Assessment of referral patterns and genetic testing after implementation of Pediatric Cancer Predisposition Clinic

by

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Bachelors of Science in Molecular & Cellular Biology, Carlow University, 2014

Submitted to the Graduate Faculty of the

Department of Human Genetics

Graduate School of Public Health in Partial Fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2021

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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It was defended on

April 29, 2021

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ABSTRACT

One in every 700 children is affected by pediatric cancer and 5 to 10% of all cancers are attributable to inherited genetic mutations. A subset of these cancers, referred to as Cancer Predisposition Syndromes (CPS), result from pathogenic mutations that are known to increase cancer risk. Identification of these specific mutations in these patients facilitates treatment, however, many of these patients may not be identified or referred to a genetics clinic. Clinicians at UPMC Children's Hospital of Pittsburgh developed a screening tool to identify patients that might have cancer predisposition syndromes and conducted a retrospective chart review of their patients from 2012-2017. Based on their study, an estimated 40% of pediatric cancer patients who met the criteria for a possible CPS were underdiagnosed. These results highlighted the need for a comprehensive standardized screening tool and referral program to a cancer predisposition clinic. I compared the demographics, referral patterns, and number of patients who tested positive for a genetic mutation associated with a cancer predisposition syndrome before and after the implementation of a cancer predisposition clinic. In general, the racial/ethnic composition of the two studies were similar, and also similar to the composition of western Pennsylvania. However, significantly more males than females were seen by the clinic; pediatric cancer rates and cancer predisposition syndromes were similar. The reason for this discrepancy is unclear, but similar

results were reported by the Boston Children's Hospital. Finally, the number of patients seen in the Cancer Predisposition Clinic increased a mean 26% per year compared to the number of patients that met criteria for referral in the retrospective study, indicating the screening tool and referral program is successful. Increasing access to the cancer predisposition clinic, enables better management of pediatric cancer patients, potentially increasing longevity, and decreasing morbidity and improving overall public health.

Table of Contents

List of Tables

List of Figures

PREFACE

I would like to take the time to thank the members of my essay committee, Candy and Emma. Your support, advice, time, insight, and editing of this essay made it possible to complete this requirement for my program.

Candy and Andrea, thank you for all your guidance and support throughout my time in the program. I would not be approaching graduation if it were not for you both.

I would also like to thank Kate Amodei, Elena Kessler, Kaitlin Stanley, Julia Meade, Linda, McAllister-Lucas, and Wen-I Chang. Thank you for allowing me to use the data from your retrospective study and current clinic for my essay. Thank you for the time and dedication to collect this data.

1.0 INTRODUCTION

Cancer is defined as a group of diseases in which abnormal cells divide without control and can invade nearby tissues.(National Cancer Institute,2015) Several types of risk factors affect the development of cancer including genetics, environmental factors, epigenetic changes to DNA. (Papaemmanuil et al., 2009) According to the World Health Organization (WHO) research, 35% of deaths due to cancer worldwide are due to potentially modifable risk factors some of which include smoking, diet, ultraviolet radiation, physical activty, infections, etc. (Lewandowska, Rudzki, Rudzki, Lewandowski, & Laskowska, 2019)

Currently, 80-90% of malignant tumors are caused by external environmental factors. (Lewandowska et al., 2019) External factors can contribute to epigenetic change, for example DNA methylation, the cell resulting in either cell malfunction ror cell death. Both enivronmental and epigenetic factors can affect numerous cells resulting in a accumulation of changes. When these changes occur along with genetic changes this creates an environment of genetic instability and disrupts cell function resulting in cancer. (Herceg, 2007) Although environmental factors, epigenetics, and genetic predisposition are all play a key role in the development of cancer, cancer is genetic.

Incidence of cancer: --In 2017, 1,701,315 new cases of cancer were diagnosed and between 2013-2017, the cancer incidence rate was 442.2 per 100,000 men and women per year (Centers for Disease Control and Prevention, 2019). Of the 1.7 million total cases, 15,013 (or 0.8%) were individuals <20 years of age. Cancer among individuals < 20yo are defined as pediatric cases of cancer. In Pennsylvania, the total number of new cases of cancer in the state in 2017 was 77,817 of whom 574 (or 0.7%) were <20 years of age. (Pennsylvania Department of Health, 2021) Thus,

the frequency of pediatric cancer in PA is similar to that in the USA. Among the pediatric cancer cases in PA, the frequency is slightly higher in males (51%) than females (49%). In addition, among patients under <20yo, 449 (78%) cases were white and 54 (9%) were black. (Pennsylvania Department of Health, 2021)

