain tumors. *Current Opinion in Pediatrics*, *33*(1), 26–32. https://doi.org/10.1097/MOP.0000000000000975

Fernandez, C. V., Bouffet, E., Malkin, D., Jabado, N., O'Connell, C., Avard, D., Knoppers, B. M., Ferguson, M., Boycott, K. M., Sorensen, P. H., Orr, A. C., Robitaille, J. M., & McMaster, C. R. (2014). Attitudes of parents toward the return of targeted and incidental genomic

research findings in children. *Genetics in Medicine*, *16*(8), 633–640. https://doi.org/10.1038/gim.2013.201

Fiala, E. M., Jayakumaran, G., Mauguen, A., Kennedy, J. A., Bouvier, N., Kemel, Y., Fleischut, M. H., Maio, A., Salo-Mullen, E. E., Sheehan, M., Arnold, A. G., Latham, A., Carlo, M. I., Cadoo, K., Murkherjee, S., Slotkin, E. K., Trippett, T., Glade Bender, J., Meyers, P. A., … Walsh, M. F. (2021). Prospective pan-cancer germline testing using MSK-IMPACT informs clinical translation in 751 patients with pediatric solid tumors. *Nature Cancer*, *2*, 357–365. https://doi.org/10.1038/s43018-021-00172-1

Food and Drug Administration. (2019, May 28). *Clinical Research Versus Medical Treatment*. FDA; FDA. https://www.fda.gov/patients/clinical-trials-what-patients-need-know/clinical-research-versus-medical-treatment

Forrest, S. J., Geoerger, B., & Janeway, K. A. (2018). Precision medicine in pediatric oncology. *Current Opinion in Pediatrics*, *30*(1), 17–24. https://doi.org/10.1097/MOP.0000000000000570

Freed, A. S., Gruß, I., McMullen, C. K., Leo, M. C., Kauffman, T. L., Porter, K. M., Muessig, K. R., Eubanks, D., Goddard, K. A. B., Wilfond, B. S., & Liles, E. G. (2021). A decision aid for additional findings in genomic sequencing: Development and pilot testing. *Patient Education and Counseling*, *104*(5), 960–968. https://doi.org/10.1016/j.pec.2020.10.038

Gagnon, M.-P., Desmartis, M., Gagnon, J., St-Pierre, M., Gauvin, F.-P., Rhainds, M., Lepage-Savary, D., Coulombe, M., Dipankui, M. T., & Légaré, F. (2014). Introducing the patient's perspective in hospital health technology assessment (HTA): The views of HTA producers, hospital managers and patients. *Health Expectations: An International*

Journal of Public Participation in Health Care and Health Policy, *17*(6), 888–900. https://doi.org/10.1111/hex.12010

Gattuso, J., Johnson, L. M., Pritchard, M., Walker, B., Hamilton, K., Valdez, J., Mandrell, B., & Nichols, K. (2018, November). Reasons, hopes, risks and expectations expressed by parents consenting to genomic sequencing for their child. *50th Congress of the International Society of Paediatric Oncology (SIOP)*. https://doi.org/10.1002/pbc.27455

Gröbner, S. N., Worst, B. C., Weischenfeldt, J., Buchhalter, I., Kleinheinz, K., Rudneva, V. A., Johann, P. D., Balasubramanian, G. P., Segura-Wang, M., Brabetz, S., Bender, S., Hutter, B., Sturm, D., Pfaff, E., Hübschmann, D., Zipprich, G., Heinold, M., Eils, J., Lawerenz, C., … Pfister, S. M. (2018). The landscape of genomic alterations across childhood cancers. *Nature*, *555*(7696), 321–327. https://doi.org/10.1038/nature25480

Grootens-Wiegers, P., Hein, I. M., van den Broek, J. M., & de Vries, M. C. (2017). Medical decision-making in children and adolescents: Developmental and neuroscientific aspects. *BMC Pediatrics*, *17*, 120. https://doi.org/10.1186/s12887-017-0869-x

Grover, S. A., Berman, J. N., Chan, J. A., Deyell, R. J., Eisenstat, D. D., Fernandez, C. V., Grundy, P. E., Hawkins, C., Irwin, M. S., Jabado, N., Jones, S. J., Moran, M., Rassekh, S. R., Shlien, A., Sinnett, D., Sorensen, P. H., Sullivan, P. J., Taylor, M. D., Villani, A., … on behalf of the Terry Fox PROFYLE Consortium. (2020). Abstract 5413: Terry Fox PRecision Oncology For Young peopLE (PROFYLE): A Canadian precision medicine program for children, adolescents and young adults with hard-to-treat cancer. *Cancer Research*, *80*(16_Supplement), 5413. https://doi.org/10.1158/1538-7445.AM2020-5413

Guan, Y.-F., Li, G.-R., Wang, R.-J., Yi, Y.-T., Yang, L., Jiang, D., Zhang, X.-P., & Peng, Y. (2012). Application of next-generation sequencing in clinical oncology to advance personalized treatment of cancer. *Chinese Journal of Cancer*, *31*(10), 463–470. https://doi.org/10.5732/cjc.012.10216

Halley, M. C., Young, J. L., Fernandez, L., Kohler, J. N., Undiagnosed Diseases Network, Bernstein, J. A., Wheeler, M. T., & Tabor, H. K. (2022). Perceived utility and disutility of genomic sequencing for pediatric patients: Perspectives from parents with diverse sociodemographic characteristics. *American Journal of Medical Genetics. Part A*, *188*(4), 1088–1101. https://doi.org/10.1002/ajmg.a.62619

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., & Duda, S. N. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*, *95*, 103208. https://doi.org/10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Hayeems, R. Z., Luca, S., Assamad, D., Bhatt, A., & Ungar, W. J. (2021). Utility of Genetic Testing from the Perspective of Parents/Caregivers: A Scoping Review. *Children (Basel, Switzerland)*, *8*(4). https://doi.org/10.3390/children8040259

Henderson, G. E., Wolf, S. M., Kuczynski, K. J., Joffe, S., Sharp, R. R., Parsons, D. W., Knoppers, B. M., Yu, J.-H., & Appelbaum, P. S. (2014). The Challenge of Informed Consent and Return

of Results in Translational Genomics: Empirical Analysis and Recommendations. *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics*, *42*(3), 344–355. https://doi.org/10.1111/jlme.12151

Hitchcock, E. C., Study, C., & Elliott, A. M. (2020). Shortened consent forms for genome-wide sequencing: Parent and provider perspectives. *Molecular Genetics & Genomic Medicine*, *8*(7), e1254. https://doi.org/10.1002/mgg3.1254

Howard Sharp, K. M., Jurbergs, N., Ouma, A., Harrison, L., Gerhardt, E., Taylor, L., Hamilton, K., McGee, R. B., Nuccio, R., Quinn, E., Hines-Dowell, S., Kesserwan, C., Sunkara, A., Gattuso, J. S., Pritchard, M., Mandrell, B., Relling, M. V., Haidar, C. E., Kang, G., … Nichols, K. E. (2020). Factors Associated with Declining to Participate in a Pediatric Oncology Next Generation Sequencing Study. *JCO Precision Oncology*, *4*, 202–211. https://doi.org/10.1200/PO.19.00213

INESSS. (2017). INESSS. http://www.inesss.qc.ca/

Janeway, K. A., Place, A. E., Kieran, M. W., & Harris, M. H. (2013). Future of Clinical Genomics in Pediatric Oncology. *Journal of Clinical Oncology*, *31*(15), 1893–1903. https://doi.org/10.1200/JCO.2012.46.8470

Johnson, L.-M., Hamilton, K. V., Valdez, J. M., Knapp, E., Baker, J. N., & Nichols, K. E. (2017). Ethical considerations surrounding germline next-generation sequencing of children with cancer. *Expert Review of Molecular Diagnostics*, *17*(5), 523–534. https://doi.org/10.1080/14737159.2017.1316665

Johnson, L.-M., Sykes, A. D., Lu, Z., Valdez, J. M., Gattuso, J., Gerhardt, E., Hamilton, K. V., Harrison, L. W., Hines-Dowell, S. J., Jurbergs, N., McGee, R. B., Nuccio, R., Ouma, A. A.,

Pritchard, M., Quinn, E. A., Baker, J. N., Mandrell, B. N., & Nichols, K. E. (2019). Speaking genomics to parents offered germline testing for cancer predisposition: Use of a 2-visit consent model. *Cancer*, *125*(14), 2455–2464. https://doi.org/10.1002/cncr.32071

Johnson, L.-M., Valdez, J. M., Quinn, E. A., Sykes, A. D., McGee, R. B., Nuccio, R., Hines-Dowell, S. J., Baker, J. N., Kesserwan, C., Nichols, K. E., & Mandrell, B. N. (2017). Integrating next-generation sequencing into pediatric oncology practice: An assessment of physician confidence and understanding of clinical genomics. *Cancer*, *123*(12), 2352–2359. https://doi.org/10.1002/cncr.30581

Joly, Y., Ngueng Feze, I., & Simard, J. (2013). Genetic discrimination and life insurance: A systematic review of the evidence. *BMC Medicine*, *11*, 25. https://doi.org/10.1186/1741-7015-11-25

Keegan, T. H. M., & Parsons, H. M. (2018). Adolescent angst: Enrollment on clinical trials. *Hematology. American Society of Hematology. Education Program*, *2018*(1), 154–160. https://doi.org/10.1182/asheducation-2018.1.154

Keogh, L. A., Niven, H., Rutstein, A., Flander, L., Gaff, C., & Jenkins, M. (2017). Choosing not to undergo predictive genetic testing for hereditary colorectal cancer syndromes: Expanding our understanding of decliners and declining. *Journal of Behavioral Medicine*, *40*(4), 583–594. https://doi.org/10.1007/s10865-016-9820-0

Kesserwan, C., Friedman Ross, L., Bradbury, A. R., & Nichols, K. E. (2016). The Advantages and Challenges of Testing Children for Heritable Predisposition to Cancer. *American Society of Clinical Oncology Educational Book*, *36*, 251–269. https://doi.org/10.1200/EDBK_160621

Khater, F., Vairy, S., Langlois, S., Dumoucel, S., Sontag, T., St-Onge, P., Bittencourt, H., Dal Soglio, D., Champagne, J., Duval, M., Leclerc, J.-M., Laverdiere, C., Tran, T. H., Patey, N., Ellezam, B., Perreault, S., Piché, N., Samson, Y., Teira, P., … Sinnett, D. (2019). Molecular Profiling of Hard-to-Treat Childhood and Adolescent Cancers. *JAMA Network Open*, *2*(4), e192906. https://doi.org/10.1001/jamanetworkopen.2019.2906

Kinsey, S. E., & Picton, S. V. (2021). Childhood cancer in high resource settings. *Cancer Epidemiology*, *71*(Pt B), 101838. https://doi.org/10.1016/j.canep.2020.101838

