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Integrating Genetic Counseling And Testing In The Pediatric Oncology Setting: Parental Attitudes And Influencing Factors

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Integrating Genetic Counseling and Testing in the Pediatric Oncology Setting: Parental Attitudes and Influencing Factors

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ABSTRACT

Cancer predisposition syndromes (CPS), caused by germline pathogenic variants in tumor suppressor genes and oncogenes, are genetic conditions that put an individual at increased risk to develop cancer. It is estimated that 10-15% of children with cancer have an underlying CPS. Although genetic testing for these conditions has become routine in the adult setting, incorporation of germline genomic technologies into pediatric cancer care has not occurred as rapidly. The purpose of this study is to assess desire for genetic counseling and testing services among parents of children with cancer to provide parental insight in the incorporation of genomic technologies in this health care setting. Forty-two parents of individuals diagnosed with cancer less than 18 years of age completed either a paper (n=8) or online survey (n=34) regarding their child's cancer history, personal perspectives on genetic counseling, and family/demographic information. Interest in genetic testing for CPS was variable, with 50% of respondents indicating they would be interested in pursuing genetic testing for their affected child while one-third of respondents indicated that they were unsure if they would pursue genetic testing. The factors most commonly cited as impacting interest in genetic counseling/testing include the potential for

modification of medical care for family members and for the child's treatment based on results. A subset of parents expressed that concerns for genetic discrimination and potential negative impact on mental health would negatively influence their interest in genetic testing for CPS. Genetic counselors have an ideal skillset to help families weigh the benefits and drawbacks of genetic testing for CPS in childhood in order to facilitate decision-making among this population as the availability and clinical utility of genomic testing increases.

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LIST OF ABBREVIATIONS

AACR.....American Association of Cancer Research

ACC.....Adrenocortical carcinoma

BWS.....Beckwith-Wiedemann syndrome

CGES.....Clinical genomic and exome sequencing

CMMRD.....Constitutional mismatch repair deficiency

CPS.....Cancer predisposition syndrome

FAP.....Familial adenomatous polyposis

FDR.....First-degree relative

HIPAA.....Health Insurance Portability and Accountability Act

JMML.....Juvenile myelomonocytic leukemia

LFS.....Li-Fraumeni syndrome

MIPOGG.....McGill Interactive Pediatric OncoGenetic Guidelines

MMR.....Mismatch repair

NCCN.....National Comprehensive Cancer Network

NF1.....Neurofibromatosis type 1

NF2.....Neurofibromatosis type 2

NGS.....Next generation sequencing

PCGP ..... Pediatric Cancer Genome Project

SDR ..... Second-degree relative

TuPS ..... Tumor Predisposition Syndromes in Childhood Cancer Patients

VHL ..... Von Hippel Lindau syndrome

WES ..... Whole exome sequencing

WTS ..... Whole transcriptome sequencing

CHAPTER 1

LITERATURE REVIEW

1.1 Overview of pediatric cancer predisposition syndromes

Cancer predisposition syndromes (CPS), caused by germline pathogenic variants in tumor suppressor genes and oncogenes, are conditions that put an individual at increased risk to develop a specific set of cancers throughout their lifetime. CPS, also called hereditary cancer syndromes, have been recognized since Alfred Knudson Jr.'s 1971 publication on hereditary retinoblastoma and the two-hit hypothesis but have become more widely acknowledged by the medical community and the general public due in part to articles about the *BRCA1* and *BRCA2* genes in mainstream media as well as the availability of clinical genetic testing (Jolie, 2013; Knudson, 1971). Historically, scientific knowledge about cancer predisposition in childhood (<18 years old) was limited to the context of complex genetic conditions such as Beckwith-Wiedemann syndrome (BWS) and Down syndrome, which increase a child's risk for embryonal tumors and hematologic malignancies, respectively (Clericuzio, 1999). With the advent of next generation sequencing (NGS) and incorporation of genetic testing for adult hereditary cancer syndromes into routine clinical care, cancer genetics research

has expanded to include the use of genomic testing for tumor and germline analysis in pediatric cancer populations. Through these efforts, further links between germline variants and increased risk of childhood cancer are becoming more well defined.

It is estimated that approximately 10-15% of childhood cancers can be attributed to an underlying germline mutation. A study by Zhang et al. (2015) found an overall prevalence of germline mutations in 8.5% of patients with all major subtypes of childhood cancer under 20 years of age enrolled in the Pediatric Cancer Genome Project (PCGP). The proportion of germline mutations in their cohort was significantly greater than the prevalence of cancer predisposition syndromes in the 1000 genomes project, which was used as a control group (Zhang et al., 2015).

In addition to research on germline mutations associated with cancer, multiple groups have performed genomic analysis of tumor samples by using whole exome sequencing (WES), whole transcriptome/RNA sequencing (WTS), and copy number analysis via microarray to identify clinically actionable findings in the treatment of a wide variety of childhood tumor types. Genomic analysis of tumors in these studies resulted in clinically actionable findings for between 38% and 51% of patients. For the purposes of these research projects, clinically actionable findings most often referred to those that would directly

impact medical management such as using a targeted therapy. In these studies, WES was also performed on germline tissues, to assess prevalence of cancer predisposition syndromes. Prevalence of CPS varied from 10-14%, with the highest prevalence identified in a cohort of children that were considered clinically high-risk (Chang et al., 2016; Mody et al., 2015; Oberg et al., 2016; Parsons et al., 2016). The inclusion criteria for each study were different, which may have contributed to the prevalence ranges, and the prevalence of germline mutations in cancer predisposition genes varied based on cancer type.

Certain cancer types have strong associations with hereditary cancer predisposition syndromes, such as adrenocortical carcinoma and Li-Fraumeni syndrome; whereas many childhood hematologic malignancies, such as acute promyelocytic leukemia, are less likely to be associated with a specific cancer syndrome. Aside from cancer type there are a few other clues that healthcare providers can use to identify individuals with an inherited cancer predisposition syndrome, thus facilitating appropriate clinical management. Genetics professionals such as genetic counselors and medical geneticists combine information such as family history and clinical features with information about an individual's tumor type, pattern and age of onset to determine the likelihood of a cancer predisposition syndrome (Knapke, Zelley, Nichols, Kohlmann, & Schiffman, 2012; Schiffman, 2012; Schiffman et al., 2013). Despite the sizable

prevalence of CPS among patients with childhood cancers, in 2016 there were only 16 pediatric cancer genetic counselors in the United States of America according to the Professional Status Survey of the National Society of Genetic Counselors (National Society of Genetic Counselors, n.d.). This means that many medical centers that provide childhood cancer care do not yet have genetics professionals integrated into their pediatric oncology departments.

Due to these recent studies and the subsequent increasing awareness of childhood hereditary cancer syndromes, organizations including the Society for Pediatric Oncology and Hematology and members of the National Society of Genetic Counselors have published review articles for their members. These reviews provide general overviews of the types of cancer seen in childhood and their associations with known cancer predisposition syndromes. Recommendations on when to consider a childhood cancer predisposition syndrome, colloquially referred to as "red-flags", are also mentioned in the reviews. Although these do not encompass every syndrome with childhood cancer risk, these articles are intended to provide succinct information about common cancer predisposition syndromes as well as tips for how to identify individuals who may benefit from genetics consultation (Ripperger et al., 2017; Saletta, Dalla Pozza, & Byrne, 2015; Scollon, Anglin, Thomas, Turner, & Schneider, 2017).

1.2 Genetic counseling referral criteria

Although these review articles provide a general introduction to childhood cancer predisposition and "red-flags" that should prompt consideration of a genetics referral, specific referral criteria are out of the scope of these reviews. In one of the first studies of pediatric cancer genetic risk assessment, Knapke et al (2012) reviewed charts of individuals in a pediatric cancer survivorship clinic and determined that 29% of individuals in their cohort would be eligible for a genetics consultation, with pediatric cancer or family history of cancer as the primary referral indication (Knapke, Nagarajan, Correll, Kent, & Burns, 2012). In response to the Knapke study, several institutions have developed clinical screening tools to identify individuals at risk for childhood cancer predisposition syndromes that would justify referral to genetic counseling and/or clinical genetics. These clinical screening tools incorporate tumor type, clinical features, and family history to identify those individuals that would be most appropriate for genetics referral.

There are three main referral tools that range in complexity and are variable in their approach to eliciting information. The simplest of the three is a one-page document published by Jongmans et al. in 2016, which provides general criteria that can be applied to any child with cancer (Jongmans et al., 2016). The second referral tool, called the Tumor Predisposition Syndromes in

Childhood Cancer Patients (TuPS) was first developed in 2013 and revised in 2017 by the Department of Pediatric Oncology of Emma Children's Hospital. In both iterations of the TuPS, clinicians are prompted to include more detailed information about patient and family history targeted towards specific CPS, yet the tool still remains applicable to all pediatric cancer types (Hopman et al., 2013; Postema, Hopman, de Borgie, et al., 2017). Lastly, the McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG) is the most specialized of the referral tools. The authors outlined a set of universal criteria, similar to those in the tool by Jongmans et al., but also provide information on the development of tumor-specific algorithms that ultimately will be reviewed by panels of experts and incorporated into a mobile application (Goudie et al., 2017). Although these instruments vary in their approach, the three primary categories of tumor type, clinical features, and family history are reflected in each referral tool.

1.2.1 Tumor types associated with automatic referral

Perhaps the most straightforward referral criteria captured by these clinical screening tools are malignancies that automatically warrant referral to a genetics team even in the absence of congenital anomalies or significant family history. The referral tools include several pediatric tumor types that automatically warrant genetics referral, but the number of tumor types included varies between 20 and 34 depending on the tool. These tumor types are selected

for inclusion in the referral tool based on the incidence of cancer predisposition syndromes among individuals diagnosed with a specific tumor type. Incidence to appropriately warrant automatic referral is often defined as greater than 5-10%.

Although not a formal referral tool, Plon and Nathanson (2005) discuss twelve pediatric tumor types in which there is at least a 10% incidence of cancer predisposition. Among these tumor types is retinoblastoma, with the chance of a germline pathogenic variant in the *RB1* gene up to 15% in individuals with unilateral disease and approaches 100% in individuals with bilateral disease. Other tumor types in their list include adrenocortical carcinoma (ACC), 50-80% of which are due to an inherited *TP53* mutation resulting in a diagnosis of Li-Fraumeni syndrome (LFS), and a host of cancers associated with neurofibromatosis type 1 (NF1) including juvenile myelomonocytic leukemia (JMML), optic pathway tumors, and malignant peripheral nerve sheath tumors (Plon & Nathanson, 2005). Age of tumor diagnosis is also incorporated into some of the tumor type criteria with the most common example being any carcinoma diagnosed in childhood (Jongmans et al., 2016; Postema, Hopman, Aalfs, et al., 2017). The presence of multiple malignancies is also addressed in the referral tools, although their focus is divergent. In the Jongmans tool, the authors include comments regarding secondary malignancies that can be attributed to treatment

modality. The MIPOGG by Goudie et al., however, put more emphasis on bilateral and multifocal tumors (Goudie et al., 2017).

1.2.2 Clinical and family history related to genetics referral

The incorporation of clinical features in the referral tools can be more challenging due to demanding clinic schedules of pediatric oncologists, and the fact that many pediatric cancer predisposition syndromes are not associated with congenital anomalies or dysmorphic features. A systematic approach to identify children with cancer who may have a cancer predisposition syndrome based on clinical features was published in 1999 by Carol Clericuzio. In the article, she identifies 11 categories of major and minor malformations that can be evaluated on physical exam and may help providers recognize the presence of a childhood tumor predisposition syndrome (Clericuzio, 1999). The abnormalities described by Clericuzio include differences in growth, various dermatologic findings, and abnormalities of the gastrointestinal and genitourinary tracts among others, all of which are associated with syndromic forms of cancer predisposition. The tool published by Jongmans et al. provides general guidelines for relevant clinical features like the categories of malformations described by Clericuzio. These include congenital anomalies, growth and skin abnormalities, hematological conditions, and immune deficiency (Jongmans et al., 2016). The TuPS screening instrument incorporates specific examples of clinical features which may be

indicative of a cancer predisposition syndrome. Each body system included on the tool has between one and seven distinct features to guide a targeted physical examination (Hopman et al., 2013; Postema, Hopman, de Borgie, et al., 2017). In the MIPOGG, Goudie et al. discuss the associations of specific tumor types and clinical features that together can be indicative of a cancer predisposition syndrome. Since the information gained from this approach is much more detailed, it is likely that the integration of clinical information into the tool provides a more comprehensive and targeted assessment of the utility of genetics referral for a given patient. However, with increased detail comes added complexity; this can be time consuming in already busy practices (Goudie et al., 2017).

All the screening instruments incorporate family history information; however, some are more comprehensive than others. In the simplest referral tool published by Jongmans et al., the family history section addresses general patterns, such as "a first degree relative (parent or sibling) with cancer < 45 years of age" and consanguinity (Jongmans et al., 2016). The universal criteria of the MIPOGG are comparable to the Jongmans criteria in level of detail, but incorporate different factors such as family member(s) with cancer in the same organ regardless of age (Goudie et al., 2017). The TuPS tool, however, provides space to include more detailed family history information. The original TuPS

screening instrument included in the 2013 publication by Hopman et al. has space to indicate both cancer and morphological abnormalities in the family. The revision in 2017 expanded this section by asking users to indicate ethnic background and prompting about non-oncologic features of the family history including intellectual and learning disabilities (Hopman et al., 2013; Postema, Hopman, de Borgie, et al., 2017). While the information captured by the TuPS instrument is more comprehensive, the additional time required to complete it may not be practical in a clinical setting.