Cancer mortality rates. -- Cancer is the second leading cause of death in the United States; In 2019, 599,601 people died from cancer. (CDC, 2021) The cancer mortality rate was 158.3 per 100,000 men and women per year and the rate of mortality due to cancer is higher in men than women. (National Cancer Institute, 2020) Among children (aged 0-19 years old), cancer is the leading cause of death in the United States. In Pennsylvania, 28,318 people died of cancer in 2017 of whom, 53 (or 0.18%) were individuals <20 years old. Of these 53 pediatric cancer deaths, 31 (58%) were females and 22 (42%) were males. The majority of these pediatric cancer deaths were white (37 or 70%) with 9 (17%) Hispanics, 6 (11%) blacks, and 1 (2%) Asian/Pacific Islander. (Pennsylvania Department of Health, 2021)

Types of pediatric cancer:-- Two of the most common types of pediatric cancer are acute leukemia and central nervous system tumors. The two types of acute leukemias [Acute Lymphoblastic Leukemia (ALL) and Acute Myelogenous Leukemia (AML)] account for 25% of newly diagnosed tumors in children under the age of 15. Of the patients diagnosed with leukemia 75% are ALL and 20% are AML. (Hastings, Torkildson, Agrawal, & Hastings, 2012)The overall incidence of pediatric ALL from 2001-2014 was 34.0 cases per 1,000,000 among all ethnic groups. (Siegel et al., 2017) Data provided from the United States Cancer Statistics Data Set reported the highest rate of ALL is among Hispanic males aged 1-4 years. Furthermore, the highest incidence rate of ALL is in the west region of the United States (38.5 per 1,000,000 people), whereas the second highest region was in the northeast with an incidence rate of 34.8 per 1,000,000 people. The risk factors contributing to the high prevalence in the Hispanic population are unknown. Some

potential risk factors discussed were genetic susceptibility, high rate of environmental exposures including household chemicals, and obesity. (CDC, 1997)

Hastings et al. (2012) proposed that most of leukemia cases result from somatic genetic alteration, instead of inherited genetic predisposition. However, several studies have reported genetic variants that are associated with increased risk of ALL. Papaemmanuil et al. (2009) analyzed genotype data that was collected as part of several clinical trials. Some of the participants in these clinical trials had ALL. The investigators conducted a genome-wide association (GWA) study using genotype data on patients with ALL and controls. They identified 10 genetic variants (or single nucleotide variants, SNVs) that were more frequent in patients with ALL than in the control patients. In addition, Treviño et al. (2009) identified 18 SNVs whose allele frequency differed between pediatric ALL patients and controls. They reported that these 18 SNVs influenced an individual's susceptibility to developing ALL. These reports identified variants that should be tested for a predisposition to inherited ALL.

Central nervous system (CNS) tumors are the second most common type of cancer, but the most common type of solid tumor in children, and account for 20% of all pediatric malignancies (Hastings et al., 2012) Based on Surveillance, Epidemiology, and End Results Program (SEER) data, the incidence rate of brain and other CNS tumors is 5.67 per 100,000 persons per year (Udaka & Packer, 2018). The most common type of brain tumor is the medulloblastoma and accounts for 20% of pediatric brain tumors under the age of 10. Between 250 and 500 children are diagnosed with medulloblastomas each year.(Medulloblastoma-Childhood:Statistics,2020) The NCDB 1998-2011 showed that in patients 0-19 diagnosed with a medulloblastoma, 62.9% were males and 37.1% were females, 81.3% were white, 10.7% black, 8% unknown(Dressler, Dolecek, Liu, & Villano, 2017).

1.1 CANCER GENETICS

Cancer genetics has become increasingly integrated into the field of modern oncology, in part because inherited genetic mutations contribute to the development of 5 to 10% of all cancers. (National Cancer Institute,2020) A subset of these cancers, cancer predisposition syndromes (CPS), result from a pathogenic germline mutation in tumor suppressor genes, which confers an increased risk in cancer. (Garber, 2005) Although individuals with genetic predisposition comprise a small portion of the overall cancer patient population, successful implementation of cancer surveillance and prevention programs may significantly decrease this number of cases. By identifying these cancer predisposition patients, physicians would be able to screen other at-risk family members for the specific mutation. If this mutation is detected in a family member, an individualized preventative cancer surveillance plan could be implemented. Cancer screening and prevention program could also decrease the cancer mortality rate. For example, in the 1950s, the mortality rate for cervical cancer in the United State was 12 in every 100,000 women. In 2015, after implementation of Pap smears tests, the mortality rate was 2 in every 100,00 women. (Pinsky, 2015) Thus, the mortality rate of cervical cancer decreased 60%. between 1950 and 2015. Although the current estimate of pediatric cancers associated with cancer predispositions syndromes is 5-10% of all pediatric cancers, this frequency may be higher due to underdiagnosis in pediatric populations. For example, an estimated 181,000 childhood cancers will not be diagnosed in 2020 as part of a cancer predisposition syndrome. (ACCO, 2021) Thus, the need for improvements in referral patterns and standard of care for individuals with pediatric cancers associated with cancer predisposition syndromes is evident.