Kline, C. N., Joseph, N. M., Grenert, J. P., van Ziffle, J., Talevich, E., Onodera, C., Aboian, M., Cha, S., Raleigh, D. R., Braunstein, S., Torkildson, J., Samuel, D., Bloomer, M., Campomanes, A. G. de A., Banerjee, A., Butowski, N., Raffel, C., Tihan, T., Bollen, A. W., … Solomon, D. A. (2017). Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro-Oncology*, *19*(5), 699–709. https://doi.org/10.1093/neuonc/now254

Kraft, S. A., Porter, K. M., Duenas, D. M., Guerra, C., Joseph, G., Lee, S. S.-J., Shipman, K. J., Allen, J., Eubanks, D., Kauffman, T. L., Lindberg, N. M., Anderson, K., Zepp, J. M., Gilmore, M. J., Mittendorf, K. F., Shuster, E., Muessig, K. R., Arnold, B., Goddard, K. A. B., & Wilfond, B. S. (2021). Participant Reactions to a Literacy-Focused, Web-Based Informed Consent Approach for a Genomic Implementation Study. *AJOB Empirical Bioethics*, *12*(1), 1–11. https://doi.org/10.1080/23294515.2020.1823907

Krippendorff, K. (2019). *Content Analysis: An Introduction to Its Methodology*. SAGE Publications, Inc. https://doi.org/10.4135/9781071878781

Ku, C. S., Cooper, D. N., Ziogas, D. E., Halkia, E., Tzaphlidou, M., & Roukos, D. H. (2013). Research and clinical applications of cancer genome sequencing. *Current Opinion in Obstetrics & Gynecology*, *25*(1), 3–10. https://doi.org/10.1097/GCO.0b013e32835af17c

Kuhlen, M., & Borkhardt, A. (2015). Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. *European Journal of Pediatrics*, *174*(8), 987–997. https://doi.org/10.1007/s00431-015-2565-x

Levac, D., Colquhoun, H., & O'Brien, K. K. (2010). Scoping studies: Advancing the methodology. *Implementation Science*, *5*(1), 69. https://doi.org/10.1186/1748-5908-5-69

Levenseller, B. L., Soucier, D. J., Miller, V. A., Harris, D., Conway, L., & Bernhardt, B. A. (2014). Stakeholders' Opinions on the Implementation of Pediatric Whole Exome Sequencing: Implications for Informed Consent. *Journal of Genetic Counseling*, *23*(4), 552–565. https://doi.org/10.1007/s10897-013-9626-y

Lewis, K. L., Han, P. K. J., Hooker, G. W., Klein, W. M. P., Biesecker, L. G., & Biesecker, B. B. (2015). Characterizing Participants in the ClinSeq Genome Sequencing Cohort as Early Adopters of a New Health Technology. *PLOS ONE*, *10*(7), e0132690. https://doi.org/10.1371/journal.pone.0132690

Lin, B., Gutman, T., Hanson, C. S., Ju, A., Manera, K., Butow, P., Cohn, R. J., Dalla-Pozza, L., Greenzang, K. A., Mack, J., Wakefield, C. E., Craig, J. C., & Tong, A. (2020). Communication during childhood cancer: Systematic review of patient perspectives. *Cancer*, *126*(4), 701–716. https://doi.org/10.1002/cncr.32637

Lockwood, C., dos Santos, K. B., & Pap, R. (2019). Practical Guidance for Knowledge Synthesis: Scoping Review Methods. *Asian Nursing Research*, *13*(5), 287–294. https://doi.org/10.1016/j.anr.2019.11.002

Ma, X., Liu, Y., Liu, Y., Alexandrov, L. B., Edmonson, M. N., Gawad, C., Zhou, X., Li, Y., Rusch, M. C., Easton, J., Huether, R., Gonzalez-Pena, V., Wilkinson, M. R., Hermida, L. C., Davis, S., Sioson, E., Pounds, S., Cao, X., Ries, R. E., … Zhang, J. (2018). Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature*, *555*(7696), 371–376. https://doi.org/10.1038/nature25795

MacFarlane, I. M., Veach, P. M., & LeRoy, B. S. (2014). Quantitative Data Analysis: I've Got Data, How Do I Get Answers? In I. M. MacFarlane, P. McCarthy Veach, & B. S. LeRoy (Eds.), *Genetic Counseling Research: A Practical Guide* (p. 0). Oxford University Press. https://doi.org/10.1093/med/9780199359097.003.0007

Malek, J., Pereira, S., Robinson, J. O., Gutierrez, A. M., Slashinski, M. J., Parsons, D. W., Plon, S. E., & McGuire, A. L. (2019). Responsibility, culpability, and parental views on genomic testing for seriously ill children. *Genetics in Medicine*, *21*(12), Article 12. https://doi.org/10.1038/s41436-019-0570-6

Malek, J., Slashinski, M. J., Robinson, J. O., Gutierrez, A. M., Parsons, D. W., Plon, S. E., McCullough, L. B., & McGuire, A. L. (2017). Parental Perspectives on Whole Exome Sequencing in Pediatric Cancer: A Typology of Perceived Utility. *JCO Precision Oncology*, *1*. https://doi.org/10.1200/PO.17.00010

Mallinger, J. B., Shields, C. G., Griggs, J. J., Roscoe, J. A., Morrow, G. R., Rosenbluth, R. J., Lord, R. S., & Gross, H. (2006). Stability of decisional role preference over the course of cancer therapy. *Psycho-Oncology*, *15*(4), 297–305. https://doi.org/10.1002/pon.954

Malvezzi, M., Santucci, C., Alicandro, G., Carioli, G., Boffetta, P., Ribeiro, K. B., Levi, F., La Vecchia, C., Negri, E., & Bertuccio, P. (2021). Childhood cancer mortality trends in the Americas and Australasia: An update to 2017. *Cancer*, *127*(18), 3445–3456. https://doi.org/10.1002/cncr.33642

Mandrell, B. N., Gattuso, J. S., Pritchard, M., Caples, M., Howard Sharp, K. M., Harrison, L., Ouma, A. A., Valdez, J. M., Johnson, L.-M., & Nichols, K. E. (2021). Knowledge Is Power: Benefits, Risks, Hopes, and Decision-Making Reported by Parents Consenting to Next-Generation Sequencing for Children and Adolescents with Cancer. *Seminars in Oncology Nursing*, 151167. https://doi.org/10.1016/j.soncn.2021.151167

Marron, J. M., DuBois, S. G., Bender, J. G., Kim, A., Crompton, B. D., Meyer, S. C., Janeway, K. A., & Mack, J. W. (2016). Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: The Individualized Cancer Therapy (iCat) experience. *Pediatric Blood & Cancer*, *63*(11), 1974–1982. https://doi.org/10.1002/pbc.26137

McCullough, L. B., Slashinski, M. J., McGuire, A. L., Street, R. L., Eng, C. M., Gibbs, R. A., Parsons, D. W., & Plon, S. E. (2016). Is Whole Exome Sequencing an Ethically Disruptive Technology? Perspectives of Pediatric Oncologists and Parents of Pediatric Patients with Solid Tumors. *Pediatric Blood & Cancer*, *63*(3), 511–515. https://doi.org/10.1002/pbc.25815

McGuire, A. L., & Beskow, L. M. (2010). INFORMED CONSENT IN GENOMICS AND GENETIC RESEARCH. *Annual Review of Genomics and Human Genetics*, *11*, 361–381. https://doi.org/10.1146/annurev-genom-082509-141711

Mody, R. J., Prensner, J. R., Everett, J., Parsons, D. W., & Chinnaiyan, A. M. (2017). Precision medicine in pediatric oncology: Lessons learned and next steps. *Pediatric Blood & Cancer*, *64*(3), e26288. https://doi.org/10.1002/pbc.26288

Mody, R. J., Wu, Y.-M., Lonigro, R. J., Cao, X., Roychowdhury, S., Vats, P., Frank, K. M., Prensner, J. R., Asangani, I., Palanisamy, N., Dillman, J. R., Rabah, R. M., Kunju, L. P., Everett, J., Raymond, V. M., Ning, Y., Su, F., Wang, R., Stoffel, E. M., … Chinnaiyan, A. M. (2015). Integrative Clinical Sequencing in the Management of Refractory or Relapsed Cancer in Youth. *JAMA*, *314*(9), 913–925. https://doi.org/10.1001/jama.2015.10080

Mollison, L., O'Daniel, J. M., Henderson, G. E., Berg, J. S., & Skinner, D. (2020). Parents' perceptions of personal utility of exome sequencing results. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *22*(4), 752–757. https://doi.org/10.1038/s41436-019-0730-8

Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

National Health Service. (2019). *The NHS Long Term Plan*. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

Newman, S., Nakitandwe, J., Kesserwan, C. A., Azzato, E. M., Wheeler, D. A., Rusch, M., Shurtleff, S., Hedges, D. J., Hamilton, K. V., Foy, S. G., Edmonson, M. N., Thrasher, A., Bahrami, A., Orr, B. A., Klco, J. M., Gu, J., Harrison, L. W., Wang, L., Clay, M. R., … Nichols, K. E. (2021). Genomes for Kids: The Scope of Pathogenic Mutations in Pediatric Cancer Revealed by Comprehensive DNA and RNA Sequencing. *Cancer Discovery*, *11*(12), 3008–3027. https://doi.org/10.1158/2159-8290.CD-20-1631

Oberg, J. A., Bender, J. L. G., Cohn, E. G., Morris, M., Ruiz, J., Chung, W. K., Appelbaum, P. S., Kung, A. L., & Levine, J. M. (2015). Overcoming challenges to meaningful informed consent for whole genome sequencing in pediatric cancer research. *Pediatric Blood & Cancer*, *62*(8), 1374–1380. https://doi.org/10.1002/pbc.25520

Oberg, J. A., Glade Bender, J. L., Sulis, M. L., Pendrick, D., Sireci, A. N., Hsiao, S. J., Turk, A. T., Dela Cruz, F. S., Hibshoosh, H., Remotti, H., Zylber, R. J., Pang, J., Diolaiti, D., Koval, C., Andrews, S. J., Garvin, J. H., Yamashiro, D. J., Chung, W. K., Emerson, S. G., … Kung, A. L. (2016). Implementation of next generation sequencing into pediatric hematology-oncology practice: Moving beyond actionable alterations. *Genome Medicine*, *8*(1), 133. https://doi.org/10.1186/s13073-016-0389-6

Oberg, J. A., Ruiz, J., Ali-Shaw, T., Schlechtweg, K. A., Ricci, A., Kung, A. L., Chung, W. K., Appelbaum, P. S., Glade Bender, J. L., & Levine, J. M. (2018). Whole-Genome and Whole-Exome Sequencing in Pediatric Oncology: An Assessment of Parent and Young Adult Patient Knowledge, Attitudes, and Expectations. *JCO Precision Oncology*, *2*. https://doi.org/10.1200/PO.17.00104

Odgis, J. A., Gallagher, K. M., Suckiel, S. A., Donohue, K. E., Ramos, M. A., Kelly, N. R., Bertier, G., Blackburn, C., Brown, K., Fielding, L., Lopez, J., Aguiniga, K. L., Maria, E., Rodriguez, J. E., Sebastin, M., Teitelman, N., Watnick, D., Yelton, N. M., Abhyankar, A., … Kenny, E. E. (2021). The NYCKidSeq project: Study protocol for a randomized controlled trial incorporating genomics into the clinical care of diverse New York City children. *Trials*, *22*(1), 56. https://doi.org/10.1186/s13063-020-04953-4