1.3 Genetic counseling utility

From a clinical perspective, identification of a pediatric cancer predisposition syndrome can be critical for a child's clinical management. Like many adult cancer predisposition syndromes, a clinical or molecular diagnosis of a cancer predisposition syndrome can influence cancer screening initiation or frequency to either prevent or detect cancer at an earlier and more treatable stage. Cancer screening and management guidelines for genetic syndromes have been proposed in the literature as early as the 1990s, and often were embedded in articles discussing cancer predisposition syndromes and genetic testing considerations for these syndromes (Clericuzio, 1999; Strahm & Malkin, 2006; Teplick, Kowalski, Biegel, & Nichols, 2011). In the summer of 2017, however, members of the Pediatric Cancer Working Group established by the American

Association of Cancer Research (AACR) collaborated to publish several syndrome-specific management guidelines in the Clinical Cancer Research Pediatric Oncology Series. Screening guidelines proposed by the AACR for each syndrome meet a list of criteria, including the existence of effective screening modalities and a 5% or greater risk of developing cancer by the age of 20. These AACR management guidelines were published in an effort to promote consistency of care among pediatric oncology centers internationally (Brodeur, Nichols, Plon, Schiffman, & Malkin, 2017).

Although there are several publications regarding appropriate clinical indications for genetics referral and management guidelines for individuals diagnosed with a pediatric tumor predisposition syndrome, recent research of physicians in pediatric oncology has demonstrated a majority of providers lack of comfort with the genetic testing process (Johnson et al., 2017). This study identified a general lack of confidence in ordering, interpreting and discussing results of somatic and germline clinical genomic and exome sequencing (CGES), with 35% of providers expressing confidence with somatic results and 27% expressing confidence with germline results. Regardless of provider confidence, however, 93% of respondents stated a preference to include genetic counselors in the process of germline results disclosure. The authors concluded that even among specialized pediatric hematology and oncology providers at a National

Comprehensive Cancer Network (NCCN) facility there is a need for additional education and training about genomic testing and further argue in support of incorporating genetic counselors into the subspecialty of pediatric oncology.

While providers indicate a preference for incorporation of genetic counseling into pediatric cancer care, parent interest in genetic counseling among this population remains unknown. Research of this type, however, has been done in the adult population, which can provide a framework through which to address this topic in the pediatric cancer population. In a systematic review, Willis et al (2016) identified sociodemographic, psychosocial, and clinical factors implicated in the utilization of genetic counseling services for adult hereditary cancer. Age, sex, ethnicity, socioeconomic status, and marital status are among the sociodemographic factors cited in their research. Psychosocial factors impacting uptake of genetic counseling in the adult population include knowledge of genetic counseling, perceived risk of cancer or a mutation, perceived utility, and general distress. Referral characteristics such as timing have also been studied in relation to genetic counseling interest and uptake. Studies in adult populations have demonstrated that longer length of time between treatment and referral, as well as poor referral timing in relation to treatment is associated with decreased uptake of genetic counseling services. Willis et al. provide a review of these findings, as well as the findings of other

groups who have failed to confirm the association (Willis et al., 2016). These factors may also impact parental interest in genetic counseling for pediatric cancer predisposition syndromes.

1.3.1 Genetic counseling considerations

In addition to the factors identified by Willis et al., there are multiple unique considerations in pediatric cancer genetic testing that are not applicable in the adult cancer realm. For instance, genetic testing of minors is a highly-debated topic, and it is generally agreed among healthcare professionals that genetic testing should not be pursued in minors unless the results would directly impact clinical management. This concept is often boiled down to the question, "is this testing in the best interest of the child?" (Kesserwan, Friedman Ross, Bradbury, & Nichols, 2016). Pediatric cancer predisposition syndromes often blur this line, as recommendations for surveillance and management of these conditions have previously been institution specific, prior to the publication of formal national guidelines. The best interest for the child can be interpreted in a variety of ways depending on who is asking the question. Healthcare providers and families have differing perspectives and will pull upon different beliefs to make decisions regarding genetic testing.

Brozou et al. assessed interest in trio WES among parents of children recently diagnosed with cancer. Of the 94 families invited to participate, 83

(88.3%) consented to WES. Fear of the results was the most common reason for refusal among the 11 families that chose not to participate. It was concluded that knowledge of an underlying CPS is preferred by the majority of families involved in their study (Brozou et al., 2017). In the genetic counseling recommendations made by the AACR, Druker et al. stress the importance of pre-test genetic counseling to ensure families have been given the information required in order to truly provide informed consent (Druker et al., 2017). Decisions about pursuing genetic testing should not only be made based on medical relevance but also on the psychosocial impact testing and subsequent changes in medical management may have on the patient and family. The age of the child also plays a large role in the decision of whether to pursue genetic testing. Whenever possible, the child should be included in the decision-making process, and informed assent is often required from older children.

To further complicate the matter, genetic testing for CPS in childhood could also provide risk information that is not relevant until adulthood. Some cancer predisposition syndromes that present in childhood are caused by biallelic mutations in adult cancer predisposition genes, such as those in the mismatch repair (MMR) pathway. Heterozygous mutations in MMR genes are consistent with a diagnosis of Lynch syndrome, an adult onset colorectal cancer predisposition syndrome; however, biallelic mutations in an MMR gene are

consistent with a diagnosis of constitutional mismatch repair deficiency (CMMRD) which predisposes to multiple pediatric and adult cancer types. Lynch syndrome can inadvertently be diagnosed in a child if CMMRD is suspected and only one pathogenic mutation in a MMR gene is identified. It is therefore critical to introduce the possibility of inadvertently diagnosing an adult-onset condition in both the adult as well as the child during pre-test counseling.

As next-generation sequencing becomes more affordable, many institutions that care for children with cancer now include tumor genomic testing as a tool to refine risk stratification and modify treatment. This process is often initiated by the patient's primary treatment team and usually does not include the same informed consent process as germline genetic testing does. Tumor testing, however, can uncover germline status either using a germline sample for comparison or even based on allele frequency. Patterns of somatic mutations within the tumor can also be suggestive of an underlying CPS such as tumor hyper-mutation in individuals with a defect in the MMR pathway (Everett, Mody, Stoffel, & Chinnaiyan, 2016). It has been debated whether these incidental findings should be disclosed to patients and their families, especially when obtained through research protocols (Kesserwan et al., 2016). In general, researchers advocate incorporation of information about incidental germline

findings into the pre-test counseling process for testing that utilizes NGS technology (Kuhlen & Borkhardt, 2015). Lolkema et al. discuss the ethical, legal and social implications of this matter in the adult oncology setting, supporting return of clinically actionable results due to the ethical principle of the duty to warn (Lolkema et al., 2013).

The process of results disclosure to the patient and family is also a complex process and can be stressful. Schneider and Jasperson advocate honest and age appropriate results disclosure, which is associated with better outcomes (Schneider & Jasperson, 2015). In contrast to results disclosure in the adult setting, the results of genetic testing in the pediatric oncology realm are disclosed to the parents or guardians of the child; depending on the patient's age, results may not be initially given to them. Follow-up in adolescence is especially important for children diagnosed with cancer predisposition syndromes as they transition to managing their own care to ensure they are cognizant of their health risks and potential risks to future children. Return of results after the death of the patient also produces ethical dilemmas, although federal regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, provide guidance in these situations. Scollon et al. also encourage discussion of post-mortem results return during the pre-test counseling process (Scollon et al., 2015). As results of genetic testing also have an impact on other family members

including siblings and more distant relatives, this should be factored into the results disclosure process regardless of whether the patient is living or deceased.

1.3.2 Attitudes toward presymptomatic genetic testing

The myriad of ethical considerations when deciding whether to pursue genetic testing and how to approach results disclosure continue to challenge health professionals and families. Although these are fundamentally personal decisions for families, some case studies and professional commentary have provided insight into decision-making about genetic testing in this population. Evans et al., discusses factors influencing predictive genetic testing among two families with Li-Fraumeni syndrome (LFS), caused by mutations in the *TP53* gene. Between the two families who elected to pursue predictive *TP53* testing in childhood, parental anxiety was cited as the primary reason for pursuing testing (Evans, Lunt, Clancy, & Eeles, 2010). Although genetic testing guidelines in childhood discourage testing if the results would have no immediate impact on medical management, Michael Parker discusses scenarios in which those guidelines may be at odds with clinical judgement. Situations in which a clinician's judgement may support genetic testing for adult-onset conditions in a minor include instances where it is believed that proceeding with genetic testing will enhance the child's well-being. This can include suspicion for an autosomal recessive condition in which heterozygote carriers have increased adult cancer

risks such as Fanconi Anemia and CMMRD (Parker, 2010). Physicians and other healthcare providers must exercise caution when considering predictive testing for cancer predisposition syndromes in childhood and will need to incorporate the clinical judgement in the decision-making process.

Parental perceptions of predictive testing in pediatric oncology have been explored among cohorts of individuals with a family history of familial adenomatous polyposis (FAP), Li-Fraumeni syndrome, neurofibromatosis type 2 (NF2) and von Hippel Lindau (VHL). All four conditions predispose individuals to cancer during childhood and have some screening options available to at-risk individuals. Uptake of predictive testing in childhood for FAP, LFS, NF2 and VHL was assessed in a study by Evans et al. (1997), which showed a 95% uptake of genetic testing for those four conditions in children aged 10-16. Testing specifically for VHL was pursued for children 5-9 years of age and the rate of uptake in that group was 6 out of 18 (Evans, Maher, Macleod, Davies, & Craufurd, 1997).

In a study of parental decision-making regarding genetic testing for familial *TP53* variants, Alderfer et al. found that most parents elected to pursue genetic testing for their children at risk to inherit the variant. The perceived advantages to testing cited in their study included a "need to know", a desire to understand why their child had cancer, and interest in research involvement.

Perceived disadvantages, however, were primarily focused on psychosocial concerns such as cancer worry and privacy or insurance concerns (Alderfer et al., 2015).

Among parents of children at risk for FAP, factors influencing the decision to pursue genetic testing included personalized medical management. Perceived barriers to predictive FAP testing were insurance concerns in addition to lack of provider recommendation, which underscores the importance of individualized risk assessment and discussions of medical management for individuals who are known to have FAP as well as those at risk (Levine et al., 2010). Although interest in genetic counseling and testing have been studied in individuals at risk for these well-known childhood cancer predisposition syndromes, these studies only represent a small proportion of children diagnosed with cancer who may have an underlying cancer predisposition syndrome.

1.4 Rationale

Although there are several publications regarding appropriate clinical indications for genetics referral in pediatric oncology, the perceived utility of genetic counseling from the parental perspective remains unknown. The pediatric oncology subspecialty provides a unique set of genetic counseling and testing considerations relative to other genetics specialties, including testing minors for adult-onset conditions and the possibility of uncovering a germline

cancer predisposition syndrome within the context of routine tumor testing. These unique considerations in pediatric cancer genetic testing have been discussed by genetics professionals; however, parental perspectives of genetic counseling and testing for the pediatric cancer population have not been explored.

1.5 Purpose

The purpose of this study is to assess desire for genetic counseling services among parents of children with cancer, which can be used to inform future genetic counseling referral practices in the pediatric oncology setting. Information gleaned from this study will provide genetic counselors with a better understanding of which patient/parent population(s) may be inherently more receptive to pediatric cancer genetic counseling referral. The results will also give a glimpse into the motivating factors in this group of families, as well as provide crucial information about perceived barriers to genetic counseling services, which in turn can be used to better meet the needs of this population. Administration of the study survey will also serve to increase awareness of genetic counseling and testing among both patients and pediatric oncologists.

CHAPTER 2

INTEGRATING GENETIC COUNSELING AND TESTING IN THE PEDIATRIC ONCOLOGY SETTING: PARENTAL ATTITUDES AND INFLUENCING FACTORS[1]

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2.1 Abstract

Cancer predisposition syndromes (CPS), caused by germline pathogenic variants in tumor suppressor genes and oncogenes, are genetic conditions that put an individual at increased risk to develop cancer. It is estimated that 10-15% of children with cancer have an underlying CPS. Although genetic testing for these conditions has become routine in the adult setting, incorporation of germline genomic technologies into pediatric cancer care has not occurred as rapidly. The purpose of this study is to assess desire for genetic counseling and testing services among parents of children with cancer to provide parental insight in the incorporation of genomic technologies in this health care setting. Forty-two parents of individuals diagnosed with cancer less than 18 years of age completed either a paper (n=8) or online survey (n=34) regarding their child's cancer history, personal perspectives on genetic counseling, and family/demographic information. Interest in genetic testing for CPS was variable, with 50% of respondents indicating they would be interested in pursuing genetic testing for their affected child while one-third of respondents indicated that they were unsure if they would pursue genetic testing. The factors most commonly cited as impacting interest in genetic counseling/testing include the potential for modification of medical care for family members and for the child's treatment based on results. A subset of parents expressed that concerns for genetic

discrimination and potential negative impact on mental health would negatively influence their interest in genetic testing for CPS. Genetic counselors have an ideal skillset to help families weigh the benefits and drawbacks of genetic testing for CPS in childhood to facilitate decision-making among this population as the availability and clinical utility of genomic testing increases.

2.2 Introduction

Cancer predisposition syndromes (CPS) are conditions caused by germline pathogenic variants that put an individual at increased risk to develop cancer throughout their lifetime. CPS, also called hereditary cancer syndromes, have been recognized since Alfred Knudson Jr.'s 1971 publication on hereditary retinoblastoma and the two-hit hypothesis, but have become more widely acknowledged due in part to articles about the *BRCA1* and *BRCA2* genes in mainstream media as well as the availability of clinical genetic testing (Jolie, 2013; Knudson, 1971). Genetic testing for CPS has become increasingly integrated into clinical care for adult patients, in large part due to advances in next generation sequencing (NGS). However, these technologies have not been as rapidly incorporated into routine pediatric cancer care.