Cancer genetics may be approached from the identification of cancerous cells which lead to genetic testing or vice versa where patients are identified with a cancer predisposition syndrome

that leads to preventative cancer screening. Li-Fraumeni Syndrome (LFS) is an aggressive cancer predisposition syndrome caused by a mutation in the *TP53* gene. This syndrome can cause numerous different tumors types including brain tumors, hematologic malignances, and soft tissue sarcomas.(Kratz et al., 2017) In 2016, the American Association for Cancer Research held a meeting to discuss LFS and determine the recommended guidelines for surveillance for both pediatric and adult patients. These patient populations should follow the screening guidelines due to lifelong cancer risk.(Kratz et al., 2017)

1.2 CANCER PREDISPOSITION SCREENING TOOLS

To mitigate this issue of under diagnosis of Cancer Predisposition Syndromes, the American Association for Cancer Research held a workshop in 2016 with the primary objective to establish guidelines for surveillance of common pediatric cancer predisposition syndromes. (AACR, 2017) Health professionals from different backgrounds worked together to develop a standardized screening tool to identify patients that are at risk for a CPS. These patients would then be referred for genetic counseling or testing. (Jongmans et al., 2016) After a review of literature, these practitioners developed a tool with five criteria to identify patients at high risk for genetic susceptibility to a cancer predisposition syndrome. These five criteria (Table 1) represent common features of genetic predisposition syndromes. (Brodeur, Nichols, Plon, Schiffman, & Malkin, 2017)

Table 1 Five criteria used to identify a Cancer Predisposition Syndrome (CPS)

1. Family history 2. Bilateral, multifocal, or multiple cancers 3. Earlier age at diagnosis that sporadic tumors of the same type 4. Physical Findings suggestive of a Cancer Predisposition Syndrome 5. Occurrence of specific tumor type that frequently occurs in the context of genetic predisposition. Brodeur et al. (2017)

1.3 UPMC Retrospective Study to Analyze Referral Rates

1.3.1 Development of Screening Tool

In 2017, the Hematology/Oncology Department at UPMC Children's Hospital of Pittsburgh developed a screening tool to identify patients that met criteria for at least one of the six questions on the tool. The complete screening tool is listed under Appendix A. The team created the screening tool based off of screening tools used at other institutions and articles on screening tools that were found through reviewing the literature. The six criteria questions in the tool are based upon the five measures used to classify a cancer predisposition syndrome. One additional question was added (#4) which states, "Does the child have one of the following inherited conditions?". There are 37 at-risk genetic conditions included for this question.(Amodei, 2017)

Of the articles reviewed, there was an article in The European Journal of Medicine, that discussed an easy-to-use selection tool for patients at high risk for a genetic predisposition

syndrome created by a group of physicians in the Netherlands. They created their tool based upon the five characteristics of pediatric cancer predisposition syndromes.(Jongmans et al., 2016) These additional tools reviewed by the hematology/oncology team are listed in the references. (Postema et al., 2017)

1.3.2 Retrospective Study Data Collection

After developing a tool, the physicians and medical students in Hematology/Oncology Department of Children's Hospital of Pittsburgh conducted a small study to analyze the referral rate of individuals with pediatric cancer predisposition syndromes in their clinic to either genetics or cancer predisposition clinics. They conducted a retrospective chart review of pediatric patients who were seen in the past five years (2012-2017) and were identified based on ICD10 codes for congenital abnormalities, pediatric malignancies/tumors associated with cancer predisposition syndromes. They then used the screening tool to classify patients into one of three categories: (1) patients referred for genetic evaluation, (2) patients who met criteria for referral but were not referred, and (3) patients who did not meet criteria for referral. (Amodei, 2017)

1.3.3 Results of Retrospective Study

A total of 562 patients were identified in the retrospective study who met the criteria of a patient identified with a congenital abnormality or pediatric malignancy/tumor associated with cancer predisposition syndromes (Figure 1).