O'Neill, S. C., Rini, C., Goldsmith, R. E., Valdimarsdottir, H., Cohen, L. H., & Schwartz, M. D. (2009). Distress among women receiving uninformative BRCA1/2 results: 12-month outcomes. *Psycho-Oncology*, *18*(10), 1088–1096. https://doi.org/10.1002/pon.1467

Ormond, K. E., Borensztein, M. J., Hallquist, M. L. G., Buchanan, A. H., Faucett, W. A., Peay, H. L., Smith, M. E., Tricou, E. P., Uhlmann, W. R., Wain, K. E., Coughlin, C. R., & On Behalf Of The Clinical Genome CADRe Workgroup, null. (2021). Defining the Critical Components of Informed Consent for Genetic Testing. *Journal of Personalized Medicine*, *11*(12), 1304. https://doi.org/10.3390/jpm11121304

Ortiz, M. V., Kobos, R., Walsh, M., Slotkin, E. K., Roberts, S., Berger, M. F., Hameed, M., Solit, D., Ladanyi, M., Shukla, N., & Kentsis, A. (2016). Integrating Genomics Into Clinical Pediatric Oncology Using the Molecular Tumor Board at the Memorial Sloan Kettering Cancer Center. *Pediatric Blood & Cancer*, *63*(8), 1368–1374. https://doi.org/10.1002/pbc.26002

Pace, C., Miller, F. G., & Danis, M. (2003). Enrolling the uninsured in clinical trials: An ethical perspective. *Critical Care Medicine*, *31*(3), S121. https://doi.org/10.1097/01.CCM.0000054907.33928.48

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Parsons, D. W., Roy, A., Yang, Y., Wang, T., Scollon, S., Bergstrom, K., Kerstein, R. A., Gutierrez, S., Petersen, A. K., Bavle, A., Lin, F. Y., López-Terrada, D. H., Monzon, F. A., Hicks, M. J., Eldin, K. W., Quintanilla, N. M., Adesina, A. M., Mohila, C. A., Whitehead, W., … Plon, S. E. (2016). Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. *JAMA Oncology*, *2*(5), 616–624. https://doi.org/10.1001/jamaoncol.2015.5699

Pervola, J., Myers, M. F., McGowan, M. L., & Prows, C. A. (2019). Giving adolescents a voice: The types of genetic information adolescents choose to learn and why. *Genetics in Medicine*, *21*(4), 965–971. https://doi.org/10.1038/s41436-018-0320-1

Peters, M., Godfrey, C., McInerney, P., Munn, Z., Trico, A., & Khalil, H. (2020). Chapter 11: Scoping Reviews. In E. Aromataris & Z. Munn (Eds.), *JBI Manual for Evidence Synthesis*. JBI. https://doi.org/10.46658/JBIMES-20-12

Pfeifer, J. D. (2013). Clinical next generation sequencing in cancer. *Cancer Genetics*, *206*(12), 409–412. https://doi.org/10.1016/j.cancergen.2013.10.004

Pipitprapat, W., Pattanaprateep, O., Iemwimangsa, N., Sensorn, I., Panthan, B., Jiaranai, P., Chantratita, W., Sorapipatcharoen, K., Poomthavorn, P., Mahachoklertwattana, P., Sura, T., Tunteeratum, A., Srichan, K., & Sriphrapradang, C. (2021). Cost-minimization analysis

of sequential genetic testing versus targeted next-generation sequencing gene panels in patients with pheochromocytoma and paraganglioma. *Annals of Medicine*, *53*(1), 1243–1255. https://doi.org/10.1080/07853890.2021.1956687

Printz, C. (2020). Precision medicine for pediatric cancers lags behind that for adult cancers. *Cancer*, *126*(2), 239–240. https://doi.org/10.1002/cncr.32685

Public Health Agency of Canada. (2017). *Cancer in young people in Canada: A report from the enhanced childhood cancer surveillance system.* http://publications.gc.ca/collections/collection_2018/aspc-phac/HP35-93-2017-eng.pdf

Public Health Agency of Canada. (2020). *Centre for Surveillance and Applied Research, Public Health Agency of Canada. Cancer in Young People in Canada Data Tool. 2020 Edition. Public Health Infobase.* https://health-infobase.canada.ca/data-tools/cypc/

Rand, L., Dunn, M., Slade, I., Upadhyaya, S., & Sheehan, M. (2019). Understanding and using patient experiences as evidence in healthcare priority setting. *Cost Effectiveness and Resource Allocation: C/E*, *17*, 20. https://doi.org/10.1186/s12962-019-0188-1

Read, K., Fernandez, C. V., Gao, J., Strahlendorf, C., Moghrabi, A., Pentz, R. D., Barfield, R. C., Baker, J. N., Santor, D., Weijer, C., & Kodish, E. (2009). Decision-making by Adolescents and Parents of Children With Cancer Regarding Health Research Participation. *Pediatrics*, *124*(3), 959–965. https://doi.org/10.1542/peds.2008-2878

Rego, S., Grove, M. E., Cho, M. K., & Ormond, K. E. (2020). Informed Consent in the Genomics Era. *Cold Spring Harbor Perspectives in Medicine*, *10*(8), a036582. https://doi.org/10.1101/cshperspect.a036582

Reichman, L., & Goudie, C. (2021). Recognition of Cancer Predisposition Syndromes. In D. Malkin (Ed.), *The Hereditary Basis of Childhood Cancer* (pp. 473–482). Springer International Publishing. https://doi.org/10.1007/978-3-030-74448-9_16

RI-MUHC: Our Vision and Mission. (n.d.). Research Institute of the McGill University Health Centre. Retrieved September 15, 2022, from https://rimuhc.ca/our-vision-and-mission

Rockowitz, S., LeCompte, N., Carmack, M., Quitadamo, A., Wang, L., Park, M., Knight, D., Sexton, E., Smith, L., Sheidley, B., Field, M., Holm, I. A., Brownstein, C. A., Agrawal, P. B., Kornetsky, S., Poduri, A., Snapper, S. B., Beggs, A. H., Yu, T. W., … Sliz, P. (2020). Children's rare disease cohorts: An integrative research and clinical genomics initiative. *Npj Genomic Medicine*, *5*(1), Article 1. https://doi.org/10.1038/s41525-020-0137-0

Rodriguez-Galindo, C., Friedrich, P., Alcasabas, P., Antillon, F., Banavali, S., Castillo, L., Israels, T., Jeha, S., Harif, M., Sullivan, M. J., Quah, T. C., Patte, C., Pui, C.-H., Barr, R., & Gross, T. (2015). Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge. *Journal of Clinical Oncology*, *33*(27), 3065–3073. https://doi.org/10.1200/JCO.2014.60.6376

Rosenkötter, N., Vondeling, H., Blancquaert, I., Mekel, O. C. L., Kristensen, F. B., & Brand, A. (2011). The contribution of health technology assessment, health needs assessment, and health impact assessment to the assessment and translation of technologies in the field of public health genomics. *Public Health Genomics*, *14*(1), 43–52. https://doi.org/10.1159/000318317

Rusch, M., Nakitandwe, J., Shurtleff, S., Newman, S., Zhang, Z., Edmonson, M. N., Parker, M., Jiao, Y., Ma, X., Liu, Y., Gu, J., Walsh, M. F., Becksfort, J., Thrasher, A., Li, Y., McMurry, J.,

Hedlund, E., Patel, A., Easton, J., … Zhang, J. (2018). Clinical cancer genomic profiling by three-platform sequencing of whole genome, whole exome and transcriptome. *Nature Communications*, *9*(1), Article 1. https://doi.org/10.1038/s41467-018-06485-7

Sabour, L., Sabour, M., & Ghorbian, S. (2017). Clinical Applications of Next-Generation Sequencing in Cancer Diagnosis. *Pathology Oncology Research: POR*, *23*(2), 225–234. https://doi.org/10.1007/s12253-016-0124-z

Salzer, E., & Hutter, C. (2021). Therapy concepts in the context of precision medicine for pediatric malignancies—Children are not adults. *Memo - Magazine of European Medical Oncology*, *14*(3), 273–277. https://doi.org/10.1007/s12254-021-00743-z

Sanderson, S. C., Lewis, C., Hill, M., Peter, M., McEntagart, M., Gale, D., Morris, H., Moosajee, M., Searle, B., Hunter, A., Patch, C., & Chitty, L. S. (2022). Decision-making, attitudes, and understanding among patients and relatives invited to undergo genome sequencing in the 100,000 Genomes Project: A multisite survey study. *Genetics in Medicine*, *24*(1), 61–74. https://doi.org/10.1016/j.gim.2021.08.010

Scholz, E., Dorer, B., & Zuell, C. (2022). Coding Issues of Open-Ended Questions in a Cross-Cultural Context. *International Journal of Sociology*, *52*(1), 78–96. https://doi.org/10.1080/00207659.2021.2015664

Schupmann, W., Miner, S. A., Sullivan, H. K., Glover, J. R., Hall, J. E., Schurman, S. H., & Berkman, B. E. (2021). Exploring the motivations of research participants who chose not to learn medically actionable secondary genetic findings about themselves. *Genetics in Medicine*, *23*(12), Article 12. https://doi.org/10.1038/s41436-021-01271-1

Scollon, S., Bergstrom, K., Kerstein, R. A., Wang, T., Hilsenbeck, S. G., Ramamurthy, U., Gibbs, R. A., Eng, C. M., Chintagumpala, M. M., Berg, S. L., McCullough, L. B., McGuire, A. L., Plon, S. E., & Parsons, D. W. (2014). Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients. *Genome Medicine*, *6*(9), 69. https://doi.org/10.1186/s13073-014-0069-3

Sedig, L. K., Jacobs, M. F., Mody, R. J., Le, L. Q., Bartnik, N. J., Gornick, M. C., Anderson, B., Chinnaiyan, A. M., & Roberts, J. S. (2022). Adolescent and parent perspectives on genomic sequencing to inform cancer care. *Pediatric Blood & Cancer*, *n/a*(n/a), e29791. https://doi.org/10.1002/pbc.29791

Simons, M., Van De Ven, M., Coupé, V., Joore, M., IJzerman, M., Koffijberg, E., Frederix, G., Uyl - De Groot, C., Cuppen, E., Van Harten, W., & Retèl, V. (2021). Early technology assessment of using whole genome sequencing in personalized oncology. *Expert Review of Pharmacoeconomics & Outcomes Research*, *21*(3), 343–351. https://doi.org/10.1080/14737167.2021.1917386

Sisk, B. A., Canavera, K., Sharma, A., Baker, J. N., & Johnson, L.-M. (2019). Ethical issues in the care of adolescent and young adult oncology patients. *Pediatric Blood & Cancer*, *66*(5), e27608. https://doi.org/10.1002/pbc.27608