Through studies of large cohorts of children with cancer using whole exome sequencing (WES), it has been determined that approximately 10-15% of children with cancer have an underlying CPS (Chang et al., 2016; Mody et al.,

2015; Oberg et al., 2016; Parsons et al., 2016; Zhang et al., 2015). In addition to the general prevalence of CPS, relationships have been established between specific pediatric tumor types and germline genetic changes. For example, retinoblastoma is highly associated with pathogenic changes in the *RB1* gene, with pathogenic variants identified in 15% of patients with unilateral retinoblastoma and nearly 100% of patients with bilateral disease (Plon & Nathanson, 2005). Despite the prevalence of CPS among patients with pediatric cancers and the established associations between cancer types and specific genetic changes, many medical centers do not yet have genetics professionals integrated into their pediatric oncology departments.

Childhood CPS have, however, begun to receive more attention from the medical community in the form of review articles published by Society for Pediatric Oncology and Hematology as well as the National Society of Genetic Counselors (Ripperger et al., 2017; Scollon et al., 2017). In addition to increasing attention to these syndromes, several institutions have developed clinical screening tools to identify individuals at risk for childhood cancer predisposition syndromes that would justify referral to genetic counseling and/or clinical genetics. These clinical screening tools incorporate tumor type, clinical features, and family history with or without dysmorphology evaluation to select those individuals that would be most appropriate for genetics referral (Goudie et al.,

2017; Hopman et al., 2013; Jongmans et al., 2016; Postema, Hopman, de Borgie, et al., 2017).

Although there are several publications regarding appropriate clinical indications for genetics referral, the perceived utility of genetic counseling from the parental perspective remains unknown. Formal guidelines for treatment and management of specific CPS were published in the summer 2017 Clinical Cancer Research Pediatric Oncology Series to promote uniformity of care in this patient population (Brodeur et al., 2017). With the increasing attention on pediatric CPS, studies have been done to assess provider interest in and comfort with incorporating genetic/genomic testing into childhood cancer care. These studies have demonstrated a lack of comfort with the process of genetic testing and an interest in incorporating genetic counselors into this aspect of cancer care (Johnson et al., 2017). Despite the push to incorporate genomic testing into pediatric cancer care from the scientific and medical communities, little is known about parental perspectives on this topic.

In addition to limited provider comfort and uncertainty surrounding parent interest in these technologies, there are several other genetic counseling considerations in the realm of pediatric cancer. Historically, genetic testing for cancer predisposition and other adult-onset conditions in minors has been discouraged due to the principles of autonomy and right to an open future

(Kesserwan et al., 2016). Pediatric CPS genetic testing falls in an ethical grey-zone, as genes implicated in childhood CPS overlap with adult-onset hereditary cancer syndromes. Germline genetic status can also be identified incidentally during routine tumor genetic profiling, which is used for risk assessment and treatment decisions. This produces an ethical dilemma for providers in determining whether to disclose these results to families since somatic tumor testing does not have a rigorous consent process like germline genomic testing (Everett et al., 2016).

As genetic testing for pediatric cancer predisposition syndromes becomes more accessible, it will be critical incorporate the technology in a thoughtful manner due to the associated ethical complexities. One step towards this end is to gain a deeper understanding of parental attitudes toward genomic technologies among the pediatric cancer population. The purpose of this study is to assess desire for genetic counseling services including motivating factors and perceived barriers to genetic counseling and testing among parents of children with cancer. It is anticipated that most parents surveyed will be interested in genetic counseling and/or testing for their child. Among the factors influencing interest in pediatric cancer genetic counseling, it is expected that prior knowledge of genetic counseling, desire for additional information regarding medical management, and perceived cost will play the largest role in predicting

parental desire for genetic counseling services. As one of the first steps to promoting awareness of CPS among patients and providers, this research may in turn promote access to specialized care for individuals with these rare pediatric cancer predisposition syndromes in the future.

2.3 Materials and Methods

2.3.1 Design and Participants

Both paper and online surveys were conducted to assess attitudes towards genetic counseling and testing among parents of children diagnosed with cancer younger than 18 years of age. Participants were recruited in person at the Palmetto Health Children's Center for Cancer & Blood Disorders clinic during the check-in process for routine office visits. Eligible individuals were given a copy of the questionnaire (Appendix A) as well as a participant resource sheet that provided additional information about genetic counseling (Appendix B). The online questionnaire (Appendix C) was posted on Facebook parent support pages by representatives of "Alex's Lemonade Stand Foundation" (www.alexslemonade.org) and "St. Baldricks Foundation" (www.stbaldricks.org) in order to maintain anonymity of the members of each of these parent support pages.

Responses were collected from October 1st, 2017 until March 1st, 2018. Inclusion criteria for participation consisted of individuals over 18 years old who

are the parent or legal guardian of a child diagnosed with any type of cancer. Any parents who were less than 18 years of age at the time of data collection were excluded from participation. A total of forty-two responses were obtained via paper (n=8) and online (n=34) versions of the questionnaire that met inclusion criteria for the study. An additional 6 paper and 2 online survey responses were obtained but did not meet the inclusion criteria because an insufficient number of questions were answered (n=3), a cancer diagnosis was not indicated (n=2), and/or a patient completed the questionnaire instead of a parent (n=4).

2.3.2 Instrument

The questionnaire consisted of twenty-four and thirty-four questions for the paper and online versions respectively. Differences in the number of questions were necessitated by the format of the online survey program (SurveyMonkey), but the text was maintained between the two delivery models. Survey items were divided into four sections comprising cancer history, perspective on genetic counseling, information about your child/children, and demographic information. The survey instrument was reviewed and edited by all members of the committee prior to submission to the Institutional Review Board (IRB). Informed consent was implied by completion of the questionnaire in accordance with protocol approval by the University of South Carolina IRB (Pro00067851).

2.3.3 Data Analysis

Both quantitative and qualitative data were captured in survey responses. Numerical and categorical responses from the questionnaire were analyzed using descriptive statistics. Chi-square tests for association were used to determine significance ($p < 0.05$) of the association between both patient and parent demographics and parental perspectives on genetic counseling/testing. Factors influencing interest in genetic counseling/testing were assessed using a Likert-type scale (1=strongly disagree; 5=strongly agree) and were represented with descriptive statistics. Lastly, responses to open-ended questions were assigned themes and sub-themes by the principal investigator and reviewed by the committee members.

2.4 Results

2.4.1 Demographic Information

Of the fifty individuals who initiated the questionnaire, data were analyzed for the forty-two participants who both met the inclusion criteria and responded to enough survey items (>50%). Demographic characteristics of the participants are summarized in Table 2.1, which demonstrates that the sample population consisted of mostly female (82.9%; n=34) and Caucasian (80.5%; n=33) participants. Ages of the sample population ranged from 31 to 64 years, with a mean age of 43.78 years. Most participants reported an education level of

Table 2.1 Demographic characteristics of study participants.

Characteristics	Frequency	Percent
Sex (n=41)		
Male	7	17.1%
Female	34	82.9%
Age (n=40)		
31-40y	16	40.0%
41-50y	17	42.5%
51-60y	6	15.0%
61-70y	1	2.5%
Race/Ethnicity (n=41)		
Caucasian	33	80.5%
Hispanic/Latin American	1	2.4%
Black	3	7.3%
Asian/Pacific Islander	2	4.9%
Biracial	2	4.9%
Education Level (n=41)		
Some high school	1	2.4%
High school or GED	1	2.4%
Some college	8	19.5%
Associate degree	4	9.8%
Bachelor degree	11	26.8%
Graduate degree	16	39.0%
Annual Household Income (n=41)		
Less than $25,000	3	7.3%
$25,001-$50,000	3	7.3%
$50,001-$75,000	7	17.1%
$75,001-$100,000	10	24.4%
More than $100,000	14	34.1%
Prefer not to respond	4	9.8%
Region of Residence (n=40)		
Northeast	16	40.0%
Southeast	15	37.5%
West	9	22.5%

a Bachelor's degree or higher (65.8%; n=27) and annual household income greater than $75,000 (58.5%; n=24); however, all education levels and annual income categories were represented in the sample. Most participants also reported that they are married (77.5%; n=31). Fifteen different states of residence were reported, with most participants residing in the northeast [CT, NJ, NY, PA and RI] (40.0%; n=16) or southeast [FL, GA, NC, SC and VA] (37.5%; n=15) United States. Due to the limited number of participants from states that are not on the east coast, the remaining states were categorized as west [AZ, CA, HI, WA and WI] (22.5%; n=9).

2.4.2 Cancer Diagnoses

Participants were asked to provide information about their child who was diagnosed with cancer, which is summarized in Table 2.2. Among the reported childhood cancer diagnoses, most affected individuals were male (64.3%; n=27). Average age at diagnosis was 5.26 years, ranged from 1 to 16 years, and most children were living at the time of the study (88.1%; n=37). On average, children were 6.71 years from diagnosis; however, time since diagnosis ranged from 0-19 years. The cancers reported by participants via a free-text response were sorted into three categories: hematologic (35.7%; n=15), nervous system (38.1%; n=16) and solid cancers (26.2%; n=11) that were approximately equally represented. In addition, two children were diagnosed with more than

Table 2.2 Cancer history and demographic characteristics of the child[ren] diagnosed with cancer.

Characteristics	Frequency	Percent
Sex (n=42)		
Male	27	64.3%
Female	15	35.7%
Age at Diagnosis (n=41)		
Infancy	4	9.8%
Toddler	9	22.0%
Preschool	8	19.5%
Early Childhood	13	31.7%
Middle Childhood	1	2.4%
Adolescence	6	14.6%
Current Age (n=35)		
Toddler	1	2.9%
Preschool	2	5.7%
Early Childhood	10	28.6%
Middle Childhood	7	20.0%
Adolescence	11	31.4%
Adult	4	11.4%
Living or Deceased (n=42)		
Living	37	88.1%
Deceased	5	11.9%
Cancer Type (n=42)		
Hematologic Malignancies	15	35.7%
Solid Tumor	11	26.2%
Nervous System Tumor	16	38.1%
Number of Malignancies (n=42)		
One	40	4.8%
Two or More	2	95.2%
Siblings (n=41)		
None	8	19.5%
One	18	43.9%
Two or more	15	36.6%

one cancer. Participants also provided information about other medical and/or special needs of their child with cancer. Of the 42 children with cancer, 57.1% (n=24) have no additional medical needs aside from cancer treatment. The remaining 18 children had a total of 26 pre-existing or treatment-related health complications depicted in Figure 2.1, the most common of which was learning difficulties (n=7).

Information about cancers in first degree relatives (FDR) and second degree relatives (SDR) of the child with cancer was also collected and outlined in Table 2.3. Of all participants, 64% reported that their child had a family history of cancer (n=27). Two participants reported a family history of other childhood cancers; these were acute lymphoblastic leukemia and choroid plexus carcinoma. Approximately 10% of respondents (n=4) indicated that a parent or sibling of their child was diagnosed with cancer <45 years of age, and 26% (n=11) reported a grandparent, aunt, or uncle was diagnosed with cancer <45 years of age. Among first and second-degree relatives, the most common cancer type was breast cancer (n=8) followed by prostate (n=3) and skin (n=2) cancers. Multiple other cancer types were indicated in family members, and five participants provided history for more distant relatives such as third and fourth degree in the free-text question responses.

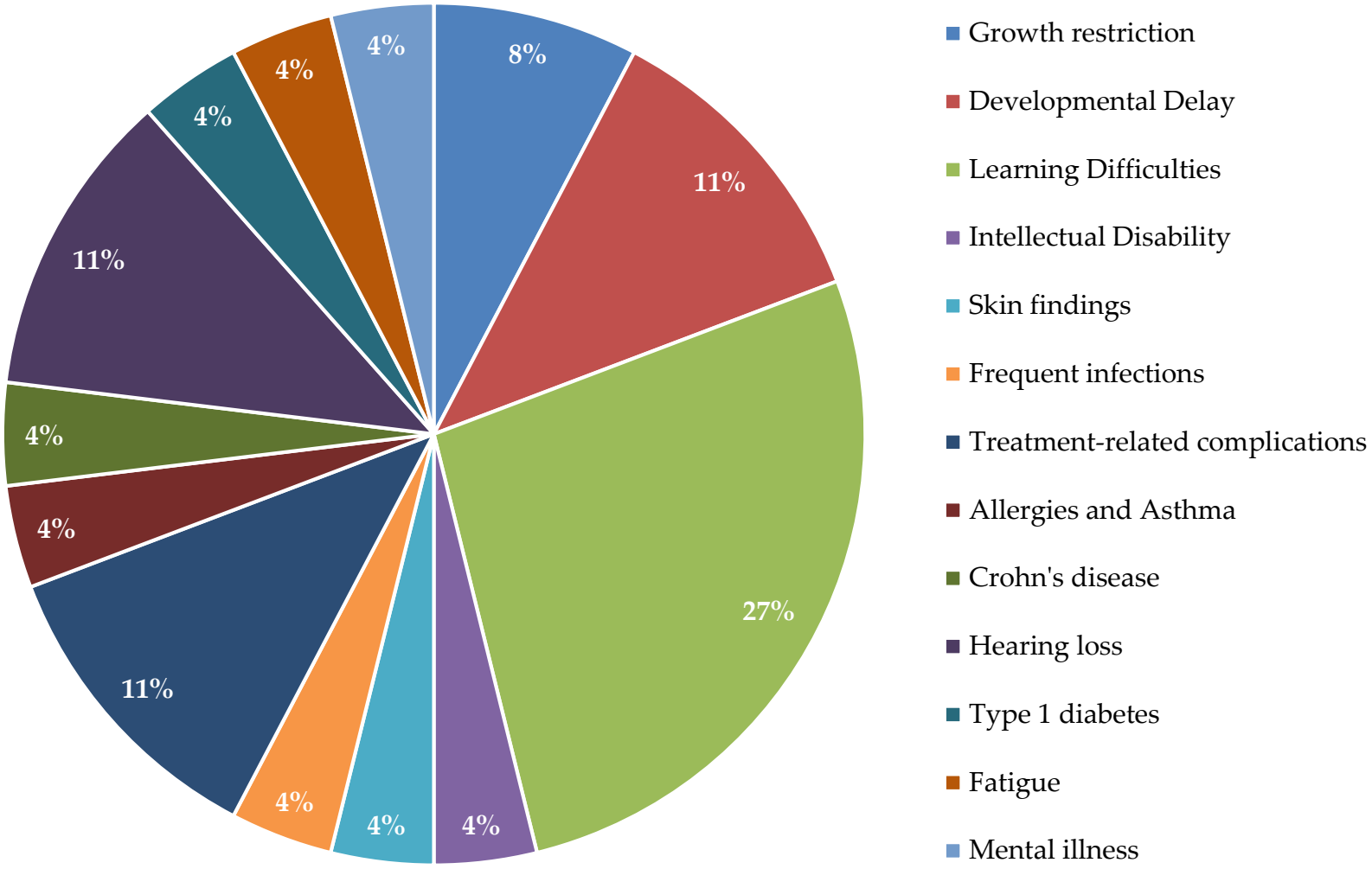


Figure 2.1 Other reported medical and/or special needs of the children with cancer.