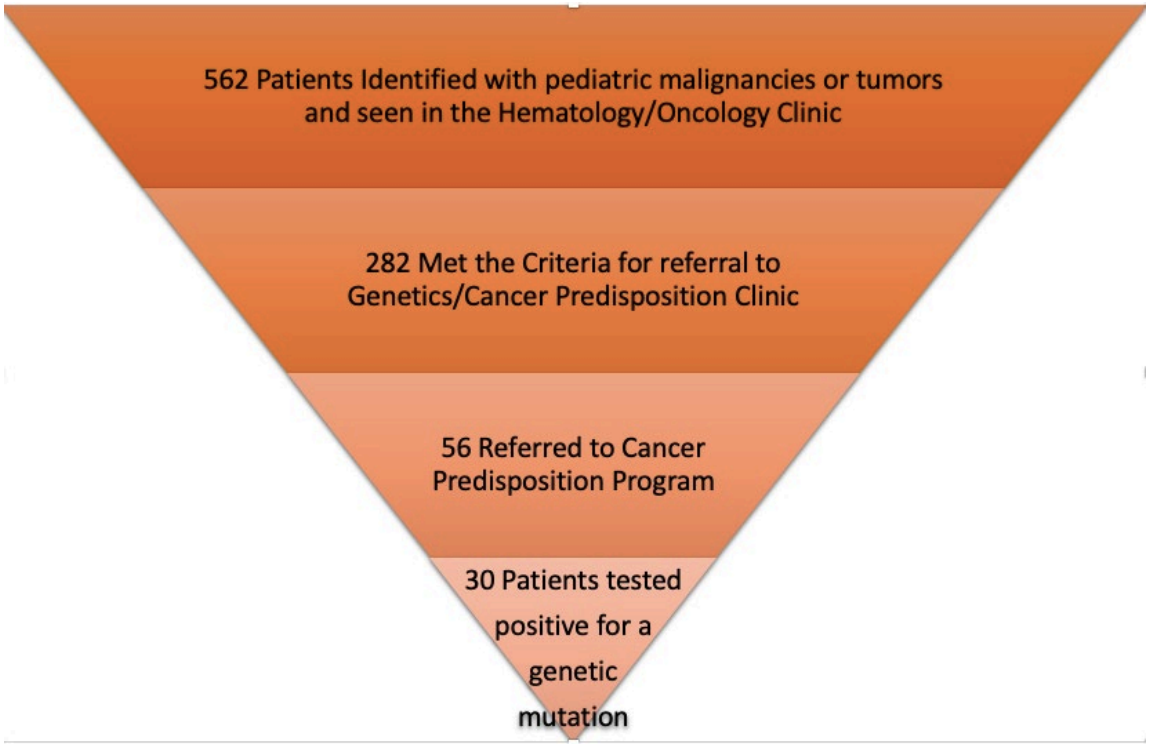

Figure 1 Retrospective Study Results

As displayed in Figure 1, of the total of 562 patients, 280 (50% of 562) patients met the criteria for referral to Cancer Predisposition Clinic. Of the 280 patients, 56 (20% of 280) were referred to Genetics/Cancer Predisposition Clinic. Finally, 30/56 patients (54%) tested positive for genetic mutation associated with a known cancer predisposition risk. (Amodei et al., 2017).

In summary, the results of this retrospective chart review showed that 50% of patients met the criteria for referral for follow-up genetic testing. These results confirmed the need for a standardized screening tool to identify patients with suspected cancer predisposition syndromes. Furthermore, 20% of patients who met the criteria were referred for followup genetic testing of whom 54% received a genetic diagnosis. Therefore, based on this retrospective study, and estimated 44% of patients who met the criteria for referral were underdiagnosed because they were not referred (54% of 80% of patients who were not referred). Thus, an estimated ~20% of patients overall were underdiagnosed and did not receive the potential benefits for care and identification

of other at-risk family members. This result highlights the critical need for a comprehensive, standardized referral program. Based on the results of this study, a multidisciplinary Cancer Predisposition Clinic and referral program were developed. (Amodei et al., 2017).

1.4 Implementation of the Cancer Predisposition Clinic

In 2017, the hematology/oncology department at UPMC Children's Hospital of Pittsburgh established a pediatric cancer predisposition program. This program is currently implemented in an outpatient setting to help families understand hereditary factors that play a role in childhood cancer. The goal of this multidisciplinary clinic is to improve the overall care for children with a genetic risk factor of cancer susceptibility. This clinic comprises several services including oncology physicians, nurses, child life specialists, therapists, and a certified genetic counselor. As part of the multidisciplinary team, a genetic counselor is involved in educating the families about genetic risk factors and future surveillance of predisposition syndromes. The information that is being documented includes, initial diagnosis, confirmed diagnosis and the ICD10 code used to classify the malignancy.