Smith, E. E., du Souich, C., Dragojlovic, N., Study, C., Study, R., & Elliott, A. M. (2019). Genetic counseling considerations with rapid genome-wide sequencing in a neonatal intensive care unit. *Journal of Genetic Counseling*, *28*(2), 263–272. https://doi.org/10.1002/jgc4.1074

Statistics Canada. (2022, January 24). *Table 13-10-0394-01 Leading causes of death, total population, by age group*. Statistics Canada. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401

Summers, R. J., Castellino, S. M., Porter, C. C., MacDonald, T. J., Basu, G. D., Szelinger, S., Bhasin, M. K., Cash, T., Carter, A. B., Castellino, R. C., Fangusaro, J. R., Mitchell, S. G., Pauly, M. G., Pencheva, B., Wechsler, D. S., Graham, D. K., & Goldsmith, K. C. (2022). Comprehensive Genomic Profiling of High-Risk Pediatric Cancer Patients Has a Measurable Impact on Clinical Care. *JCO Precision Oncology*, *6*, e2100451. https://doi.org/10.1200/PO.21.00451

Suurmeijer, A. J. H., Kao, Y.-C., & Antonescu, C. R. (2019). New advances in the molecular classification of pediatric mesenchymal tumors. *Genes, Chromosomes and Cancer*, *58*(2), 100–110. https://doi.org/10.1002/gcc.22681

Sweet-Cordero, E. A., & Biegel, J. A. (2019). The genomic landscape of pediatric cancers: Implications for diagnosis and treatment. *Science (New York, N.Y.)*, *363*(6432), 1170–1175. https://doi.org/10.1126/science.aaw3535

Syrimi, E., Lewison, G., Sullivan, R., & Kearns, P. (2020). Analysis of Global Pediatric Cancer Research and Publications. *JCO Global Oncology*, *6*, 9–18. https://doi.org/10.1200/JGO.19.00227

Tan, O., Shrestha, R., Cunich, M., & Schofield, D. j. (2018). Application of next-generation sequencing to improve cancer management: A review of the clinical effectiveness and cost-effectiveness. *Clinical Genetics*, *93*(3), 533–544. https://doi.org/10.1111/cge.13199

Tomlinson, A. N., Skinner, D., Perry, D. L., Scollon, S. R., Roche, M. I., & Bernhardt, B. A. (2016). "Not Tied Up Neatly with a Bow": Professionals' Challenging Cases in Informed Consent for Genomic Sequencing. *Journal of Genetic Counseling*, *25*(1), 62–72. https://doi.org/10.1007/s10897-015-9842-8

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Vaismoradi, M., Turunen, H., & Bondas, T. (2013). Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & Health Sciences*, *15*(3), 398–405. https://doi.org/10.1111/nhs.12048

van Dijk, S., Timmermans, D. R. M., Meijers-Heijboer, H., Tibben, A., van Asperen, C. J., & Otten, W. (2006). Clinical characteristics affect the impact of an uninformative DNA test result: The course of worry and distress experienced by women who apply for genetic testing for breast cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *24*(22), 3672–3677. https://doi.org/10.1200/JCO.2005.03.7259

Vears, D. F., Borry, P., Savulescu, J., & Koplin, J. J. (2021). Old Challenges or New Issues? Genetic Health Professionals' Experiences Obtaining Informed Consent in Diagnostic Genomic Sequencing. *AJOB Empirical Bioethics*, *12*(1), 12–23. https://doi.org/10.1080/23294515.2020.1823906

Vears, D. F., Minion, J. T., Roberts, S. J., Cummings, J., Machirori, M., Blell, M., Budin-Ljøsne, I., Cowley, L., Dyke, S. O. M., Gaff, C., Green, R., Hall, A., Johns, A. L., Knoppers, B. M., Mulrine, S., Patch, C., Winkler, E., & Murtagh, M. J. (2021). Return of individual research results from genomic research: A systematic review of stakeholder perspectives. *PloS One*, *16*(11), e0258646. https://doi.org/10.1371/journal.pone.0258646

Villani, A., Tabori, U., Schiffman, J., Shlien, A., Beyene, J., Druker, H., Novokmet, A., Finlay, J., & Malkin, D. (2011). Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: A prospective observational study. *The Lancet. Oncology*, *12*(6), 559–567. https://doi.org/10.1016/S1470-2045(11)70119-X

Vlooswijk, C., Poll-Franse, L. V. van de, Janssen, S. H. M., Derksen, E., Reuvers, M. J. P., Bijlsma, R., Kaal, S. E. J., Kerst, J. M., Tromp, J. M., Bos, M. E. M. M., Hulle, T. van der, Lalisang, R. I., Nuver, J., Kouwenhoven, M. C. M., van der Graaf, W. T. A., & Husson, O. (2022). Recruiting Adolescent and Young Adult Cancer Survivors for Patient-Reported Outcome Research: Experiences and Sample Characteristics of the SURVAYA Study. *Current Oncology (Toronto, Ont.)*, *29*(8), 5407–5425. https://doi.org/10.3390/curroncol29080428

Ward, Z. J., Yeh, J. M., Bhakta, N., Frazier, A. L., Girardi, F., & Atun, R. (2019). Global childhood cancer survival estimates and priority-setting: A simulation-based analysis. *The Lancet Oncology*, *20*(7), 972–983. https://doi.org/10.1016/S1470-2045(19)30273-6

Werner-Lin, A., Ashley, T., Victoria, M., & Barbara, A. (2016). Adolescent engagement during assent for exome sequencing. *AJOB Empirical Bioethics*, *7*, 00–00. https://doi.org/10.1080/23294515.2016.1197983

Weymann, D., Pataky, R., & Regier, D. A. (2018). Economic Evaluations of Next-Generation Precision Oncology: A Critical Review. *JCO Precision Oncology*, *2*, 1–23. https://doi.org/10.1200/PO.17.00311

Wise, J. (2019). Genome sequencing of children promises a new era in oncology. *BMJ*, *364*, l105. https://doi.org/10.1136/bmj.l105

Wong, M., Mayoh, C., Lau, L. M. S., Khuong-Quang, D.-A., Pinese, M., Kumar, A., Barahona, P., Wilkie, E. E., Sullivan, P., Bowen-James, R., Syed, M., Martincorena, I., Abascal, F., Sherstyuk, A., Bolanos, N. A., Baber, J., Priestley, P., Dolman, M. E. M., Fleuren, E. D. G., … Cowley, M. J. (2020). Whole genome, transcriptome and methylome profiling enhances actionable target discovery in high-risk pediatric cancer. *Nature Medicine*, *26*(11), 1742–1753. https://doi.org/10.1038/s41591-020-1072-4

Yu, J.-H., Appelbaum, P. S., Brothers, K. B., Joffe, S., Kauffman, T. L., Koenig, B. A., Prince, A. E., Scollon, S., Wolf, S. M., Bernhardt, B. A., & Wilfond, B. S. (2019). Consent for clinical genome sequencing: Considerations from the Clinical Sequencing Exploratory Research Consortium. *Personalized Medicine*, *16*(4), 325–333. https://doi.org/10.2217/pme-2018-0076

Zhang, J., Walsh, M. F., Wu, G., Edmonson, M. N., Gruber, T. A., Easton, J., Hedges, D., Ma, X., Zhou, X., Yergeau, D. A., Wilkinson, M. R., Vadodaria, B., Chen, X., McGee, R. B., Hines-Dowell, S., Nuccio, R., Quinn, E., Shurtleff, S. A., Rusch, M., … Downing, J. R. (2015). Germline Mutations in Predisposition Genes in Pediatric Cancer. *The New England Journal of Medicine*, *373*(24), 2336–2346. https://doi.org/10.1056/NEJMoa1508054

Appendix

Quebec pediatric cancer LSGS research programs

LSGS study	Age criteria	Eligibility criteria	Centres involved	LSGS type				Tissue type(s)	Start date
				WES	WGS	Germline cancer panel	Tumor RNA sequencing		
TRICEPS	≤18 years of age at diagnosis	Relapsed or refractory cancer	All four pediatric oncology centres in Quebec	✓		✓	✓	Paired (somatic and germline)	April 2014 (CHU Sainte-Justine only) April 2016 (all four pediatric oncology centres in Quebec)
PROFYLE (PRecision Oncology For Young peopLE)	≤29 years of age	Hard-to-treat cancer	>16 institutions Canada-wide		✓	✓	✓	Paired (somatic and germline)	April 2016
ORCYD (Oncology Repository for Children and Young aDults)	No strict age criteria	"[A] confirmed or suspected diagnosis from among a wide array of cancers"	McGill University Health Centre	Biobank with access to LSGS				Paired (somatic and germline)	April 2017

SIGNATURE	<19 years of age at diagnosis	Solid, brain or hematological cancer, treated with chemotherapy/radiotherapy	All four pediatric oncology centres in Quebec	✓		✓	✓	Paired (somatic and germline)	December 2019 (CHU Sainte-Justine only) March 2021 (all four pediatric oncology centres in Quebec)

Appendix Table 1 *– Characteristics of the four research programs currently offering LSGS access to children with cancer in the province of Quebec.*

Scoping review search terms

Database	Sequencing terms	Cancer terms	Attitude terms	Child terms	Parent terms
MEDLINE	sequence analysis, dna/ or whole genome sequencing/ or whole exome sequencing/ or genomics/ or (dna sequenc* or cancer panel* or sequenc* panel* or multigene panel* or exome sequenc* or genom* sequenc*).mp	exp Neoplasms/ or (cancer* or tumor* or tumour* or malignan* or lesion* or sarcoma* or carcinoma* or neoplasm* or melanoma* or onco*).mp	Health Knowledge, Attitudes, Practice/ or (perception* or benefit* or barrier* or motivator* or concern* or advantage* or disadvantage* or facilitator* or limitation* or hope or expectation* or uptake or acceptance or preference* or perspective* or patient perspective* or attitude* or belief* or motivation* or incentive*).mp	exp infant/ or exp child/ or adolescent/ or exp pediatrics/ or (child* or pediatric* or paediatric* or pediatric oncology or infan* or toddler* or boy* or girl* or kid$1 or school* or juvenil* or underage* or under age* or teen* or minor$1 or youth$1 or adolescen*).mp or (infan* or child* or adolescen* or pediatric* or paediatric*).jw	exp Parents/ or (parent* or guardian* or carer* or caregiver* or parent perspective* or mother* or father*).mp or Parental Consent/
Embase	dna sequencing/ or whole exome sequencing/ or whole exome sequencing/ or genome analysis/ or (dna sequenc* or cancer panel* or sequenc* panel* or multigene panel* or exome sequenc* or genom* sequenc*).mp	exp neoplasm/ or (cancer* or tumor* or tumour* or malignan* or lesion* or sarcoma* or carcinoma* or neoplasm* or melanoma* or onco*).mp	exp attitude to health/ or (perception* or benefit* or barrier* or motivator* or concern* or advantage* or disadvantage* or facilitator* or limitation* or hope or expectation* or uptake or acceptance or preference* or perspective* or patient perspective* or attitude* or belief* or motivation* or incentive*).mp	exp infant/ or exp child/ or adolescent/ or juvenile/ or exp pediatrics/ or (child* or pediatric* or paediatric* or pediatric oncology or infan* or toddler* or boy* or girl* or kid$1 or school* or juvenil* or underage* or under age* or teen* or minor$1 or youth$1 or adolescen*).mp or (infan* or child* or adolescen* or pediatric* or paediatric*).jw	exp parent/ or exp parental attitude/ or (parent* or guardian* or carer* or caregiver* or parent perspective* or mother* or father*).mp or exp parental consent/