Table 2.3 Family history characteristics of the children diagnosed with cancer.

Family History Characteristics	Frequency	Percent
Reported Family History		
1 or more childhood cancers	2	4.8%
1 or more FDR with cancer <45 years	4	9.5%
2 or more SDR with cancer <45 years	11	26.2%
Childhood Cancers		
Acute lymphoblastic leukemia	1	2.4%
Choroid plexus, brain tumor	1	2.4%
FDR Cancer Type		
Breast	2	33.33%
Sarcoma	1	16.67%
Lymphoma	1	16.67%
Thyroid	1	16.67%
Skin	1	16.67%
SDR Cancer Type		
Breast	6	46.15%
Prostate	3	23.08%
Brain	1	7.69%
Skin	1	7.69%
Leukemia	1	7.69%
Ovarian	1	7.69%
Jongmans Criteria		
Meets Criteria	18	42.9%
Does not meet criteria	24	57.1%

The five criteria for genetics referral proposed by Jongmans et al. (2016) were used to determine those participants most likely to benefit from cancer genetic counseling and/or testing. These criteria include: (1) family history of cancer, (2) specific cancer types, (3) two or more malignancies, (4) other anomalies or features, and (5) excessive treatment toxicity (Jongmans et al., 2016). Information from participant report was used to determine whether the criteria were met. Based on the information provided about the child and family's cancer histories, 42.9% (n=18) of participants met the referral criteria outlined in Appendix D.

In addition to cancer history, participants were asked about medical conditions for their other children. In contrast with the 42.9% (n=18) of children with cancer who had additional medical and/or special needs, 9.6% (n=4) reported the child with cancer had a sibling with additional medical and/or special needs. These included 2 individuals with autism spectrum disorder, 1 with chronic sinus infections due to nasal polyps, and 1 with von Willebrand disease.

2.4.3 Perspective on Genetic Counseling

Prior awareness, experience and interest in genetic counseling was assessed in the section of the questionnaire that followed the child's cancer history, which is summarized in Figure 2.2. Many participants (64.3%; n=27)

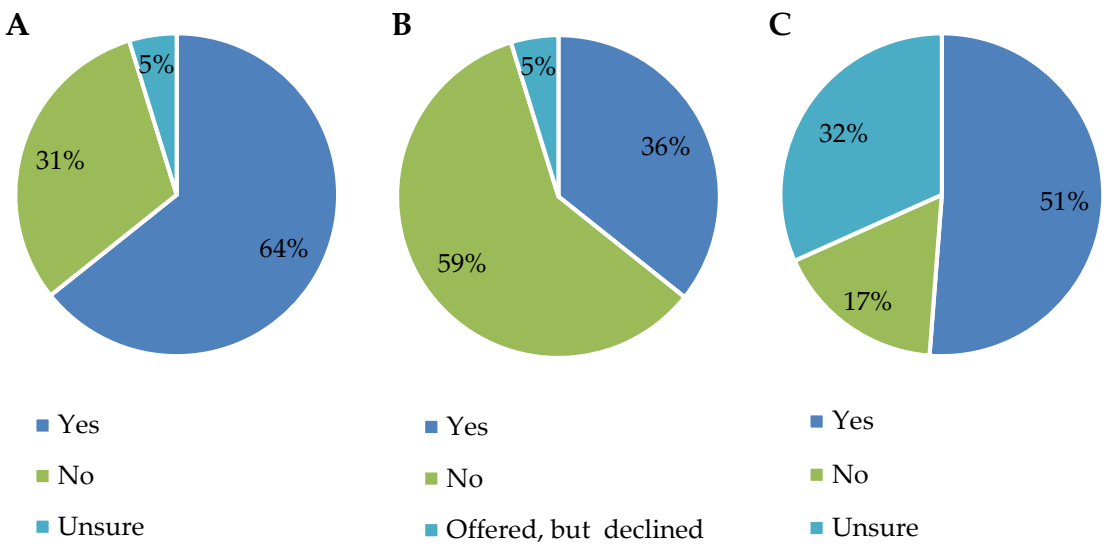


Figure 2.2 Participant perspectives on genetic counseling and/or testing. (**A**) knowledge of genetic counseling prior to participation in the study; (**B**) previous experience with genetic counseling and/or testing regardless of specialty; (**C**) reported interest in genetic testing for hereditary cancer for their child.

reported awareness of genetic counseling prior to participating in the questionnaire. Of the individuals who reported prior awareness, 17 participants reported that they were offered genetic counseling (40.5%), two of which declined (4.8%). The reasons for genetic counseling referral were provided via free-text response and assigned one of the three common referral indications: prenatal, cancer or general genetics. Most participants who were offered genetic counseling reported the referral indication as cancer (52.9%; n=9); however, others reported either prenatal (29.4%; n=5) or general (17.6%; n=3) indications for genetics referral. Examples of non-cancer related referrals included advanced maternal age, testing for chromosome conditions during pregnancy, and

evaluation for Marfan syndrome. These non-cancer related indications accounted for 47.0% of genetic counseling referrals reported among participants.

Participants were also asked about their interest in genetic counseling for their child's cancer history. While half (50.0%; n=21) of participants reported interest in pursuing genetic counseling and/or testing for pediatric cancer indications, 31.0% (n=13) of participants reported they were unsure. Less than 20% (n=7) of participants reported no interest in genetic testing.

2.4.4 Factors Influencing Interest in Genetic Counseling/Testing

In addition to general interest in pursuing genetic testing, participants were presented with seven statements about factors that might influence their interest in genetic counseling/testing. For each statement, participants were asked to rank the level of influence that the factor would have on their interest in pursuing genetic counseling/testing. Each statement had a range of responses on a numerical scale from 1-5; the averages of responses were all greater than 3 (Figure 2.3). The statement with the highest mean score was "if it would impact my family members'/my own healthcare" (mean = 4.64), while "If my child's treatment was complete" had the lowest mean at 3.38.

Participants were also asked what the ideal age would be for pursuing genetic counseling and testing for their child. Over one-third of participants (40.5%; n=17) did not provide any insight into their ideal age for genetic

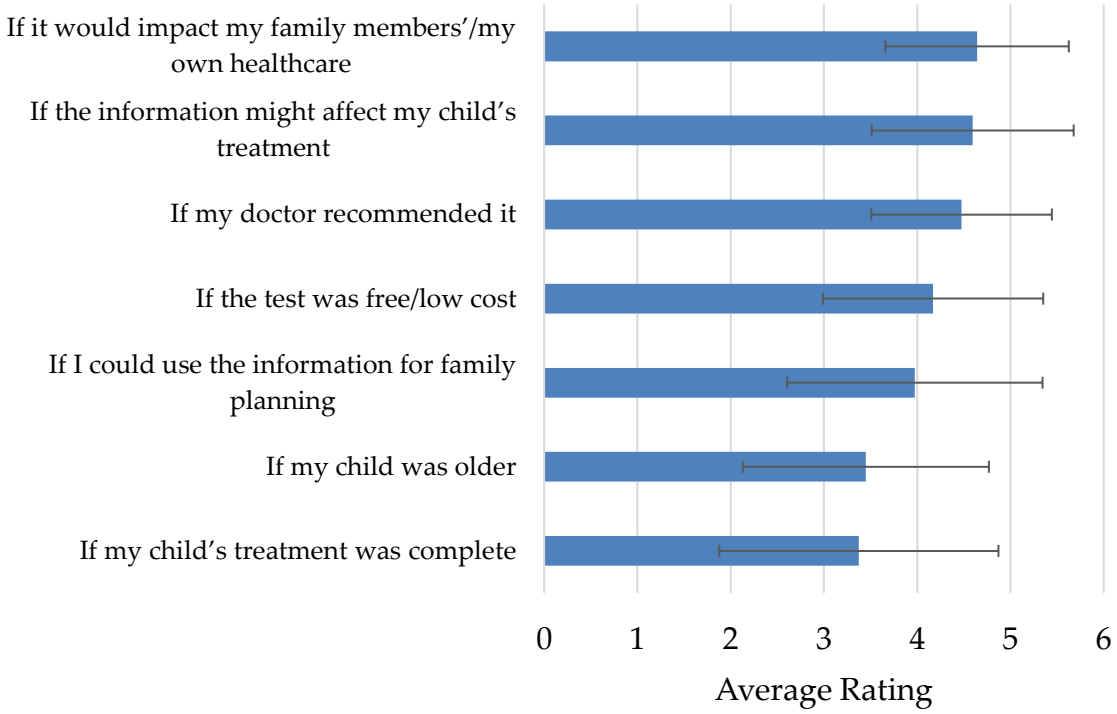


Figure 2.3 Average ratings of factors influencing interest in genetic counseling/testing (1=strongly disagree; 5=strongly agree).

counseling/testing. Of participants that responded to the question about timing (n=25), 28.0% indicated uncertainty (n=7). Most responses did not specify a certain age range, rather they indicated that testing could be pursued at any age (n=5) or when needed (n=7) which accounts for 48.0% of responses. Of those that specified a certain age range, there was not a clear preference for testing in childhood (7.1%; n=3) or waiting until adulthood (4.8%; n=2).

Trends emerged between groups regarding interest in genetic counseling and/or testing with three different demographic factors. These factors were the child's age at diagnosis, sex of the child, and the average household income. A

chi-square test for association was conducted that demonstrated a statistically significant association between the child's age at diagnosis and interest in genetic counseling (p=0.021). Interest in genetic counseling among each age group at diagnosis is represented in Figure 2.4. The highest proportion of parents who were interested in genetic counseling/testing was among parents of children diagnosed as toddlers (35.0%), whereas parents of children diagnosed as adolescents accounted for the smallest proportion of those interested in genetic counseling (10.0%). The greatest uncertainty regarding interest in genetic counseling/testing was among parents of children diagnosed in early childhood (66.7%). None of the parents of children diagnosed in infancy or as toddlers

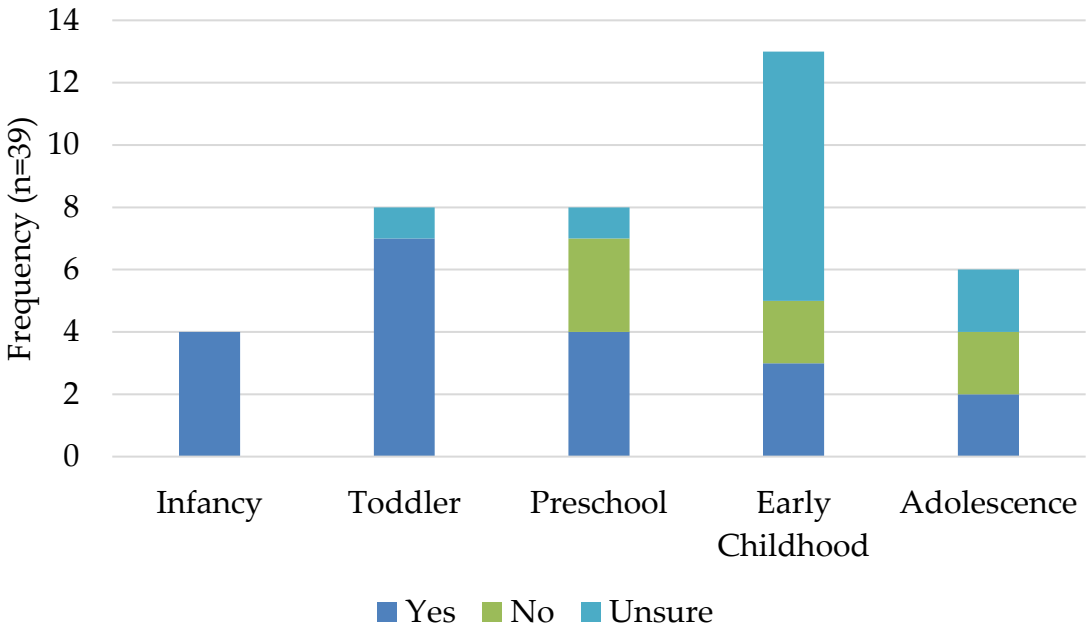


Figure 2.4 Relationship between age of the child's cancer diagnosis and interest in genetic counseling/testing.

reported that they were not interested in pursuing genetic counseling and/or testing. Age at diagnosis was compared with participant ranking of the statement "I would be interested in genetic counseling if my child was older." However, no statistical significant association was identified between the two variables. In contrast with the statistically significant association between age at diagnosis and interest in genetic counseling/testing, there was no evidence of an association between the child's current age (p=0.60), or the duration of time since diagnosis (p=0.80) and interest in genetic counseling/testing.