Both the screening tool and the referral process currently being used are based on (1) results from retrospective study and (2) methods being used by other centers that have a cancer predisposition program.

1.0 Gaps in knowledge

The usefulness of the Cancer Predisposition Program at UPMC Children's hospital and the screening tool has not been assessed. A comparison of the proportions of pediatric patients who were diagnosed with hereditary cancers in the retrospective study and after implementation of the intervention program is not known. In addition, the demographics of the patient population for the retrospective study or from the current Cancer Predisposition Program have not been assessed.

This information would indicate if specific subgroups of the population are being underserved and indicate that additional outreach should be initiated. Finally, the relative frequency of hereditary cancers that are being identified has not been assessed.

To fill in these gaps in knowledge, I conducted a study with the following specific aims.

1.5 Specific Aims

Specific Aim 1.

Describe demographic characteristics of the retrospective and predisposition clinic study populations., using from data obtained from hospital records.

Specific Aim 2

Assess the changes in the screening tool (addition of tumor types and inherited conditions) between the retrospective study and predisposition clinic populations.

Specific Aim 3

Assess possible differences between the Retrospective Study and the Genetic Predisposition Clinic patient populations.

a. Assess whether any demographic characteristics differed between the two patient populations

b. Assess whether the number of genetic diagnoses changed between the two patient populations.

2.0 Methods and Data

I compared results from two different cohorts: (1) 562 patients from the retrospective study (from 2012-2017) conducted by the hematology department at CHP and (2) 216 patients seen in the Cancer Predisposition Clinic at CHP from 2017-2020. I completed a review of the 216 patients from the Cancer Predisposition Clinic to have the same data collected in the retrospective study.

2.1 Retrospective Study Population

A total of 562 patients were identified in the retrospective study who met the criteria of a patient identified with a congenital abnormality or pediatric malignancy/tumor associated with cancer predisposition syndromes. This information was collected through a review of each patient's electronic medical records at CHP that came to the Hematology/Oncology clinic between 2012-2017. The initial data collection was completed by a fellow and medical student in the Hematology/Oncology Department.

Data on the demographics of the 280 patients that met the criteria for referral to Genetics and/or a Cancer Predisposition clinic were collected from electronic medical records at CHP. These data included age, sex, ethnicity, geographical location (zip code).

2.2 Predisposition Clinic Population

The Cancer Predisposition Clinic was implemented in 2017 and 216 patients were seen in the clinic through December 2020. Demographic information (including age, sex, ethnicity, and geographical location (zip code) for these patients were obtained from electronic medical records at CHP.

In addition, given the advancements in cancer genetics and the identification of new tumor types and genetic mutations and conditions associated with cancer predisposition syndromes, I also determined whether the specific tumor types had been added (or subtracted) from the screening tool used in the retrospective study versus the one use on the predisposition clinic population.

2.3 Methods

Descriptive data are presented as n (%). Chi-square tests were used to assess possible differences in demographics or genetic diagnoses between the two patient populations.

I collected the zip code for each patient from the electronic medical records at UMPC Children's Hospital of Pittsburgh. Zip codes were collected and grouped together by state. Two custom maps were made of patient zip codes grouped together by county and www.mapchart.net was used to generate visual representation to show the distribution of patient zip codes by county in Pennsylvania.

I reviewed the screening tools used in the retrospective study and the predisposition clinic and identified the new tumor types that were added.

3.0 Results

3.1 Changes in the screening tool

The screening tool developed for the retrospective study in 2017 had 34 tumor types. Since that time, and in the three years that the cancer predisposition clinic has been operating, an additional 4 tumor types have been added to the screening tool utilized by the cancer predisposition clinic (Appendix 1). These 2 tumor types were low hypodiploid acute lymphoblastic leukemia, and myelodysplastic syndrome. All other components of the tools used for the retrospective study and in the current cancer predisposition clinic were the same.

3.2 Demographics of the retrospective and current populations

As part of the Retrospective Study, a total of 282 patients (who would have met criteria for referral to a Genetic Predisposition Clinic) were identified over a period of 5 years (from 2012 and 2017), approximately 56 children/year. As can be seen in Table 3, the majority (62%) of patients who met the criteria for referral in the retrospective study were female. Almost all (91%) of patients were Caucasian, 6.9% were African American, less than 1% were Guam, less than 1% were Asian/Pacific Islander, and less than 2% were unknown or declined to provide their ethnicity. Most patients resided in Pennsylvania (96%), less than 1% were from Ohio, 1.2% were from West Virginia, and 1.4% were unknown.