APA PsycInfo	exp Genome/ or exp Genomic Sequencing/ or (dna sequenc* or cancer panel* or sequenc* panel* or multigene panel* or exome sequenc* or genom* sequenc*).mp	exp Neoplasms/ or (cancer* or tumor* or tumour* or malignan* or lesion* or sarcoma* or carcinoma* or neoplasm* or melanoma* or onco*).mp	health attitudes/ or attitudes/ or health attitude measures/ or health behavior/ or (perception* or benefit* or barrier* or motivator* or concern* or advantage* or disadvantage* or facilitator* or limitation* or hope or expectation* or uptake or acceptance or preference* or perspective* or patient perspective* or attitude* or belief* or motivation* or incentive*).mp	exp Child Attitudes/ or exp Adolescent Attitudes/ or exp Adolescent Health/ or exp Pediatrics/ or (child* or pediatric* or paediatric* or pediatric oncology or infan* or toddler* or boy* or girl* or kid$1 or school* or juvenil* or underage* or under age* or teen* or minor$1 or youth$1 or adolescen*).mp or (infan* or child* or adolescen* or pediatric* or paediatric*).jw	exp Parents/ or (parent* or guardian* or carer* or caregiver* or parent perspective* or mother* or father*).mp or exp Informed Consent/ or exp Parental Attitudes/
ProQuest Dissertations & Theses Global	noft((dna sequenc* OR cancer panel* OR sequenc* panel* OR multigene panel* OR exome sequenc* OR genom* sequenc*))	noft((cancer* OR tumor* OR tumour* OR malignan* OR lesion* OR sarcoma* OR carcinoma* OR neoplasm* OR melanoma* OR onco*))	noft((perception* OR benefit* OR barrier* OR motivator* OR concern* OR advantage* OR disadvantage* OR facilitator* OR limitation* OR hope OR expectation* OR uptake OR acceptance OR preference* OR perspective* OR patient perspective* OR attitude* OR belief* OR motivation* OR incentive*))	noft((child* or pediatric* or paediatric* or pediatric oncology or infan* or toddler* or boy* or girl* or kid$1 or school* or juvenil* or underage* or under age* or teen* or minor$1 or youth$1 or adolescen*))	noft((parent* or guardian* or carer* or caregiver* or parent perspective* or mother* or father*))

Appendix Table 2 *– Search terms used in the scoping review. Two searches were performed in each database: one combining the sequencing-, cancer-, attitude- and child-related terms and one combining the sequencing-, cancer-, attitude- and parent-related terms.*

MUHC questionnaire: Parent REDCap version

Confidential

Parent Perspectives of Research Genetic Sequencing in Pediatric Cancer

Thank you for completing the following questionnaire.

Parent Perspectives of Research Genetic Sequencing in Pediatric Cancer

The following questions ask your thoughts and opinions about the decision to participate or not participate in a research genetic sequencing program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS) for your child. There are no right or wrong answers. We are interested in what you think and what may be important to you personally in making that decision. For each question, please choose whichever option best reflects your experience. All questions are optional, you may decline to respond to any question(s) without providing a reason.

All questionnaires will be confidential, so that neither you nor your family member(s) can be identified. Your answers here will have no impact on your/your child's eligibility for ORCYD, PROFYLE, SIGNATURE or TRICEPS or on your/your child's healthcare. The questionnaire should take about 10-15 minutes to complete.

---

1) Study ID

_____

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2) When did you receive your child's cancer diagnosis?

_____
(Example: 3 weeks or 2.5 months ago)

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3) Which research genetic sequencing program(s) was your child offered participation in?

☐ ORCYD
☐ PROFYLE
☐ SIGNATURE
☐ TRICEPS
☐ Other program
☐ I don't remember the name of the program(s)
(Please select all the programs that you were offered.)

---

4) Is this the first time your child was offered participation in a research genetic sequencing program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS)?

◯ Yes
◯ No
◯ I don't remember
◯ Not applicable
(Example: Was participation offered at initial diagnosis if this is a recurrence?)

The next few questions will focus on potential motivations and concerns about participating.

Parents may have reasons they wish to participate in sequencing programs (motivations) and reasons they may be hesitant or may not wish to participate in sequencing programs (concerns). We would like to understand more about which motivations and concerns are personally important to you when making this decision for your child.

5) What was the main reason you chose to participate or not participate in sequencing through this research program?

_____

For each of the potential motivations listed below, please note how personally important it was for you when deciding whether or not to participate in sequencing through a research program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS).

		Extremely unimportant	Somewhat unimportant	Neither important or unimportant	Somewhat important	Extremely important
6)	I want to learn information about my child's future health risks.	○	○	○	○	○
7)	I want to learn about why my child developed cancer.	○	○	○	○	○
8)	I hope it will improve my child's treatment options.	○	○	○	○	○
9)	I want to contribute to research which may help future children diagnosed with cancer.	○	○	○	○	○
10)	I want to know if my child's cancer is genetic (hereditary) so that we can consider tumor surveillance programs, if needed.	○	○	○	○	○
11)	I want to learn about my own future health risks.	○	○	○	○	○
12)	I want to learn about the future health risks of my child's siblings.	○	○	○	○	○

13) Other personally important motivations

_____

For each of the potential concerns listed below, please note how personally important it was for you when deciding whether or not to participate in sequencing through a research program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS).

		Extremely unimportant	Somewhat unimportant	Neither important or unimportant	Somewhat important	Extremely important
14)	I am currently overwhelmed by my child's diagnosis and the decisions associated with it.	○	○	○	○	○
15)	I am concerned about the possibility of a loss of privacy.	○	○	○	○	○
16)	I am concerned that the results may affect my child's future insurance or employment opportunities.	○	○	○	○	○
17)	I am concerned that sequencing conflicts with my religious or cultural beliefs.	○	○	○	○	○
18)	I am concerned that the results will be uninformative or uncertain.	○	○	○	○	○
19)	I am concerned that the results may have an emotional impact on my child.	○	○	○	○	○
20)	I am concerned that the results may have an emotional impact on me.	○	○	○	○	○
21)	I am concerned that the results may have an emotional impact on other family members.	○	○	○	○	○

22) Other personally important concerns

_____

23) Overall, I have no concerns about participating in sequencing through a research program (such as ORCYD, PROFYLE, SIGNATURE or TRICEPS).

○ True for me
○ False for me

24) Please select the answer below that best describes how you feel about the balance between the motivations and concerns in your decision-making process about participating in sequencing.

○ My motivations far outweigh my concerns
○ My motivations slightly outweigh my concerns
○ My motivations are equal to my concerns
○ My concerns slightly outweigh my motivations
○ My concerns far outweigh my motivations

The next few questions will focus on your beliefs around the possible cause(s) of your child's cancer.

25) On a scale of 0 to 100, how likely do you think it is that your child's cancer is genetic (hereditary)? In this context, 100 would mean that you think there is a 100% likelihood that the cancer is genetic (hereditary).

0 50 100

(Place a mark on the scale above)

Below is a list of causes/reasons that some people believe contribute to cancer development. Please group these possible causes/reasons by which ones you feel are likely or unlikely contributing factors to your child's cancer.

		Unlikely contributing factor to my child's cancer	Likely contributing factor to my child's cancer	Uncertain
26)	Chance/bad luck	○	○	○
27)	Environmental causes	○	○	○
28)	Genetics	○	○	○
29)	God's will	○	○	○
30)	Lifestyle	○	○	○
31)	Prior illness or injury	○	○	○
32)	Multiple causes	○	○	○

33) Other cause(s) that I consider likely contributing factor(s) to my child's cancer

_____

34) I don't know what possible causes/reasons contributed to my child's cancer. ○ True for me ○ False for me

35) On a scale of 0 to 100, how likely do you think it is that the sequencing results will suggest a genetic (hereditary) cause of your child's cancer? In this context, 100 would mean that you think there is a 100% likelihood that the results will suggest that the cancer is genetic (hereditary).

0 50 100

(Place a mark on the scale above)

The final question will focus on demographic information.

As mentioned in the consent form, we are collecting additional demographic information such as the type of cancer your child has, the approximate distance you reside from the clinic and your family history of related cancers. We are obtaining this information from your child's medical record; it will not be stored with any identifying information. Below is an additional question exploring demographic information that may potentially impact the decisions parents make about research genetic testing.

36) Do you work in a health- or health research-related field? ◯ Yes ◯ No ◯ Prefer not to answer

Summary of articles included in the scoping review

Reference	LSGS program, center, country	Population(s) served by the LSGS program	Attitude-related study aims	Sample	Attitude assessment methods	Dates of data collection
Scollon et al., 2014	BASIC3 (Baylor Advancing Sequencing into Childhood Cancer Care), Texas Children's Cancer Center (TCCC), United States	All patients with newly diagnosed solid tumors (including central nervous system (CNS) tumors) under the age of 18 years who have at least one parent who speaks English or Spanish	[D]escribe [...] the proportion of parents who decline enrollment of their child in [BASIC3] and their reasons for doing so	Parents of 21 patients that declined participation in BASIC3	Recorded reason for declining during consent process	Aug 2012 - Sept 2013
McCullough et al., 2016			[D]etermine whether a sample of parents […] report that they expect themselves to be […] unprepared to incorporate [LSGS] into decision making about the care of children with cancer.	40 parents of pediatric patients participating in the BASIC3 (analyzed English transcripts only)	Semi-structured interviews	Aug 2012 - Jan 2014
Malek et al., 2017			[E]xplore the expected benefits for parents of pediatric patients with cancer who received clinical [LSGS]	64 parents of pediatric patients participating in the BASIC3	Semi-structured interviews	Aug 2012 - April 2016
Amendola et al., 2018			[E]xamine [LSGS] decline across a diverse set of potential participants that vary in age and indication for testing.	118 families actively declining BASIC3*	Recorded reason for declining during consent process	Approx. Sept 2012 - April 2016*
Malek et al., 2019			[D]evelop a more holistic understanding of how parenthood shapes perceptions about [LSGS] information for parents of children with cancer.	64 parents of pediatric patients participating in the BASIC3	Semi-structured interviews (English or Spanish)	Aug 2012 - Feb 2017