Another statistically significant finding by chi-square test for association was between the child's sex and interest in genetic counseling (p=0.039). Interest in genetic counseling stratified by child's sex is illustrated in Figure 2.5. Parents of female children with cancer were more likely to be interested in genetic counseling/testing (52.4%) than parents of male children with cancer (47.6%). Lack of interest in and uncertainty about genetic counseling/testing were more common among parents of male children with cancer. All the individuals who reported that they were not interested in genetic counseling/testing were parents of male children with cancer. Of those that reported uncertainty regarding genetic counseling/testing, 69.2% were parents of males with cancer. The child's sex was compared with participant ranking of the statement "I would be interested in genetic counseling if I could use the information for family

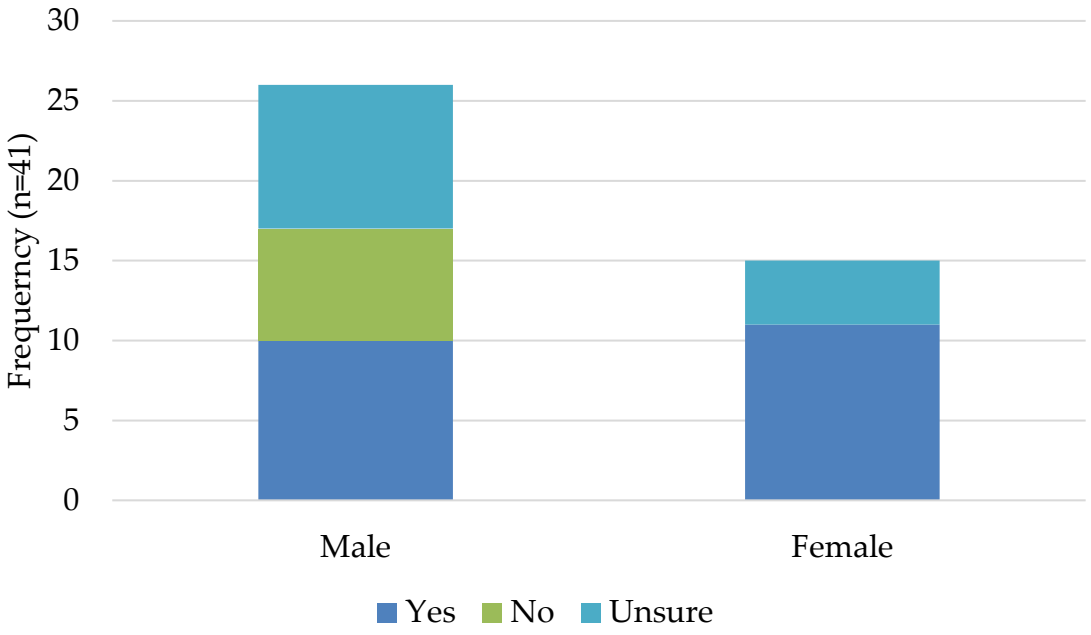


Figure 2.5 Relationship between the child's sex and interest in genetic counseling/testing.

planning." However, no statistical significant association was identified between the two variables.

Participant annual income also demonstrated a statistically significant association with interest in genetic counseling and/or testing (p=0.050). Interest in genetic counseling broken down by annual income is illustrated in Figure 2.6. A higher proportion of individuals who replied "Yes" regarding interest in genetic counseling/testing reported annual income less than $100,000 (70.0%) as compared with those who reported annual income greater than $100,000 (30.0%). In contrast, 35.7% of participants who reported annual income greater than $100,000 indicated that they were not interested in pursuing genetic

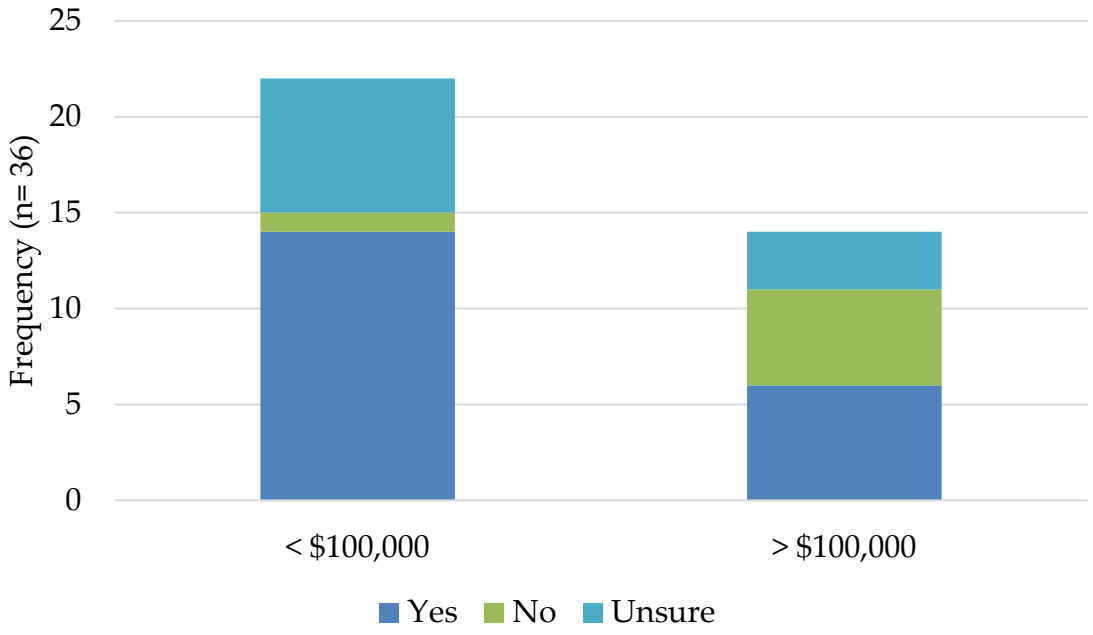


Figure 2.6 Relationship between participant annual income and interest in genetic counseling/testing.

counseling/testing, which accounted for 83.3% of the total respondents who replied "No" regarding interest in genetic counseling/testing. There was no statistical association between annual income and participant responses to the statement "I would be interested in genetic counseling if the test was free/low cost." No statistically significant difference in prior knowledge of or experience with genetic counseling was identified between participants who made less than or equal to $100,000 and greater than $100,000 annually.

Chi-square tests for association were done for all other demographic factors and interest in genetic counseling/testing except for participant sex, race, marital status and type of health insurance due to the limited diversity of

responses in these categories. These analyses showed no statistically significant associations. Of note, interest in genetic counseling/testing appeared to be independent from whether the child met the Jongman's criteria for genetics referral (p=0.981). No statically significant association was observed between prior knowledge of genetic counseling and interest (p=0.668).

2.4.5 Thematic Analysis

Within the questionnaire, participants were asked to provide their thoughts regarding genetic counseling and testing for pediatric cancer predisposition in a free-text format. Of the total participants, 50% (n=21) responded to this question; however, two of the responses were excluded from thematic analysis because they did not provide insight into their reasoning for or against interest in pursuing genetic testing. Themes are broken down into motivators and barriers, which are then further broken down into sub-themes. The sub-themes are organized by observation frequency, which is demonstrated in Table 2.4 and Figure 2.7. Select quotations are provided to illustrate each theme.

2.4.5.1 Motivators for genetic counseling and/or testing.

Most participants who responded to the free-text question described positive factors influencing their interest in genetic counseling and/or testing (n=14). Among the responses, two distinct themes emerged: (1) general

Table 2.4 Themes and sub-themes regarding interest in genetic counseling/ testing identified through free-text question responses.

Theme	Sub-themes
Motivators for Genetic Counseling and/or Testing	General knowledge for family members or other individuals
	Potential utility in treatment, surveillance and/or planning for the child's future
Barriers to Genetic Counseling and /or Testing	Perceived susceptibility to genetic discrimination in health insurance/employment or issues of confidentiality
	Concerns regarding impact of genetic testing results on mental health
	Cost prohibitive nature of genetic/genomic testing

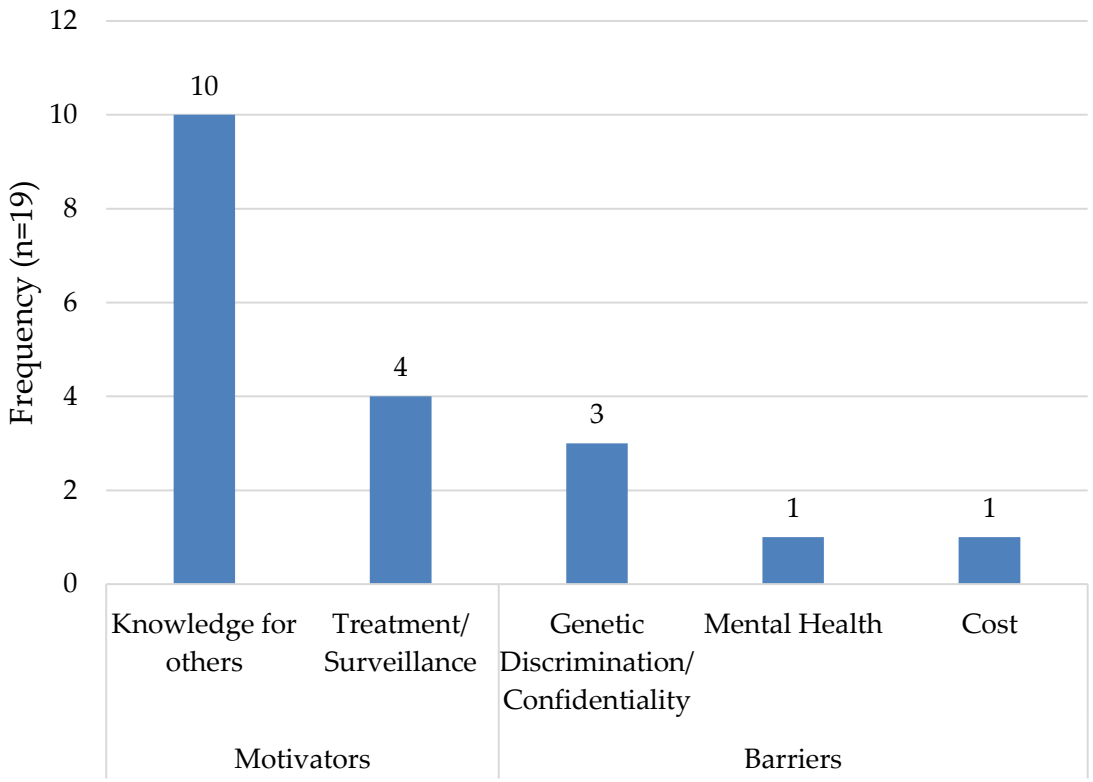


Figure 2.7 Frequency of sub-themes identified through analysis of the free-text question responses.

knowledge for family members or other individuals, and (2) potential utility in treatment, surveillance, and/or planning for the child's future.

Theme 1: General knowledge for family members or other individuals

The most commonly described factor influencing interest in genetic counseling and testing among free-text responses was the desire for knowledge that could help others. Over 50% (n=10) of the free-text responses for this question drew upon the theme of knowledge for others. Some individuals mentioned an interest in gaining the information for their immediate family, while others touched on the desire to help other individuals such as through research.

"I would be willing to do it if it helped my family or anyone else"

Theme 2: Potential utility in treatment, surveillance and/or planning for the child's future

Several individuals highlighted how information gained through genetic counseling and/or testing could be useful for their child's future. Participants expressed uncertainty and concern for their child's future, mentioning that information gained from genetic testing may help them to determine appropriate surveillance.

"I want to know if my sons [sic] cancer has a genetic link or if he holds a predisposition for other cancers. It would allivieate [sic] some of our fears and

worry. What if we stop scanning and he gets cancer again? We might not know till it's too late. If we had genetic testing we would know what to do for the future."

Others highlight the desire for additional information about options for cancer prevention.

"If we could have learned earlier about risks or possible preventative measures, we would have participated."

2.4.5.2 Barriers to genetic counseling and/or testing.

Approximately a quarter (n=5) of responses to the free-text question identified barriers to genetic counseling or testing in this population. Three themes emerged including: (1) perceived susceptibility to genetic discrimination in health insurance/employment or issues of confidentiality, (2) concerns regarding impact of genetic testing results on mental health, and (3) cost prohibitive nature of genetic/genomic testing.

Theme 1: Perceived susceptibility to genetic discrimination in health insurance/employment or issues of confidentiality

A topic of concern brought up by participants (n=3) was the potential for genetic discrimination and issues of confidentiality. One participant discussed their fears that genetic information could be used to deny health insurance coverage for treatment, saying:

"…Also concerned about health insurance companies misusing the information to deny treatment or coverage."

Another parent brought up the sensitivity of genetic information in our current society, which is contrasted by their desire to contribute to medical knowledge.