Table 2 Demographics of Retrospective and Predisposition Clinic

	Retrospective Study	Predisposition Clinic
Total number of Patients	**280**	**216**
GENDER	**NUMBER OF PATIENTS (%)**	**NUMBER OF PATIENTS (%)**
MALE	106 (38%)	121 (56%)
FEMALE	174 (62%)	95 (44%)
RACE		
WHITE	255 (91%)	194 (90%)
AFRICAN AMERICAN	19 (6.9%)	11 (5%)
GUAM	1 (0.35%)	-
INDIAN (ASIA)	1 (0.35%)	-
UNKNOWN	2 (0.7%)	8 (4%)
DECLINED	2 (0.7%)	3 (1%)
ZIP CODE		
PENNSYLVANIA	271 (96%)	211 (98%)
OHIO	2 (0.7%)	2 (1%)
WEST VIRGINIA	3 (1.2%)	3 (1%)
UNKNOWN	4 (1.4%)	-

In the three-year period between December 2017 and December 2020, the Genetic Predisposition Clinic treated 216 children, for a mean of 72 children per year. This change is a 26% per year increase in the number of children who met the criteria for referral compared to the retrospective study (from 2012-2017). Except that the proportion of males seen in the Clinic Study was higher than in the Retrospective Study patient population, the demographics of the cancer predisposition clinic patients were similar to those from the Retrospective Study. For example, most of the patients were Caucasian (90%), 5% were African American, 4% are unknown, and 1% declined to provide their ethnicity. In addition, almost all of the patients resided in Pennsylvania (98%). The proportion of males seen in the Clinic study was 50% higher than the number who met the requirements for referral in the Retrospective Study, 56% versus 38%, retrospectively. This difference was highly significant ($X^2_{1df} = 16.2036$, $p = 0.000057$, see Appendix C Table 6).

3.2.1 Geographic location by County

In addition to investigating which states the Cancer Predisposition Clinic patients resided in, Pennsylvania counties patients like in based on zip codes were investigated using heat maps. The UPMC Children's Hospital is located in Allegheny County in Pittsburgh, PA. As can be seen, the largest number of patients resided in Allegheny county. In the Retrospective Study, patients who met the criteria for referral came from a total of 19 counties, although 13 counties had >5 patients. In the Genetic Predisposition Clinic patient population, patients came from a total of 30 counties, and 14 counties had >5 patients. For details on the specific numbers of patients from each county, see **Table 5** in **Appendix B**.