Gattuso et al., 2018	G4K (Genomes for Kids), St. Jude Children's Research Hospital, United States	0–21 years with diagnosis of liquid, non-CNS solid, or CNS solid tumor.	[I]dentify reasons for participation given by parents, risks, benefits, and what they expected or hoped to learn from participation.	31 parents of pediatric oncology patients participating in G4K	Open-ended interviews	Not reported
Howard Sharp et al., 2020			[Q]ualitatively identify families' reasons for declining [LSGS]	35 families that provided a reason for declining participation in G4K	Recorded reason for declining during consent process	Aug 2015 - April 2017
Mandrell et al., 2021			[Q]ualitatively describe parent understanding and expectations of [LSGS] testing including perceived benefits, risks, hopes, and the decision-making process among those who did and did not provide consent for [LSGS].	43 parents who completed a two-phase informed consent process for G4K	Semi-structured interviews	Not reported
Marron et al., 2016	iCAT (Individualized Cancer Therapy), multi-site, United States	≤30 years at enrollment with a recurrent, refractory, or high-risk extracranial solid tumor	[A]nalyze patients' and parents' hopes, expectations, and concerns about [LSGS]	11 young adult patients (≥18 years) and 34 parents of pediatric patients (< 18 years) with relapsed/recurrent cancer, rare cancers or poor prognoses	Questionnaire	Sept 2014 - July 2015

Marron et al., 2019	GAIN (includes iCat) and LEAP consortia, multi-site, United States	Age ≤ 30 years at time of initial qualifying solid tumor diagnosis, high-risk, relapsed and refractory solid tumors OR age ≤ 30 years at time of initial, relapsed or refractory leukemia diagnosis	[Describe] patient/parent hopes and expectations for the outcomes of [LSGS]	124 parents and young adult patients participating in GAIN or LEAP	Questionnaire	Sept 2016 - Jan 2019
Oberg et al., 2015	PIPseq (Precision in Pediatric Sequencing), Columbia University Medical Center (CUMC), United States	N/A, hypothetical	[Explore] challenges to informed consent and propose elements to consider when approaching the consent process for [LSGS] research in pediatric oncology.	15 parents of children with cancer recruited from the outpatient pediatric oncology clinic	Focus groups	Focus groups: June - July 2013
Oberg et al., 2018			[A]ssess knowledge, attitudes, and expectations of parents and young adult patients about [LSGS]	76 parents of pediatric patients with cancer and 35 young adult cancer survivors who were off therapy for at least 1 year	Questionnaire	Aug 2015 - June 2016

Byrjalson et al., 2018	STAGING (Sequencing Tumor and Germline DNA—Implications and National Guidelines), multi-site, Denmark	Families of all newly diagnosed paediatric cancer patients aged 0–17.9	[E]xplore parent perspectives on participating in [LSGS] research specifically in the weeks following diagnosis of paediatric cancer.	30 parents of 15 pediatric patients participating in STAGING	Anthropologist observations of genetic counselling sessions (and associated debriefings) Interviews	Not reported
Brozou et al., 2018	Germline mutations in children with cancer, University Children's Hospital, Germany	All children (aged 0–18 years) with any newly diagnosed malignancy	[D]etermine the interest in and acceptance of comprehensive [LSGS] in a pediatric oncology and hematology department	11 families that declined LSGS	Recorded reason for declining during consent process	Jan 2015 - Dec 2016
McCarthy et al., 2020	Unnamed, The Royal Children's Hospital, Australia	Children with hard-to-treat, relapsed and refractory cancers	[E]xplore the views and experiences of […] parents regarding […] their perspectives on [LSGS] as a pathway to identifying novel treatment options	19 parents or pediatric patients and 1 young adult patient who had consented to a pilot [LSGS] study	Semi-structured interviews	Not reported

Appendix Table 3 *– A summary of the 15 articles included in the scoping review.*

Asterix (*) indicates information was obtained by contacting corresponding authors.

Comparison of items included in the MUHC questionnaire

Two questionnaires were identified via the articles included in the scoping review: the Patients' Perspectives on Genomic Data and Individualized Cancer Therapy questionnaire utilized by Marron and colleagues (2016) and the Precision in Pediatric Sequencing Knowledge Questionnaire (PIPseqKQ) utilized by Oberg and colleagues (2018). Both questionnaires were available in the supplementary materials of the respective publications. The following table provides a comparison of motivation- and concern-related items included in the present study (MUHC questionnaire), the Patients' Perspectives on Genomic Data and Individualized Cancer Therapy questionnaire and the PIPseqKQ.

Motivation-related items		
Statement(s) assessed via Likert scale in MUHC questionnaire	**Similar statement(s) assessed via Likert scale by Marron et al., 2016**	**Similar statement(s) assessed as a risk or a benefit by Oberg et al., 2018**
I want to learn information about my/my child's future health risks.	I hoped it would teach me about my genes.	Learning information about my child's future health risks.
I want to learn about why I/my child developed cancer.	I hoped it would help provide information to me and my doctor about my cancer.	Learning the cause of my child's cancer.
I hope it will improve my/my child's treatment options.	I hoped it would increase my chance of being cured. I hoped it would give me a greater number of treatment options.	Learning information that could change the treatment for my child's cancer.
I want to contribute to research which may help future children diagnosed with cancer.	I hoped it would help find cures for future patients. I hoped to help doctors and scientists learn more about the genes involved in cancer.	Learning information may help other children in the future.
I want to know if my/my child's cancer is genetic (hereditary) so that we can consider tumor surveillance programs, if needed.		
I want to learn about other family members'/my own future health risks. I want to learn about the future health risks for my potential future children/my child's siblings.	I hoped it would teach me about my family's genes.	Learning information about my own future health risks. Learning information about health risks for other family members.
	I hoped that doing this testing would provide me with peace of mind. My doctor recommended the study. Participating in this research gave me hope.	Learning information for which the risk of disease is unknown.

Concern-related items		
Statement assessed via Likert scale in MUHC questionnaire	**Similar statement(s) assessed via Likert scale by Marron et al., 2016**	**Similar statement assessed as a risk or a benefit by Oberg et al., 2018**
I am currently overwhelmed by my diagnosis and the decisions associated with it.		
I am concerned about the possibility of a loss of privacy.	I worried that the information learned in this research study would not be kept private.	
I am concerned that the results may affect my future insurance or employment opportunities.	I worried that the information learned could have hurt my family's ability to get insurance.	
I am concerned that sequencing conflicts with my religious or cultural beliefs.	I worried that the information learned could have hurt my family's ability to get or keep a job.	
I am concerned that the results will be uninformative or uncertain.	I worried that no new information would be found to help me, causing me and my family to be disappointed.	
I am concerned that the results may have an emotional impact on me.	I worried that I would learn information about my cancer that would be stressful or cause anxiety. I worried that I would learn information about my genes that would be stressful or cause anxiety. I worried that I would learn information about my family that would be stressful or cause anxiety. I worried that I would learn that my cancer was less treatable or more aggressive than previously thought.	
I am concerned that the results may have an emotional impact on my parents.		
I am concerned that the results may have an emotional impact on other family members.		
	I worried that the results would take a long time to come back.	

Appendix Table 4 *– A comparison of motivation- and concern-related items included in the present study (MUHC questionnaire), the Patients' Perspectives on Genomic Data and Individualized Cancer Therapy questionnaire (Marron et al., 2016) and the PIPseqKQ (Oberg et al., 2018).*

Attitudes identified in the scoping review: expanded table

Motivations					
		Number of studies			
Motivation	**Subcategory**	**All participant types (n= 15) (%)**	**Participants accepting LSGS (n = 9)** (references)	**Participants declining LSGS (n = 5*)** (references)	**Participants considering hypothetical LSGS (n = 2)** (references)
Altruism	***Help other children, contribute to research***	**8 (53.3)**	**6** [a-f]	**1*** [c]	**2** [g, h]
Treatment	***Potential for improved treatment***	**8 (53.3)**	**6** [c-f, i, j]	**0**	**2** [g, h]
Information seeking	***Child's cancer genetics/CPS***	**7 (46.7)**	**7** [a-e, j, k]	**0**	**0**
	General, not specified	**5 (33.3)**	**4** [a, c, i, j]	**0**	**1** [h]
	Other health, secondary findings	4 (26.7)	2 [a, b]	0	2 [g, h]
	Family members' cancer risk	**3 (20.0)**	**3** [a-c]	**0**	**0**
	Reproductive decisions	**3 (20.0)**	**3** [c, j, k]	**0**	**0**
	About parent(s)	2 (13.3)	2 [j, k]	0	0
	About child/adolescent	1 (6.7)	1 [c]	0	0
Meaning making	***Wanting to know why***	**5 (33.3)**	**4** [a, c, i, j]	**0**	**1** [h]
Ability to prepare for the future	***Surveillance methods/prevention***	**3 (20.0)**	**2** [b, c]	**1*** [c]	**1** [g, h]
	Avoid being blindsided	2 (13.3)	2 [c, j]	0	0
	Additional genetic tests	1 (6.7)	1 [i]	0	0
Potential emotional impact	*Peace of mind, negative result*	3 (20.0)	3 [c, d, j]	0	0
	Relief from guilt, exculpatory	2 (13.3)	2 [i, k]	0	0
Parental responsibility	*Doing everything possible*	2 (13.3)	2 [j, k]	0	0

Concerns					
		Number of studies			
Concern	**Subcategory**	**All participant types (n= 15)**	**Participants accepting LSGS (n = 9)**	**Participants declining LSGS (n = 5*)**	**Participants considering hypothetical LSGS (n = 2)**
Privacy	***Insurance discrimination***	**5 (33.3)**	**3** (b-d)	**2*** (c, l)	**1** (g)
	General	**4 (26.7)**	**2** (c, d)	**3*** (c, m, n)	**0**
	Employment discrimination	**2 (13.3)**	**1** (d)	**0**	**1** (g)
Overwhelmed	***By cancer diagnosis, decisions***	**4 (26.7)**	**0**	**4** (l-o)	**0**
Potential emotional impact	***General, not specified***	**4 (26.7)**	**0**	**4** (l-o)	**0**
	Positive CPS results	2 (13.3)	2 (b, c)	1* (c)	0
	Guilt/blame	2 (13.3)	1	1 (c)	0
	Secondary findings	1 (6.7)	0	0	1 (g)
	Worse prognosis	1 (6.7)	1 (d)	0	0
	Disappointment, no new information	**1 (6.7)**	**1** (d)	**0**	**0**
Invasiveness	*Tumor biopsy, skin biopsy or blood sample*	4 (26.7)	1 (f)	2 (l, n)	1 (g)
Conflict with beliefs	***Religious or cultural***	**3 (20.0)**	**0**	**2** (c, o)	**1** (g)
Child or young adult declined	*Child, adolescent or young adult declined LSGS*	2 (13.3)	0	2 (l, o)	0
No concerns	***General, not specified***	**3 (20.0)**	**3** (b-d)	**0**	**0**
	About potential emotional impact	2 (13.3)	2 (i, j)	0	0

Appendix Table 5 *– A summary of attitudes (motivations and concerns) reported by studies included in the scoping review (total n = 15 articles). Subcategories selected for inclusion in the study questionnaire are bolded. *One article (Mandrell et al., 2021) reported attitudes of families accepting LSGS and families declining LSGS; the attitudes of the two groups were reported separately, therefore*

in some instances (denoted with an asterisk) this article is included in both the "Participants accepting LSGS" column and the "Participants declining LSGS" column.