"I understand the value of pooling genetic information, but security and confidentiality can no longer be guaranteed in our society. Sharing personal information without a definite benefit and the distinct possibility of adverse consequences make it hard to do."

Theme 2: Concerns regarding impact of genetic testing results on mental health

The subject of mental health implications of genetic testing results was also a concern identified by a participant.

"cloud hanging over your head and might affect mental health and outlook on life."

Theme 3: Cost prohibitive nature of genetic/genomic testing

Genetic testing can not only be taxing on financial resources, but also other resources such as tumor tissue as was identified by one participant:

"We didn't pursue due to cost and because they don't have much left of the tumor so we wanted to save it in case he needs treatment in the future."

Overall, participants provide more insight into the motivating factors (n=14) relative to insight about barriers (n=5).

2.5 Discussion

The incorporation of genetic and genomic testing in pediatric oncology has lagged in its adoption in the adult oncology setting; however, recent research has supported the clinical utility of NGS technologies in the pediatric population. A study of provider comfort with genomic testing demonstrated a lack of comfort and an interest in incorporating genetic counselors into the testing process (Johnson et al., 2017). Genetic counselors are trained in providing education and genetic risk assessment, and can serve as a resource for families in the decision-making process surrounding genetic testing.

2.5.1 Parental Attitudes Towards Genetic Counseling

It was hypothesized that most participants would be interested in genetic counseling/testing; however, only half responded that they were interested in pursuing genetic testing for their child. The participant population demonstrated more uncertainty regarding interest in genetic testing for their child than was expected, with 31.0% reporting they were unsure of their interest. Genetic counselors have an ideal skillset to assist families who are contemplating whether to pursue genetic testing for their child by providing information and support in the decision-making process. Of all participants, 16.7% reported that

they were not interested in genetic testing. However, genetic counseling may still be beneficial as their reasoning for lack of interest was not clearly established through this study. Research by Brozou et al. demonstrated a much higher rate of uptake of WES in families of children with cancer at 88.3%. However, this was assessed after the WES consent process, so it may be that the counseling process alleviated uncertainty leading to uptake of WES (Brozou et al., 2017).

No clear consensus was reached in the sample about an optimal age or timing for genetics referral. Forty-eight percent of participants who responded to the question about timing indicated that genetic testing should be performed either "when needed" or "at any time". Therefore, the results from this study suggest that parental preference regarding timing is not contrary to the genetic counselor recommendations provided by Druker et al. in the AACR Pediatric Oncology Series, which encouraged referral at the time of diagnosis (Druker et al., 2017).

Interest in genetic testing for cancer predisposition syndromes (CPS) among this population was independent of personal or family history characteristics suggestive of a CPS as defined by the Jongmans criteria for genetics referral. It is potentially reasonable then, to offer genetics referral regardless of history, as other research has suggested that family history may not be a reliable tool in assessing the likelihood of a CPS. In a study by Zhang et al.,

only a minority of individuals with a germline pathogenic variant in a gene associated with a known CPS had a suggestive family history (Zhang et al., 2015). Age-related penetrance of CPS and the potential for *de novo* mutations, especially in syndromic forms of CPS, may impact the utility of family history in genetic risk assessment for pediatric CPS.

2.5.2 Factors Influencing Attitudes Toward Genetic Counseling

Contrary to the hypothesis, no statistically significant association was observed between prior knowledge of genetic counseling and interest in pursuing genetic counseling/testing for pediatric CPS. Factors that show statistically significant association with interest in genetic testing were the child's age at diagnosis and sex, as well as the participant's annual household income. There was a trend towards decreased interest in genetic testing as the child's age at diagnosis increased. These findings are inconsistent with results from a 1997 study, which showed uptake of predictive testing for FAP, LFS, NF2 and VHL was 95% among children 10-16 years of age, while uptake of VHL testing from ages 5-9 was only 6 out of 18 (Evans et al., 1997). It is difficult to ascertain why these findings were inconsistent. However, the differences between predictive and diagnostic testing as well as the time since publication of the study by Evans et al. may be contributory.

Another factor associated with interest in genetic testing was the child's sex. None of the parents of female children diagnosed with cancer indicated that they were not interested in genetic testing. It was hypothesized that this may be due to the potential use of genetic information in the child's family planning, although no statistical significance was found with the statement "I would be interested in genetic counseling if I could use the information for family planning." Since this statement was aimed at participant (i.e. the parent) as opposed to their child, it cannot be assumed that participants were not interested in pursuing genetic testing for the child's future family planning. Other studies have demonstrated similar associations between uptake or interest in genetic counseling/testing and sex in both the adult and pediatric cancer populations (Evans et al., 1997; Willis et al., 2016).

Annual income was also a factor that influenced interest in genetic testing. However, instead of increased interest with higher annual income as expected, an inverse association was observed. Prior knowledge of or experience with genetic counseling and/or testing did not differ significantly between income groups and thus cannot account for the identified association between income and genetic counseling/testing interest. In addition, there was not a statistically significant association between annual income and ranking of the statement "I would be interested in genetic counseling if the test was free/low cost." The sub-

theme "cost prohibitive nature of genetic/genomic testing" was only identified in one free-text response, which was less than expected. What then, are the factors that influenced the disparate interest levels between participants in the over $100,000 and under $100,000 groups? It may be that individuals who have an annual household income greater than $100,000 have a heightened concern for the potential for genetic discrimination and concerns of confidentiality. The "perceived susceptibility to genetic discrimination in health insurance/employment or issues of confidentiality" sub-theme was the most identified barrier to genetic counseling and testing among free-text responses. Further research would be useful to clarify which factors influence the observed reduction of interest among parents with an annual income greater that $100,000.

Among the factors influencing interest in genetic counseling/testing assessed via the Likert-scale, the two with the highest average ranking were "if it would impact my family members'/my own healthcare" and "if the information might affect my child's treatment." These echo the sentiment identified by multiple individuals in the free-text responses. Themes observed from the free-test responses focused on the utility of genetic testing results for the child, their family, and others. Many individuals indicated that they would be interested in pursuing genetic counseling/testing if the information could be used to help family members. Others discuss the merits of general knowledge and/or the

benefits for research purposes. Several participants mentioned their interest in the ability to use information from genetic counseling/testing for their child's treatment and surveillance.

2.5.3 Implications for Practice

Parental perspectives on genetic counseling and testing in the pediatric cancer population gained from this study complement the pre-existing medical literature on CPS in childhood. Results from this study support the perceived utility of genetic counseling and testing by parents of children diagnosed with cancer as well as the perceived barriers to uptake of these technologies. Genetic counselors have specialized training that can be used to engage families and assist in weighing the benefits and drawbacks of genetic testing for CPS in childhood. Parental interest in genetic/genomic technology, previously demonstrated lack of provider comfort, and the currently limited number of pediatric cancer genetics professionals support further expansion of genetics professionals into childhood cancer care.

2.6 Limitations and Future Studies

2.6.1 Study Limitations

A major limitation of this study was the small sample size and homogenous participant population. Initially, the survey was administered solely on paper in the Palmetto Health Children's Center for Cancer & Blood Disorders clinic to

obtain a participant population that is representative of families impacted by pediatric cancer in South Carolina. Due to a low response rate, an online version of the questionnaire was generated and distributed via Facebook parent support pages. The smaller subset of participants that responded via paper questionnaire showed more diversity in multiple demographics categories. Due to the homogeneity of participant demographics, several demographic categories were excluded from chi-square association tests. These categories included participant sex, race, educational level, and marital status.

In addition to sample size, another unanticipated limitation was the wording certain questions, such as those in the Likert-scale. It is possible that no associations were found between responses to the Likert-questions and the statistically significant associations between genetic counseling/testing interest and child's age/child's sex, since the Likert questions were directed at the participant rather than their child with cancer. Due to the question wording, factors influencing desire for genetic counseling/testing as they relate to the child with cancer may not have been accurately assessed.

2.6.2 Future Studies

As there were significant limitations regarding sample size, these research questions should be assessed again in a larger and more diverse population. This may be feasible through recruitment in a larger pediatric cancer treatment center.

It would also be informative to compare interest in genetic testing prior to and after pre-test counseling to see how counseling impacts participant interest in pursuing genetic testing. Additional research questions that can be considered include referral timing in the context of the cancer treatment process, as well as investigation into why certain groups are less receptive to genetic counseling and testing, such as families who make greater than $100,000 annually. It would also be prudent to investigate the association between age at diagnosis and interest in genetic counseling/testing as it relates to the child's autonomy. This information is critical for genetic counselors to optimize the information and support provided to families throughout the genetic testing process. For the individuals who reported uncertainty about pursuing genetic testing, qualitative studies may illuminate the primary source(s) of ambivalence. In turn, these insights will enable genetic counselors to better engage these families in their decision-making processes.

REFERENCES

Alderfer, M. A., Zelley, K., Lindell, R. B., Novokmet, A., Mai, P. L., Garber, J. E., … Nichols, K. E. (2015). Parent decision-making around the genetic testing of children for germline TP53 mutations. *Cancer*, *121*(2), 286–293. https://doi.org/10.1002/cncr.29027

Brodeur, G. M., Nichols, K. E., Plon, S. E., Schiffman, J. D., & Malkin, D. (2017). Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *23*(11), e1–e5. https://doi.org/10.1158/1078-0432.CCR-17-0702

Brozou, T., Taeubner, J., Velleuer, E., Dugas, M., Wieczorek, D., Borkhardt, A., & Kuhlen, M. (2017). Genetic predisposition in children with cancer – affected families' acceptance of Trio-WES. *European Journal of Pediatrics*, 1–8. https://doi.org/10.1007/s00431-017-2997-6

Chang, W., Brohl, A. S., Patidar, R., Sindiri, S., Shern, J. F., Wei, J. S., … 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: An*

Official Journal of the American Association for Cancer Research, *22*(15), 3810–3820. https://doi.org/10.1158/1078-0432.CCR-15-2717

Clericuzio, C. L. (1999). Recognition and management of childhood cancer syndromes: A systems approach. *American Journal of Medical Genetics*, *89*(2), 81–90. https://doi.org/10.1002/(SICI)1096-8628(19990625)89:2<81::AID-AJMG5>3.0.CO;2-I

Druker, H., Zelley, K., McGee, R. B., Scollon, S. R., Kohlmann, W. K., Schneider, K. A., & Wolfe Schneider, K. (2017). Genetic Counselor Recommendations for Cancer Predisposition Evaluation and Surveillance in the Pediatric Oncology Patient. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *23*(13), e91–e97. https://doi.org/10.1158/1078-0432.CCR-17-0834

Evans, D. G., Lunt, P., Clancy, T., & Eeles, R. (2010). Childhood predictive genetic testing for Li-Fraumeni syndrome. *Familial Cancer*, *9*(1), 65–69. https://doi.org/10.1007/s10689-009-9245-9

Evans, D. G., Maher, E. R., Macleod, R., Davies, D. R., & Craufurd, D. (1997). Uptake of genetic testing for cancer predisposition. *Journal of Medical Genetics*, *34*(9), 746–748.

Everett, J. N., Mody, R. J., Stoffel, E. M., & Chinnaiyan, A. M. (2016). Incorporating genetic counseling into clinical care for children and

adolescents with cancer. *Future Oncology (London, England)*, *12*(7), 883–886. https://doi.org/10.2217/fon-2015-0022

Goudie, C., Coltin, H., Witkowski, L., Mourad, S., Malkin, D., & Foulkes, W. D. (2017). The McGill Interactive Pediatric OncoGenetic Guidelines: An approach to identifying pediatric oncology patients most likely to benefit from a genetic evaluation. *Pediatric Blood & Cancer*. https://doi.org/10.1002/pbc.26441

Hopman, S. M. J., Merks, J. H. M., de Borgie, C. A. J. M., Aalfs, C. M., Biesecker, L. G., Cole, T., … Hennekam, R. C. M. (2013). The development of a clinical screening instrument for tumour predisposition syndromes in childhood cancer patients. *European Journal of Cancer (Oxford, England: 1990)*, *49*(15), 3247–3254. https://doi.org/10.1016/j.ejca.2013.06.015

Johnson, L.-M., Valdez, J. M., Quinn, E. A., Sykes, A. D., McGee, R. B., Nuccio, R., … 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

Jolie, A. (2013, May 14). My Medical Choice. *The New York Times*, p. A25.

Jongmans, M. C. J., Loeffen, J. L. C. M., Waanders, E., Hoogerbrugge, P. M., Ligtenberg, M. J. L., Kuiper, R. P., & Hoogerbrugge, N. (2016). Recognition

of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. *European Journal of Medical Genetics*, *59*(3), 116–125. https://doi.org/10.1016/j.ejmg.2016.01.008

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. American Society of Clinical Oncology. Meeting*, *35*, 251–269. https://doi.org/10.14694/EDBK_160621

Knapke, S., Nagarajan, R., Correll, J., Kent, D., & Burns, K. (2012). Hereditary cancer risk assessment in a pediatric oncology follow-up clinic. *Pediatric Blood & Cancer*, *58*(1), 85–89. https://doi.org/10.1002/pbc.23283

Knapke, S., Zelley, K., Nichols, K. E., Kohlmann, W., & Schiffman, J. D. (2012). Identification, management, and evaluation of children with cancer-predisposition syndromes. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Meeting*, 576–584. https://doi.org/10.14694/EdBook_AM.2012.32.576

Knudson, A. G. (1971). Mutation and cancer: statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences of the United States of America*, *68*(4), 820–823.