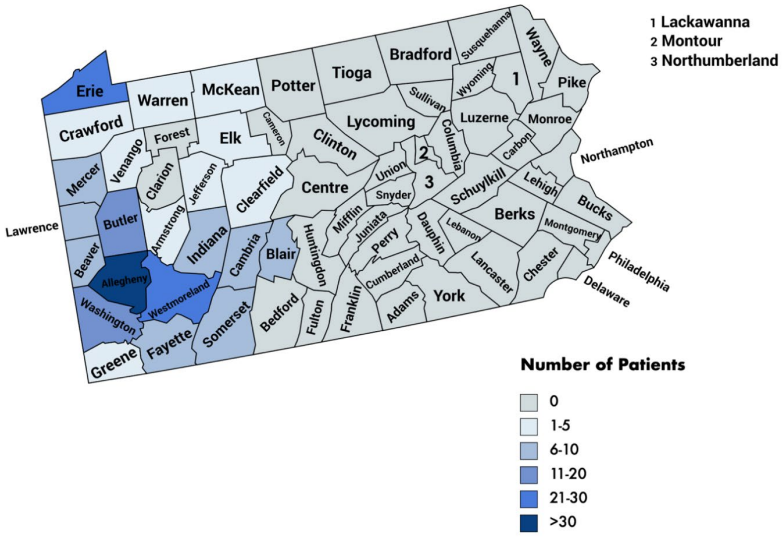

Figure 2 Retrospective County Numbers

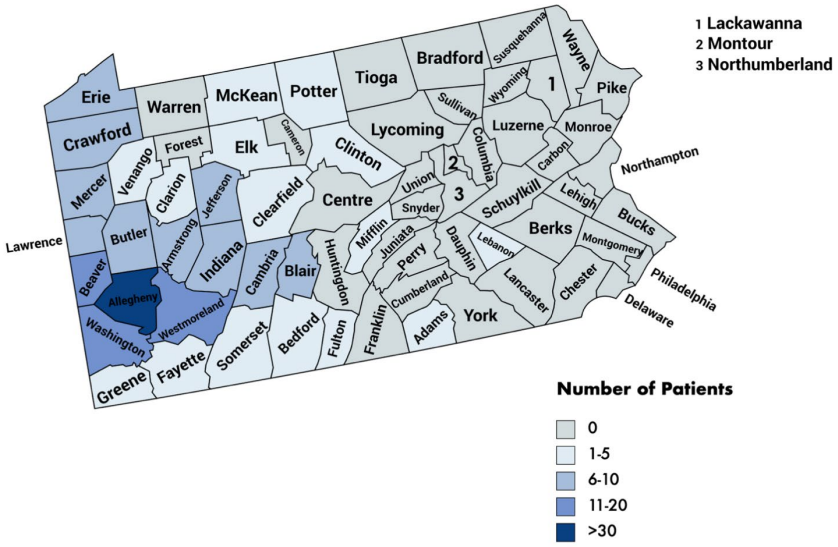

Figure 3 Predisposition Clinic County Numbers

3.3 Identification of Genetic Mutations for Specific Cancer Predisposition Syndromes

Since the Cancer Predisposition Clinic was implemented in 2017, 216 patients have been seen in the clinic through December 2020. Of the 216 patients, a specific causal mutation has been identified in 84 patients (39%). A causal mutation was not identified for the remaining 61% of the patients. Among these patients, testing did not reveal any potentially causal variants for 86 patients. For 19 patients, testing identified a variant, but the effect of the variant was unknown, that is, a variant of unknown significance (VUS) The remaining 27 patients did not undergo testing for a variety of reasons.

Table 3 Testing Results for Clinic Patients (n=216) from 2017 to 2020

TESTING RESULTS	NUMBER OF PATIENTS n (%)
POSITIVE TEST	84 (39%)
NEGATIVE TEST	86 (40%)
VARIANTS OF UNKNOWN SIGNIFICANCE (VUS)	19 (9%)
OTHER	27 (12%)

I next assessed whether the number of patients who received genetic diagnosis differed between the two patient populations (Table 4). Because information regarding VUS and Other outcomes was not available for the Retrospective Study, I only analyzed the number of positive and negative tests.

Table 4 Analysis of Genetic Testing in Two Patient Populations

	Retrospective (n)	Predisposition Clinic (n)
Positive	30	84
Negative	26	86

As can be seen, the proportion of positive genetic diagnoses in the Retrospective Study (53.5%) was similar to that in the Cancer Predisposition Clinic (49.5%) and the difference in these proportions was not statistically significant (X^2_{1df}, $p = 0.69$).

4.0 Discussion

Early detection and positive identification of genetic mutations in pediatric cancer patients will enable better management of their condition and potentially increase longevity, as well as facilitate early identification of family members at risk. Implementing an intervention to identify and refer pediatric cancer patients will facilitate this process. In early 2017, physicians at UPMC Children's Hospital of Pittsburgh conducted a retrospective chart review of pediatric cancer patients with hereditary cancers. The results of this chart review highlighted the need for a comprehensive, standardized referral program and showed that and estimated 40% of patients with hereditary cancers remained underdiagnosed. Thus, in 2017, the hematology/oncology department at UPMC Children's Hospital of Pittsburgh established a pediatric cancer predisposition program in an outpatient setting.

As described in the Results, the number of patients seen in the pediatric Cancer Predisposition Clinic increased a mean 26% per year compared to the number of patients that met the criteria for referral in the retrospective study. This increase, in part, may be due to the addition of tumor types to the screening tool. Given the advancements in cancer genetics and the identification of new tumor types and genetic mutations and conditions associated with cancer predisposition syndromes, the screening tool will continue to be updated. In particular, two of the most common childhood tumor types, ALL and AML, were added to the screening tool, after several reports in the literature identified specific variants that increased susceptibility for development of ALL and AML.

In addition, this 26% increase is likely an under-representation of the effect of using the screening tool to identify patients for referral. In the past three years, the number of patients that

were seen in the Predisposition Clinic steadily increased. In 2018, 31 patients were seen. In 2019, 85 patients were seen, an increase of 274%. In 2020, 94 patients were seen, however, this relatively lower increase may be a consequence of the COVID-19 pandemic. In support of this latter hypothesis, over 27 patients have been scheduled during the first quarter of 2021, indicating a possible backlog of patients. Thus, the number of patients in 2021 is likely to exceed the number of patients in 2020.