References for Appendix Table 5:

a. Byrjalsen A, Stoltze U, Wadt K, Hjalgrim LL, Gerdes AM, Schmiegelow K, et al. Pediatric cancer families' participation in whole-genome sequencing research in Denmark: Parent perspectives. Eur J Cancer Care (Engl). 2018 Nov;27(6):e12877.

b. Gattuso, J., Johnson, L. M., Pritchard, M., Walker, B., Hamilton, K., Valdez, J., et al. Reasons, hopes, risks and expectations expressed by parents consenting to genomic sequencing for their child. Pediatric Blood and Cancer. 2018 Nov;

c. Mandrell BN, Gattuso JS, Pritchard M, Caples M, Howard Sharp KM, Harrison L, et al. Knowledge Is Power: Benefits, Risks, Hopes, and Decision-Making Reported by Parents Consenting to Next-Generation Sequencing for Children and Adolescents with Cancer. Seminars in Oncology Nursing. 2021 Jun;151167.

d. Marron JM, DuBois SG, Bender JG, Kim A, Crompton BD, Meyer SC, et al. Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: The Individualized Cancer Therapy (iCat) experience. Pediatr Blood Cancer. 2016 Nov;63(11):1974–82.

e. Marron JM, Quach E, Pikman Y, Janeway KA, Mack JW. Participant hopes and expectations regarding outcomes of genomic sequencing research in pediatric oncology. JCO. 2019 May 20;37(15_suppl):10020–10020.

f. McCarthy MC, De Abreu Lourenco R, McMillan LJ, Meshcheriakova E, Cao A, Gillam L. Finding Out What Matters in Decision-Making Related to Genomics and Personalized Medicine in Pediatric Oncology: Developing Attributes to Include in a Discrete Choice Experiment. Patient. 2020 Jun;13(3):347–61.

g. Oberg JA, Bender JLG, Cohn EG, Morris M, Ruiz J, Chung WK, et al. Overcoming challenges to meaningful informed consent for whole genome sequencing in pediatric cancer research. Pediatric Blood & Cancer. 2015;62(8):1374–80.

h. Oberg JA, Ruiz J, Ali-Shaw T, Schlechtweg KA, Ricci A, Kung AL, et al. Whole-Genome and Whole-Exome Sequencing in Pediatric Oncology: An Assessment of Parent and Young Adult Patient Knowledge, Attitudes, and Expectations. JCO Precis Oncol. 2018;2.

i. Malek J, Slashinski MJ, Robinson JO, Gutierrez AM, Parsons DW, Plon SE, et al. Parental Perspectives on Whole Exome Sequencing in Pediatric Cancer: A Typology of Perceived Utility. JCO Precis Oncol. 2017;1.

j. McCullough LB, Slashinski MJ, McGuire AL, Street RL, Eng CM, Gibbs RA, et al. Is Whole Exome Sequencing an Ethically Disruptive Technology? Perspectives of Pediatric Oncologists and Parents of Pediatric Patients with Solid Tumors. Pediatr Blood Cancer. 2016 Mar;63(3):511–5.

k. Malek J, Pereira S, Robinson JO, Gutierrez AM, Slashinski MJ, Parsons DW, et al. Responsibility, culpability, and parental views on genomic testing for seriously ill children. Genetics in Medicine. 2019 Dec;21(12):2791–7.

l. Howard Sharp KM, Jurbergs N, Ouma A, Harrison L, Gerhardt E, Taylor L, et al. Factors Associated with Declining to Participate in a Pediatric Oncology Next Generation Sequencing Study. JCO Precis Oncol. 2020;4:202–11.

m. Amendola LM, Robinson JO, Hart R, Biswas S, Lee K, Bernhardt BA, et al. Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. Journal of Genetic Counseling. 2018;27(5):1220–7.

n. Scollon S, Bergstrom K, Kerstein RA, Wang T, Hilsenbeck SG, Ramamurthy U, et al. Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients. Genome Med. 2014;6(9):69.

o. Brozou T, Taeubner J, Velleuer E, Dugas M, Wieczorek D, Borkhardt A, et al. Genetic predisposition in children with cancer – affected families' acceptance of Trio-WES. Eur J Pediatr. 2018 Jan 1;177(1):53–60.

Attitudes towards LSGS participation among non-cancer pediatric populations.

LSGS program (reference)	Sample	Methods	Motivations reported	Concerns reported

SickKids (Anderson et al., 2017)	23 parents of patients participating in LSGS research for non-cancer reasons	Interviews	- information seeking
			  - child's condition/diagnosis
			  - parents' future health risks
			  - family planning purposes
			- potential for improved treatment
			- altruism
				- potential psychological impact of results
				- insurance discrimination
				- ambiguous findings
				- 'weight' of inflicted insight

NYCKidSeq (Donohue et al., 2021)	24 parents of 22 children who received LSGS for non-cancer reasons	Interviews	- information seeking - child's condition/diagnosis	- confidentiality - insurance discrimination
CAUSES (Hitchcock et al., 2020)	7 parents of children with undiagnosed disorders	Focus groups	- information seeking - child's condition/diagnosis - low invasiveness - altruism - potential for community with other families	

PediSeq (Levenseller et al., 2014)	20 parents of children and 7 adolescents offered LSGS for non-cancer reasons (hearing loss, mitochondrial disorder, cardiology, autism)	Focus groups	- information seeking
			  - child's condition/diagnosis
			  - child's future reproductive choices
				- invasiveness
				- stigmatization
				- discrimination (employment and insurance)
				- potential psychological impact
				- possible impact on the child's future reproductive decisions
				- burden of having information about the child's future health risks

Appendix Table 6 *– Attitudes reported among parents and adolescents considering LSGS for non-cancer pediatric reasons.*

Relevant aspects of LSGS consent processes

The aim of informed consent processes in genetic testing is to inform potential participants (or their guardians) of relevant information about the test including procedure, purpose, potential results as well as potential risks and benefits so that they can make a voluntary, autonomous decision about whether or not to participate (K. Burke & Clarke, 2016; McGuire & Beskow, 2010; Ormond et al., 2021). Due to the integral role the consent process plays in decision-making regarding LSGS, the following sections will focus on aspects of the consent process that may impact the attitudes of patients and families who are offered LSGS after a pediatric cancer diagnosis.

Consent formats

Much discussion has been raised around the suitability of traditional informed consent formats for LSGS, especially due to the broad nature of LSGS results, variants/genes of uncertain significance and unsolicited findings (Bos & Bunnik, 2022; Rego et al., 2020; Tomlinson et al., 2016; Vears, Borry, et al., 2021; Yu et al., 2019). Efforts have been made to adjust consent sessions to the context of LSGS programs, including implementing two-step consent sessions, self-guided learning modules, decision aids and/or dynamic consent practices (Budin-Ljøsne et al., 2015; Freed et al., 2021; Johnson et al., 2019; Kraft et al., 2021). These consent methods may impact the way that potential participants engage with and understand information related to LSGS.

Consent providers and settings

Recruitment for LSGS programs in pediatric oncology settings may be done by a variety of professionals including researchers, physicians, genetic counsellors and/or nurses. LSGS research programs may be offered in settings that overlap with clinical care, making the distinction between the two realms less clear for participants. Interviews conducted by Berrios and colleagues (2018) found that participants who had attended consent sessions for research LSGS reported that having their consent session with a trusted clinical care provider and/or in a trusted clinical setting increased their likelihood of participating in LSGS. This evidence suggests that the provider or setting of the consent session may affect the perspectives of potential participants towards LSGS.

Additionally, consent providers' perspectives towards LSGS may impact the manner in which they present LSGS studies to families. Some pediatric oncology clinicians have reported expectations of LSGS providing clinical utility and LSGS results to be no more complex than other diagnostic information (Johnson, Valdez, et al., 2017; McCullough et al., 2016). However, in semi-structured interviews with 16 pediatric oncologists, emerging themes included concerns that complex LSGS results may be misinterpreted by parents and may disrupt decision-making or distract parents from making treatment decisions (McCullough et al., 2016). These varying views may affect the way in which consent providers present LSGS information to families which may in turn affect families' perspectives of LSGS.

Timing of approach for consent

Families of children with cancer are often offered LSGS participation shortly after receiving their cancer diagnosis, at a time when many families are processing this information and making decisions about treatment. Amendola et al. (2018) noted that being overwhelmed was the most frequently reported reason for declining (47%) among parents of children with cancer who were approached about LSGS participation within 60 days of their diagnosis. However, this was not a significant reason for declining among parents of children with non-cancer disorders nor among adults with cancer (Amendola et al., 2018). Interviews with 15 families of children with cancer who were approached about LSGS participation via the STAGING program 2-28 days after their diagnosis reported that some families felt that they were approached too soon after diagnosis, referencing feeling overwhelmed and experiencing a crisis (Byrjalsen et al., 2018).

The unique experiences of adolescents with cancer and parents of children with cancer may have an impact on the appropriate time to approach families, ensuring they are able to fully consider participation and provide informed consent. Further research is required to determine families' preferences on this matter and how time of approach may affect perspectives towards LSGS.

Appendix references

Amendola, L. M., Robinson, J. O., Hart, R., Biswas, S., Lee, K., Bernhardt, B. A., East, K., Gilmore, M. J., Kauffman, T. L., Lewis, K. L., Roche, M., Scollon, S., Wynn, J., & Blout, C. (2018). Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. *Journal of Genetic Counseling*, *27*(5), 1220–1227. https://doi.org/10.1007/s10897-018-0243-7

Anderson, J. A., Meyn, M. S., Shuman, C., Zlotnik Shaul, R., Mantella, L. E., Szego, M. J., Bowdin, S., Monfared, N., & Hayeems, R. Z. (2017). Parents perspectives on whole genome sequencing for their children: Qualified enthusiasm? *Journal of Medical Ethics*, *43*(8), 535–539. https://doi.org/10.1136/medethics-2016-103564

Berrios, C., James, C. A., Raraigh, K., Bollinger, J., Murray, B., Tichnell, C., Applegate, C. D., & Bergner, A. L. (2018). Enrolling Genomics Research Participants through a Clinical Setting: The Impact of Existing Clinical Relationships on Informed Consent and Expectations for Return of Research Results. *Journal of Genetic Counseling*, *27*(1), 263–273. https://doi.org/10.1007/s10897-017-0143-2

Bos, W., & Bunnik, E. M. (2022). Informed consent practices for exome sequencing: An interview study with clinical geneticists in the Netherlands. *Molecular Genetics & Genomic Medicine*, *10*(3), e1882. https://doi.org/10.1002/mgg3.1882

Brozou, T., Taeubner, J., Velleuer, E., Dugas, M., Wieczorek, D., Borkhardt, A., & Kuhlen, M. (2018). Genetic predisposition in children with cancer – affected families' acceptance of Trio-WES. *European Journal of Pediatrics*, *177*(1), 53–60. https://doi.org/10.1007/s00431-017-2997-6