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

Laerd Statistics (2016). Chi-square test for association using SPSS Statistics. Statistical tutorials and software guides. Retrieved from https://statistics.laerd.com/

Levine, F. R., Coxworth, J. E., Stevenson, D. A., Tuohy, T., Burt, R. W., & Kinney, A. Y. (2010). Parental attitudes, beliefs, and perceptions about genetic testing for FAP and colorectal cancer surveillance in minors. *Journal of Genetic Counseling*, *19*(3), 269–279. https://doi.org/10.1007/s10897-010-9285-1

Lolkema, M. P., Gadellaa-van Hooijdonk, C. G., Bredenoord, A. L., Kapitein, P., Roach, N., Cuppen, E., … Voest, E. E. (2013). Ethical, Legal, and Counseling Challenges Surrounding the Return of Genetic Results in Oncology. *Journal of Clinical Oncology*, *31*(15), 1842–1848. https://doi.org/10.1200/JCO.2012.45.2789

Mody, R. J., Wu, Y.-M., Lonigro, R. J., Cao, X., Roychowdhury, S., Vats, P., … 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

National Society of Genetic Counselors. (n.d.). *2016 Professional Status Survey: Salary & Benefits* (p. 70).

Oberg, J. A., Glade Bender, J. L., Sulis, M. L., Pendrick, D., Sireci, A. N., Hsiao, S. J., … 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

Parker, M. (2010). Genetic testing in children and young people. *Familial Cancer*, *9*(1), 15–18. https://doi.org/10.1007/s10689-009-9272-6

Parsons, D. W., Roy, A., Yang, Y., Wang, T., Scollon, S., Bergstrom, K., … Plon, S. E. (2016). Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. *JAMA Oncology*. https://doi.org/10.1001/jamaoncol.2015.5699

Plon, S. E., & Nathanson, K. (2005). Inherited susceptibility for pediatric cancer. *Cancer Journal (Sudbury, Mass.)*, *11*(4), 255–267.

Postema, F. A. M., Hopman, S. M. J., Aalfs, C. M., Berger, L. P. V., Bleeker, F. E., Dommering, C. J., … Merks, J. H. M. (2017). Childhood tumours with a high probability of being part of a tumour predisposition syndrome; reason for referral for genetic consultation. *European Journal of Cancer (Oxford, England: 1990)*, *80*, 48–54. https://doi.org/10.1016/j.ejca.2017.04.021

Postema, F. A. M., Hopman, S. M. J., de Borgie, C. A. J. M., Hammond, P., Hennekam, R. C., Merks, J. H. M., … TuPS study group. (2017). Validation of a clinical screening instrument for tumour predisposition syndromes in patients with childhood cancer (TuPS): protocol for a prospective, observational, multicentre study. *BMJ Open*, *7*(1), e013237. https://doi.org/10.1136/bmjopen-2016-013237

Ripperger, T., Bielack, S. S., Borkhardt, A., Brecht, I. B., Burkhardt, B., Calaminus, G., … Kratz, C. P. (2017). Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *American Journal of Medical Genetics Part A*. https://doi.org/10.1002/ajmg.a.38142

Saletta, F., Dalla Pozza, L., & Byrne, J. A. (2015). Genetic causes of cancer predisposition in children and adolescents. *Translational Pediatrics*, *4*(2), 67–75. https://doi.org/10.3978/j.issn.2224-4336.2015.04.08

Schiffman, J. D. (2012). Hereditary cancer syndromes: if you look, you will find them. *Pediatric Blood & Cancer*, *58*(1), 5–6. https://doi.org/10.1002/pbc.23336

Schiffman, J. D., Geller, J. I., Mundt, E., Means, A., Means, L., & Means, V. (2013). Update on pediatric cancer predisposition syndromes. *Pediatric Blood & Cancer*, *60*(8), 1247–1252. https://doi.org/10.1002/pbc.24555

Schneider, K. W., & Jasperson, K. (2015). Unique Genetic Counseling Considerations in the Pediatric Oncology Setting. *Current Genetic Medicine Reports*, *3*(2), 65–73. https://doi.org/10.1007/s40142-015-0064-z

Scollon, S., Anglin, A. K., Thomas, M., Turner, J. T., & Schneider, K. W. (2017). A Comprehensive Review of Pediatric Tumors and Associated Cancer Predisposition Syndromes. *Journal of Genetic Counseling*, *26*(3), 387–434. https://doi.org/10.1007/s10897-017-0077-8

Scollon, S., Bergstrom, K., McCullough, L. B., McGuire, A. L., Gutierrez, S., Kerstein, R., … Plon, S. E. (2015). Pediatric Cancer Genetics Research and an Evolving Preventive Ethics Approach for Return of Results after Death of the Subject. *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics*, *43*(3), 529–537. https://doi.org/10.1111/jlme.12295

Strahm, B., & Malkin, D. (2006). Hereditary cancer predisposition in children: genetic basis and clinical implications. *International Journal of Cancer*, *119*(9), 2001–2006. https://doi.org/10.1002/ijc.21962

Teplick, A., Kowalski, M., Biegel, J. A., & Nichols, K. E. (2011). Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. *European Journal of Pediatrics*, *170*(3), 285–294. https://doi.org/10.1007/s00431-010-1377-2

Willis, A. M., Smith, S. K., Meiser, B., Ballinger, M. L., Thomas, D. M., & Young, M.-A. (2016). Sociodemographic, psychosocial and clinical factors associated with uptake of genetic counselling for hereditary cancer: a systematic review. *Clinical Genetics*. https://doi.org/10.1111/cge.12868

Zhang, J., Walsh, M. F., Wu, G., Edmonson, M. N., Gruber, T. A., Easton, J., … Downing, J. R. (2015). Germline Mutations in Predisposition Genes in Pediatric Cancer. *New England Journal of Medicine*, *373*(24), 2336–2346. https://doi.org/10.1056/NEJMoa1508054

APPENDIX A – PAPER QUESTIONNAIRE

The following coversheet and questionnaire were distributed to participants in the Palmetto Health Children's Center for Cancer & Blood Disorders clinic.

PARENTAL INTEREST IN GENETIC COUNSELING IN THE PEDIATRIC ONCOLOGY SETTING.

PURPOSE AND BACKGROUND:
You are being asked to volunteer for a research study conducted by Lauren Desrosiers, a graduate student in the Department of Genetic Counseling at the University of South Carolina. The purpose of this study is to assess interest in genetic counseling among parents of children diagnosed with cancer. You are being asked to participate in this study because your child has a current or previous diagnosis of cancer.

PROCEDURES:
If you agree to participate in this study, you will be asked to complete a questionnaire about your familiarity with and interest in genetic counseling, although no prior knowledge of genetic counseling is required. You will also be asked to provide information about your family, including your child's medical history pertaining to their diagnosis of cancer. Upon completion of the questionnaire, please return study materials to a member of the clinic staff.

DURATION:
Participation in the study will take approximately 5-15 minutes.

PAYMENT TO PARTICIPANTS:
You will not be paid for participating in this study.

VOLUNTARY PARTICIPATION:
Participation in this research study is voluntary. You are free not to participate, or to stop participation at any time, for any reason without negative consequences. You are not required to answer any question you do not wish to answer. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

If you have any questions, please contact Lauren Desrosiers by phone (803-545-5775) or email (lauren.desrosiers@uscmed.sc.edu).

If you are willing to be contacted for future research please provide your name and contact information below.

Name: _____

Phone: _____ Email: _____

Cancer History

Please answer the following questions regarding your child who has/had cancer.

1. What is the gender of your child?
   - ☐ Male
   - ☐ Female
   - ☐ Non-binary
   - ☐ Prefer not to respond
2. What type of cancer were they diagnosed with? _____
3. How old was your child when they were diagnosed with cancer? _____
4. Has your child been diagnosed with more than one cancer? If yes, what other cancers?
   - ☐ Yes; Please specify type(s) and age(s) at diagnosis: _____
   - ☐ No
5. Is your child living or deceased?
   - ☐ Living: Current Age _____
   - ☐ Deceased: Age of Death: _____
6. Does your child have any medical concerns or special needs besides cancer? Please provide details on the lines provided.
   - ☐ Birth Defect(s):_____
   - ☐ Growth restriction
   - ☐ Overgrowth
   - ☐ Developmental Delay
   - ☐ Learning Difficulties
   - ☐ Intellectual Disability
   - ☐ Skin differences: _____
   - ☐ Blood condition(s): _____
   - ☐ Frequent infections
   - ☐ Other: _____
7. Is there a history of cancer in the family?
   - ☐ Yes
   - ☐ No
8. If you selected "Yes" for question 7 above, please select all that apply. Please also provide the type of cancer and age at diagnosis for each selection made below.
   - ☐ There are 1 or more cancers in childhood (younger than18 years old): _____
   - ☐ Your child has a parent or sibling with cancer less than 45 years of age: _____
   - ☐ There are 2 or more grandparents or aunts/uncles with cancer diagnosed before 45 years of age (on the same side of the family): _____

Perspective on Genetic Counseling

Genetic counselors are trained health care workers that help people understand the role of genetic factors in disease. They use family and personal medical histories to determine a person's risk of having a genetic change that would increase their chance of having cancer. These changes can cause hereditary cancer syndromes, which may explain why a person developed cancer, and can also give risk information for family members.

9. Have you heard of genetic counseling before beginning this survey?
   - ☐ Yes
   - ☐ No
   - ☐ Unsure
10. Have you or your child had genetic counseling or genetic testing before? (Please select the best answer)
    - ☐ Yes: For what reason? _____
    - ☐ No
    - ☐ Unsure
    - ☐ I was offered genetic counseling or testing, but chose not to accept: For what reason? _____
11. Is genetic testing for hereditary cancer something you would be interested in pursuing for/with your child?
    - ☐ Yes
    - ☐ No
    - ☐ Unsure
12. Please indicate how each of the following statements would impact your interest in genetic counseling or testing with 1=strongly disagree and 5=strongly agree. I would be interested in genetic counseling…

	Strongly Disagree				Strongly Agree
	1	2	3	4	5
i. If my doctor recommended it	☐	☐	☐	☐	☐
ii. If the information might affect my child's treatment	☐	☐	☐	☐	☐
iii. If it would impact my family members'/my own healthcare	☐	☐	☐	☐	☐
iv. If I could use the information for family planning	☐	☐	☐	☐	☐

v. If my child was older ☐ ☐ ☐ ☐ ☐
   a. What is the best age for genetic counseling or testing? _____
vi. If my child's treatment was complete ☐ ☐ ☐ ☐ ☐
vii. If the test was free/low cost ☐ ☐ ☐ ☐ ☐
viii. Other, please specify: _____ ☐ ☐ ☐ ☐ ☐

13. Please share any thoughts you have about your reasoning for/against pursuing genetic counseling or testing.
_____
_____

Information about your child/children

Please answer the following questions about all of your children.

14. How many children do you have? _____
15. How old are your children? Please provide ages for each of them. _____
16. Do any of your other children have medical concerns or special needs besides cancer? Please provide details on the lines provided.

☐ Birth Defect(s):_____
☐ Growth restriction
☐ Overgrowth
☐ Developmental Delay
☐ Learning Difficulties
☐ Intellectual Disability
☐ Skin differences: _____
☐ Blood condition(s): _____
☐ Frequent infections
☐ Other: _____

Demographic Information

Please complete the following questions. This section helps to classify responses among subsets of the population and will not be used in any attempts to identify you.

17. What is your gender?

☐ Male
☐ Female
☐ Non-binary
☐ Prefer not to respond

18. How old are you? _____
19. What race do you most identify with? (Mark all that apply)

☐ Caucasian
☐ Hispanic/Latin American
☐ African-American
☐ Asian/Pacific Islander
☐ American Indian or Alaskan Native
☐ Other, Please specify: _____

20. What is the highest level of education you have completed?

☐ Some high school
☐ High school or GED
☐ Some college
☐ Associate degree
☐ Bachelor degree
☐ Graduate degree

21. Which of the following best describes your current relationship status?

☐ Married
☐ Divorced/Separated
☐ Widowed
☐ In a domestic partnership or civil union
☐ Single, but living with a significant other
☐ Single/Never married

22. What was your total household income last year?

☐ Less than $25,000
☐ $25,001-$50,000
☐ $50,001-$75,000
☐ $75,001-$100,000
☐ More than $100,000
☐ Prefer not to respond

23. What is your zip-code? _____
24. What type of health insurance do you have for your child(ren)?

☐ Private insurance plan (Ex. Aetna, Cigna, etc.)
☐ Medicaid/Medicare
☐ Other, Please specify: _____
☐ No Insurance

Thank you! This concludes the survey. We appreciate your participation. Please refer to accompanying flyer for more details on hereditary cancer and genetic counseling.

APPENDIX B – PARTICIPANT RESOURCES

The following participant resources sheet was distributed to interested participants in the Palmetto Health Children's Center for Cancer & Blood Disorders clinic. It was also distributed electronically to individuals who were recruited through a Facebook post.

What is Hereditary Cancer?

Most cancers are considered sporadic, which means that they happen by chance. Unlike sporadic cancer, hereditary cancers are those that happen because of a genetic change a person is born with that makes them more likely to develop cancer. There are many genes that help our bodies prevent cancer, and changes in those genes can make a person more susceptible to cancer. Researchers have found that up to 10% of children with cancer have a gene change that increased their risk of developing cancer. On their own, genetic changes do not guarantee that a person will develop cancer, but knowing about these can help doctors recommend ways to modify environmental factors or detect cancer earlier.

What is a Genetic Counselor?

Genetic counselors are trained health care workers that help people understand the role of genetic factors in disease. They use family and personal medical histories to determine a person's risk of having a genetic change that would increase their chance of having cancer. These changes can cause hereditary cancer syndromes, which may explain why a person developed cancer, and can also give risk information for family members. Cancer genetic counselors help families to decide whether genetic testing for these types of changes is right for them.