Budin-Ljøsne, I., Bentzen, H. B., Solbakk, J. H., & Myklebost, O. (2015). Genome sequencing in research requires a new approach to consent. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke*, *135*(22), 2031–2032. https://doi.org/10.4045/tidsskr.15.0944

Burke, K., & Clarke, A. (2016). The challenge of consent in clinical genome-wide testing. *Archives of Disease in Childhood*, *101*(11), 1048–1052. https://doi.org/10.1136/archdischild-2013-304109

Byrjalsen, A., Stoltze, U., Wadt, K., Hjalgrim, L. L., Gerdes, A.-M., Schmiegelow, K., & Wahlberg, A. (2018). Pediatric cancer families' participation in whole-genome sequencing research in Denmark: Parent perspectives. *European Journal of Cancer Care*, *27*(6), e12877. https://doi.org/10.1111/ecc.12877

Donohue, K. E., Dolan, S. M., Watnick, D., Gallagher, K. M., Odgis, J. A., Suckiel, S. A., Teitelman, N., Gelb, B. D., Kenny, E. E., Wasserstein, M. P., Horowitz, C. R., & Bauman, L. J. (2021). Hope versus reality: Parent expectations of genomic testing. *Patient Education and Counseling*, *104*(8), 2073–2079. https://doi.org/10.1016/j.pec.2021.01.030

Freed, A. S., Gruß, I., McMullen, C. K., Leo, M. C., Kauffman, T. L., Porter, K. M., Muessig, K. R., Eubanks, D., Goddard, K. A. B., Wilfond, B. S., & Liles, E. G. (2021). A decision aid for additional findings in genomic sequencing: Development and pilot testing. *Patient Education and Counseling*, *104*(5), 960–968. https://doi.org/10.1016/j.pec.2020.10.038

Hitchcock, E. C., Study, C., & Elliott, A. M. (2020). Shortened consent forms for genome-wide sequencing: Parent and provider perspectives. *Molecular Genetics & Genomic Medicine*, *8*(7), e1254. https://doi.org/10.1002/mgg3.1254

Howard Sharp, K. M., Jurbergs, N., Ouma, A., Harrison, L., Gerhardt, E., Taylor, L., Hamilton, K., McGee, R. B., Nuccio, R., Quinn, E., Hines-Dowell, S., Kesserwan, C., Sunkara, A., Gattuso, J. S., Pritchard, M., Mandrell, B., Relling, M. V., Haidar, C. E., Kang, G., … Nichols, K. E. (2020). Factors Associated with Declining to Participate in a Pediatric Oncology Next Generation Sequencing Study. *JCO Precision Oncology*, *4*, 202–211. https://doi.org/10.1200/PO.19.00213

Johnson, L.-M., Sykes, A. D., Lu, Z., Valdez, J. M., Gattuso, J., Gerhardt, E., Hamilton, K. V., Harrison, L. W., Hines-Dowell, S. J., Jurbergs, N., McGee, R. B., Nuccio, R., Ouma, A. A., Pritchard, M., Quinn, E. A., Baker, J. N., Mandrell, B. N., & Nichols, K. E. (2019). Speaking genomics to parents offered germline testing for cancer predisposition: Use of a 2-visit consent model. *Cancer*, *125*(14), 2455–2464. https://doi.org/10.1002/cncr.32071

Johnson, L.-M., Valdez, J. M., Quinn, E. A., Sykes, A. D., McGee, R. B., Nuccio, R., Hines-Dowell, S. J., Baker, J. N., Kesserwan, C., Nichols, K. E., & Mandrell, B. N. (2017). Integrating next-generation sequencing into pediatric oncology practice: An assessment of physician confidence and understanding of clinical genomics. *Cancer*, *123*(12), 2352–2359. https://doi.org/10.1002/cncr.30581

Kraft, S. A., Porter, K. M., Duenas, D. M., Guerra, C., Joseph, G., Lee, S. S.-J., Shipman, K. J., Allen, J., Eubanks, D., Kauffman, T. L., Lindberg, N. M., Anderson, K., Zepp, J. M., Gilmore, M. J., Mittendorf, K. F., Shuster, E., Muessig, K. R., Arnold, B., Goddard, K. A. B., & Wilfond, B. S. (2021). Participant Reactions to a Literacy-Focused, Web-Based Informed Consent Approach for a Genomic Implementation Study. *AJOB Empirical Bioethics*, *12*(1), 1–11. https://doi.org/10.1080/23294515.2020.1823907

Levenseller, B. L., Soucier, D. J., Miller, V. A., Harris, D., Conway, L., & Bernhardt, B. A. (2014). Stakeholders' opinions on the implementation of pediatric whole exome sequencing: Implications for informed consent. *Journal of Genetic Counseling*, *23*(4), 552–565. https://doi.org/10.1007/s10897-013-9626-y

Malek, J., Pereira, S., Robinson, J. O., Gutierrez, A. M., Slashinski, M. J., Parsons, D. W., Plon, S. E., & McGuire, A. L. (2019). Responsibility, culpability, and parental views on genomic testing for seriously ill children. *Genetics in Medicine*, *21*(12), 2791–2797. https://doi.org/10.1038/s41436-019-0570-6

Malek, J., Slashinski, M. J., Robinson, J. O., Gutierrez, A. M., Parsons, D. W., Plon, S. E., McCullough, L. B., & McGuire, A. L. (2017). Parental Perspectives on Whole Exome Sequencing in Pediatric Cancer: A Typology of Perceived Utility. *JCO Precision Oncology*, *1*. https://doi.org/10.1200/PO.17.00010

Mandrell, B. N., Gattuso, J. S., Pritchard, M., Caples, M., Howard Sharp, K. M., Harrison, L., Ouma, A. A., Valdez, J. M., Johnson, L.-M., & Nichols, K. E. (2021). Knowledge Is Power: Benefits, Risks, Hopes, and Decision-Making Reported by Parents Consenting to Next-Generation Sequencing for Children and Adolescents with Cancer. *Seminars in Oncology Nursing*, 151167. https://doi.org/10.1016/j.soncn.2021.151167

Marron, J. M., DuBois, S. G., Bender, J. G., Kim, A., Crompton, B. D., Meyer, S. C., Janeway, K. A., & Mack, J. W. (2016). Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: The Individualized Cancer Therapy (iCat) experience. *Pediatric Blood & Cancer*, *63*(11), 1974–1982. https://doi.org/10.1002/pbc.26137

Marron, J. M., Quach, E., Pikman, Y., Janeway, K. A., & Mack, J. W. (2019). Participant hopes and expectations regarding outcomes of genomic sequencing research in pediatric oncology. *Journal of Clinical Oncology*, *37*(15_suppl), 10020–10020. https://doi.org/10.1200/JCO.2019.37.15_suppl.10020

McCarthy, M. C., De Abreu Lourenco, R., McMillan, L. J., Meshcheriakova, E., Cao, A., & Gillam, L. (2020). Finding Out What Matters in Decision-Making Related to Genomics and Personalized Medicine in Pediatric Oncology: Developing Attributes to Include in a Discrete Choice Experiment. *The Patient - Patient-Centered Outcomes Research*, *13*(3), 347–361. https://doi.org/10.1007/s40271-020-00411-0

McCullough, L. B., Slashinski, M. J., McGuire, A. L., Street, R. L., Eng, C. M., Gibbs, R. A., Parsons, D. W., & Plon, S. E. (2016). Is Whole Exome Sequencing an Ethically Disruptive Technology? Perspectives of Pediatric Oncologists and Parents of Pediatric Patients with Solid Tumors. *Pediatric Blood & Cancer*, *63*(3), 511–515. https://doi.org/10.1002/pbc.25815

McGuire, A. L., & Beskow, L. M. (2010). INFORMED CONSENT IN GENOMICS AND GENETIC RESEARCH. *Annual Review of Genomics and Human Genetics*, *11*, 361–381. https://doi.org/10.1146/annurev-genom-082509-141711

Oberg, J. A., Bender, J. L. G., Cohn, E. G., Morris, M., Ruiz, J., Chung, W. K., Appelbaum, P. S., Kung, A. L., & Levine, J. M. (2015). Overcoming challenges to meaningful informed consent for whole genome sequencing in pediatric cancer research. *Pediatric Blood & Cancer*, *62*(8), 1374–1380. https://doi.org/10.1002/pbc.25520

Oberg, J. A., Ruiz, J., Ali-Shaw, T., Schlechtweg, K. A., Ricci, A., Kung, A. L., Chung, W. K., Appelbaum, P. S., Glade Bender, J. L., & Levine, J. M. (2018). Whole-Genome and Whole-Exome Sequencing in Pediatric Oncology: An Assessment of Parent and Young Adult Patient Knowledge, Attitudes, and Expectations. *JCO Precision Oncology*, *2*. https://doi.org/10.1200/PO.17.00104

Ormond, K. E., Borensztein, M. J., Hallquist, M. L. G., Buchanan, A. H., Faucett, W. A., Peay, H. L., Smith, M. E., Tricou, E. P., Uhlmann, W. R., Wain, K. E., Coughlin, C. R., & On Behalf Of The Clinical Genome CADRe Workgroup. (2021). Defining the Critical Components of Informed Consent for Genetic Testing. *Journal of Personalized Medicine*, *11*(12), 1304. https://doi.org/10.3390/jpm11121304

Rego, S., Grove, M. E., Cho, M. K., & Ormond, K. E. (2020). Informed Consent in the Genomics Era. *Cold Spring Harbor Perspectives in Medicine*, *10*(8), a036582. https://doi.org/10.1101/cshperspect.a036582

Scollon, S., Bergstrom, K., Kerstein, R. A., Wang, T., Hilsenbeck, S. G., Ramamurthy, U., Gibbs, R. A., Eng, C. M., Chintagumpala, M. M., Berg, S. L., McCullough, L. B., McGuire, A. L., Plon, S. E., & Parsons, D. W. (2014). Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients. *Genome Medicine*, *6*(9), 69. https://doi.org/10.1186/s13073-014-0069-3

Tomlinson, A. N., Skinner, D., Perry, D. L., Scollon, S. R., Roche, M. I., & Bernhardt, B. A. (2016). "Not Tied Up Neatly with a Bow": Professionals' Challenging Cases in Informed Consent for Genomic Sequencing. *Journal of Genetic Counseling*, *25*(1), 62–72. https://doi.org/10.1007/s10897-015-9842-8

Vears, D. F., Borry, P., Savulescu, J., & Koplin, J. J. (2021). Old Challenges or New Issues? Genetic Health Professionals' Experiences Obtaining Informed Consent in Diagnostic Genomic Sequencing. *AJOB Empirical Bioethics*, *12*(1), 12–23. https://doi.org/10.1080/23294515.2020.1823906

Yu, J.-H., Appelbaum, P. S., Brothers, K. B., Joffe, S., Kauffman, T. L., Koenig, B. A., Prince, A. E., Scollon, S., Wolf, S. M., Bernhardt, B. A., & Wilfond, B. S. (2019). Consent for clinical genome sequencing: Considerations from the Clinical Sequencing Exploratory Research Consortium. *Personalized Medicine*, *16*(4), 325–333. https://doi.org/10.2217/pme-2018-0076