Additional Information

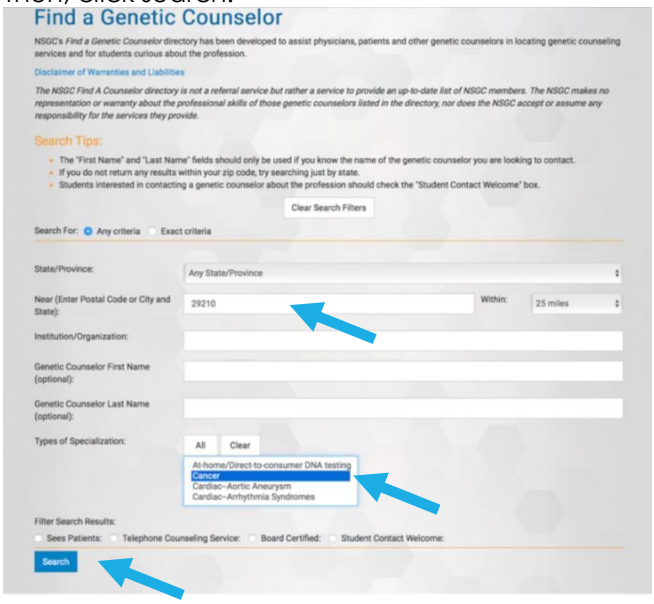
If you are interested in additional information about genetic counseling and/or testing please see the "Locate a Genetic Counselor" section on the back of this document. You may also speak with your child's physician, or contact the University of South Carolina Genetic Counseling department at 803-545-5775 with additional questions.

Locate a Genetic Counselor

If at any point during this questionnaire you became concerned about your child's chance of having a genetic mutation that would increase their risk of having cancer, consider contacting a genetic counselor by following the steps below:

1. Go to the National Society of Genetic Counselors website homepage at: www.nsgc.org
2. On the NSGC homepage, click the link titled, "Find a Genetic Counselor"

3. Enter your postal code and make sure to click "Cancer" under specialization. Then, click search!



APPENDIX C – ONLINE QUESTIONNAIRE

The text below was used to recruit participants via Facebook support groups. Staff members from "Alex's Lemonade Stand Foundation" and "St. Baldricks Foundation" were asked to post this email on the support pages on my behalf in order to protect the privacy of members.

> "Hello,
>
> My name is Lauren Desrosiers and I am a master's candidate in the University of South Carolina genetic counseling training program. For my master's research project, I am studying interest in genetic counseling among parents of children with cancer.
>
> If you are a parent or legal guardian of a child who was diagnosed with cancer under the age of 18, please consider completing my questionnaire to study parental interest as well as factors influencing interest in genetic counseling and testing services in this parent population. This questionnaire should take about 5-15 minutes to complete.
>
> https://www.surveymonkey.com/r/ypb9j2h
>
> Thank you!
>
> Lauren"

The link took participants to the online questionnaire on SurveyMonkey.com, which can be seen in subsequent pages.

Welcome!

Thank you for your interest in participating in my master's research project. Please review the study details below prior to completing this survey.

PURPOSE AND BACKGROUND:
You are being asked to volunteer for a research study conducted by Lauren Desrosiers, a graduate student in the Department of Genetic Counseling at the University of South Carolina. The purpose of this study is to assess interest in genetic counseling among parents of children diagnosed with cancer. You are being asked to participate in this study because your child has a current or previous diagnosis of cancer.

PROCEDURES:
If you agree to participate in this study, you will be asked to complete a questionnaire about your familiarity with and interest in genetic counseling, although no prior knowledge of genetic counseling is required. You will also be asked to provide information about your family, including your child's medical history pertaining to their diagnosis of cancer.

DURATION:
Participation in the study will take approximately 5-15 minutes.

PAYMENT TO PARTICIPANTS:
You will not be paid for participating in this study.

VOLUNTARY PARTICIPATION:
Participation in this research study is voluntary. You are free not to participate, or to stop participation at any time, for any reason without negative consequences. You are not required to answer any question you do not wish to answer. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

If you have any questions, please contact Lauren Desrosiers by phone (803-545-5775) or email (lauren.desrosiers@uscmed.sc.edu).

1. Are you above the age of 18?

- ◯ Yes
- ◯ No

2. Are you a parent or legal guardian of a child diagnosed with cancer under the age of 18?

- ☐ Biological parent
- ☐ Legal guardian
- ☐ Other (please specify)

Cancer History

Please answer the following questions regarding your child who has/had cancer.

3. What is the gender of your child?

- ◯ Male
- ◯ Female
- ◯ Non-binary
- ◯ Prefer not to respond

4. What type of cancer were they diagnosed with?

5. How old was your child when they were diagnosed with cancer?

6. Has your child been diagnosed with more than one cancer?

- ◯ Yes
- ◯ No

Cancer History

Please answer the following questions regarding your child who has/had cancer.

7. Please specify type(s) and age(s) of your child's additional cancer diagnoses

Cancer Type(s)	
Age(s)	

Cancer History

Please answer the following questions regarding your child who has/had cancer.

8. Is your child living or deceased?

- ◯ Living
- ◯ Deceased

Cancer History

Please answer the following questions regarding your child who has/had cancer.

9. How old is your child now?

Cancer History

Please answer the following questions regarding your child who has/had cancer.

10. Does your child have any medical concerns or special needs besides cancer?

- [ ] Birth Defect(s)
- [ ] Growth restriction
- [ ] Overgrowth
- [ ] Developmental Delay
- [ ] Learning Difficulties
- [ ] Intellectual Disability
- [ ] Skin differences
- [ ] Blood condition(s)
- [ ] Frequent infections
- [ ] Other (please specify)

11. If applicable, please provide additional details about your child's special needs.

Cancer History

Please answer the following questions regarding your child who has/had cancer.

12. Is there a history of cancer in the family?

- ◯ Yes
- ◯ No

Cancer History

Please answer the following questions regarding your child who has/had cancer.

13. Please select all that apply based on your child's family history of cancer.

- [ ] There are 1 or more cancers in childhood (younger than18 years old)
- [ ] Your child has a parent or sibling with cancer less than 45 years of age
- [ ] There are 2 or more grandparents or aunts/uncles with cancer diagnosed before 45 years of age (on the same side of the family)

14. Please provide the type of cancer and age of diagnosis for each selection made above.

Childhood cancers	
Parents or siblings	
Aunts, uncles or cousins	

Perspective on Genetic Counseling

Genetic counselors are trained health care workers that help people understand the role of genetic factors in disease. They use family and personal medical histories to determine a person's risk of having a genetic change that would increase their chance of having cancer. These changes can cause hereditary cancer syndromes, which may explain why a person developed cancer, and can also give risk information for family members.

15. Have you heard of genetic counseling before beginning this survey?

- ◯ Yes
- ◯ No
- ◯ Unsure

16. Have you or your child had genetic counseling or genetic testing before? (Please select the best answer)

- ◯ Yes
- ◯ No
- ◯ Unsure
- ◯ I was offered genetic counseling or testing, but chose not to accept

Perspective on Genetic Counseling

Genetic counselors are trained health care workers that help people understand the role of genetic factors in disease. They use family and personal medical histories to determine a person's risk of having a genetic change that would increase their chance of having cancer. These changes can cause hereditary cancer syndromes, which may explain why a person developed cancer, and can also give risk information for family members.

17. For what reason were you offered genetic counseling?

Perspective on Genetic Counseling

Genetic counselors are trained health care workers that help people understand the role of genetic factors in disease. They use family and personal medical histories to determine a person's risk of having a genetic change that would increase their chance of having cancer. These changes can cause hereditary cancer syndromes, which may explain why a person developed cancer, and can also give risk information for family members.

18. Is genetic testing for hereditary cancer something you would be interested in pursuing for/with your child?

- ◯ Yes
- ◯ No
- ◯ Unsure

19. Please indicate how each of the following statements would impact your interest in genetic counseling or testing with 1=strongly disagree and 5=strongly agree. I would be interested in genetic counseling…

	Strongly Disagree				Strongly Agree
If my doctor recommended it	◯	◯	◯	◯	◯
If the information might affect my child's treatment	◯	◯	◯	◯	◯
If it would impact my family members'/my own healthcare	◯	◯	◯	◯	◯
If I could use the information for family planning	◯	◯	◯	◯	◯
If my child was older	◯	◯	◯	◯	◯
If my child's treatment was complete	◯	◯	◯	◯	◯
If the test was free/low cost	◯	◯	◯	◯	◯

Other (please specify)

20. What is the best age for genetic counseling or testing?

21. Please share any thoughts you have about your reasoning for/against pursuing genetic counseling or testing.

Information about your child/children

Please answer the following questions about all of your children.

22. How many children do you have?

23. How old are your children? Please provide ages for each of them.

24. Do any of your ***other children*** have medical concerns or special needs besides cancer?

- [ ] Birth Defect(s)
- [ ] Growth restriction
- [ ] Overgrowth
- [ ] Developmental Delay
- [ ] Learning Difficulties
- [ ] Intellectual Disability
- [ ] Skin differences
- [ ] Blood condition(s)
- [ ] Frequent infections
- [ ] Other (please specify)

25. If applicable, please provide additional details about your other children's special needs.

Demographic Information

Please complete the following questions. This section helps to classify responses among subsets of the population and will not be used in any attempts to identify you.

26. What is your gender?

- ◯ Male
- ◯ Female
- ◯ Non-binary
- ◯ Prefer not to respond

27. How old are you?

28. What race do you most identify with? (Mark all that apply)

- ☐ Caucasian
- ☐ Hispanic/Latin American
- ☐ African-American
- ☐ Asian/Pacific Islander
- ☐ American Indian or Alaskan Native
- ☐ Other (please specify)

29. What is the highest level of education you have completed?

- ◯ Some high school
- ◯ High school or GED
- ◯ Some college
- ◯ Associate degree
- ◯ Bachelor degree
- ◯ Graduate degree

30. Which of the following best describes your current relationship status?

- Married
- Divorced/Separated
- Widowed
- In a domestic partnership or civil union
- Single, but living with a significant other
- Single/Never married

31. What was your total household income last year?

- Less than $25,000
- $25,001-$50,000
- $50,001-$75,000
- $75,001-$100,000
- More than $100,000
- Prefer not to respond

32. What type of health insurance do you have for your child(ren)?

- Private insurance plan (Ex. Aetna, Cigna, etc.)
- Medicaid/Medicare
- No Insurance
- Other (please specify)

33. What is your zip-code?

Thank you for participating!

34. If you are willing to be contacted for future research please provide your name and contact information below.

Name	
Email Address	
Phone Number	

APPENDIX D – JONGMANS ET AL. GENETICS REFERRAL CRITERIA

The referral criteria used to identify whether participants had personal or family history characteristics suggestive of a CPS was developed by researchers from the Netherlands and published in the journal article cited below. The article is published under a Creative Commons license, which permits reproduction of Figure 1 from their paper on the subsequent page.

Jongmans, M. C. J., Loeffen, J. L. C. M., Waanders, E., Hoogerbrugge, P. M., Ligtenberg, M. J. L., Kuiper, R. P., & Hoogerbrugge, N. (2016). Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. *European Journal of Medical Genetics*, *59*(3), 116–125. https://doi.org/10.1016/j.ejmg.2016.01.008

Childhood cancer, indication for referral to a clinical geneticist?

If your patient fulfills one or more of the criteria mentioned below (one or more circles filled), he or she may benefit from referral to a clinical geneticist.

1. Family history of the child with cancer

- ○ ≥ 2 malignancies at childhood age (≤ 18 years of age)
- ○ a first degree relative (parent or sibling) with cancer < 45 years of age
- ○ ≥ 2 second degree relatives with cancer < 45 years of age on the same side of the family
- ○ the parents of the child with cancer are related, i.e. consangious

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2. A person with one of these tumors in childhood

- ○ Adrenocortical carcinoma
- ○ Atypical teratoid rhabdoid tumor
- ○ Cerebellar gangliocytoma
- ○ Choroid plexus carcinoma
- ○ Endolymphatic sac tumors
- ○ Hemangioblastoma
- ○ Hepatoblastoma
- ○ JMML
- ○ Low hypodiploid ALL
- ○ Malignant peripheral nerve sheath tumor
- ○ Medullary thyroid carcinoma
- ○ Medulloblastoma
- ○ Optic glioma
- ○ Ovarian sertoli-leydig cell tumor
- ○ Pleuropulmonary blastoma
- ○ Pituitary blastoma
- ○ Pineoblastoma
- ○ Retinoblastoma
- ○ Schwannoma
- ○ Subependymal giant cell tumor

Or ○ A cancer of adult age, i.e. colorectal cancer, ovarian cancer, basal cell carcinoma etc.

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3. ○ **A child with two malignancies** one of those with onset < 18 years of age (unless the 2nd malignancy is consistent in time and/or tissue type with these expected from their treatment regimen).

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4. ○ **A child with cancer and congenital anomalies or other specific symptoms**

Sign	***Think of***
Congenital anomalies	Organs, bones, oral clefting, teeth, eyes, ears, brain, urogenital anomalies, etc.
Facial dysmorphisms	
Intellectual disability	
Aberrant growth	Length, head circumference, birth weight, asymmetric growth
Skin anomalies	Aberrant pigmentation i.e. > 2 café-au-lait spots, vascular skin changes, hypersensitivity for sunlight, multiple benign tumors of the skin
Hematological disorders	Pancytopenia, anemia, thrombocytopenia, neutropenia
Immune deficiency	

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5. ○ **A child with excessive treatment toxicity**