Finally, the increase in the number of patients may be attributable, in part, to increasing awareness of the pediatric Cancer Predisposition Clinic by health care professionals and the public and the expansion of the UPMC system. Support for this hypothesis is based on the observation that patients seen by the Clinic reside in 30 counties, whereas the patients in the retrospective study resided in 19 counties (Figure 2 and 3). However, assessment of this latter hypothesis is beyond the scope of this essay.

As described in the Introduction, all cancer is genetic (due to changes in genes and gene expression), although the causes of these changes may be due to endogenous and exogenous environmental factors.(Lewandowska et al., 2019) Also, most cancers are due to sporadic mutations and most of the genes and variants that contribute to the development of different cancers are unknown. Therefore, as additional tumor types are added to the screening tool, and more patients are referred to the Cancer Predisposition Clinic, the proportion of positive genetic diagnoses will decrease, and the proportion of negative results and variants of unknown significance will increase. This outcome is observed in Table 4, the proportion of positive results decreased (39%) in the Cancer Predisposition Clinic and the number of VUS increased (to 9%). Some of these VUS may be recategorized as pathogenic (i.e., a positive test result), whereas other will be classified as nonpathogenic (a negative test result). For example, based on a study of 4644

individuals carrying 2383 BRCA1/2 variants, bioinformatic analyses indicated that 22 VUS had odds >10:1 in favor of pathogenicity. (Li et al., 2020) Thus, in this small study, only ~1% of VUS may be pathogenic. The remainder will be reclassified as non-pathogenic (negative test results) or remain unknown. St. Jude Children's Research Hospital developed PeCan-PIE (Pediatric Cancer Variant Pathogenicity Exchange Program) a cloud based variant classification and interpretation service following ACMG Guidelines. The portal contains a repository of expert-reviewed germline mutations that may predispose individuals to cancer. Researchers and physicians have access to this portal. Thus, they are able to use this site to determine VUS from their patients and compare them to the information in the portal and determine variants that may cause a cancer predisposition syndrome. (St. Jude Children's Research Hospital, 2020)

The racial/ethnic composition of the patient population in the retrospective study and the Clinic were similar. Most of the patients self-identified as white (91% and 90% in the retrospective study and clinic, respectively). Slightly more patients from the retrospective study (6.9%) versus the clinic (4%?) identified as African American. In PA, 81.6% of the population identifies as Caucasian and 12% of the population is African American. Furthermore, among all pediatric cancer cases in PA, 78% are white and 9% were black. (Pennsylvania Department of Health, 2021) Thus, the clinic is seeing more whites and fewer blacks. Although the numbers are small, this potential disparity may be due to differential rates of genetic predisposition syndromes between blacks and whites, however I think this is unlikely given the overall prevalence of pediatric cancer in PA. This potential disparity may also be due to several factors that are known to affect use of healthcare among under-represented populations such as lack of insurance, transportation, and access, as well as distrust of the medical establishment; all of which may lead to a longer time to diagnosis. Because the numbers are small, more research needs to be done.

The proportion of males seen in the Clinic study was 50% higher than the number who met the requirements for referral in the Retrospective Study, 57% versus 38%, retrospectively. Siegal and colleagues reported that in adults, between 2009-2013, the incidence of cancer was ~20% higher in men than in women and the mortality rate was 40% higher in men than women in the United States. (Siegel et al., 2018) The PA Cancer Statistic Board reported that the incidence rate of cancer in persons <20 years was higher in males (0.8%) than females (0.7%) from 2012-2017. (Pennsylvania Department of Health, 2021) Thus, in Pennsylvania, males <20 years old, have higher risks of developing cancer than females. However, the magnitude of the difference in risk is less than the that observed in the clinic. Similarly, the reason for the large differences in the proportion of males and females in the retrospective study versus the clinic study is unclear. However, these values for the Retrospective Study and the Clinic Study are based on different baselines. The Retrospective Study was a chart review that identified all children who met the criteria for referral. In contrast, the clinic study represents all children who met the criteria, were referred, and attended the clinic. I have been unable to obtain information regarding the number of patients who were referred.

Boston Children's Hospital (BCH) has also implemented a pediatric cancer genetic risk program similar to the clinic at Children's Hospital of Pittsburgh. Their program provides cancer risk assessment, comprehensive recommendations for managing cancer risk in children, and psychosocial support for both patients and families. (Groves et al., 2019) In Massachusetts, the total number of new cases of cancer in the state in 2017 was 38,079 of whom 311 (or 0.8%) were <20 years of age. (Massachusetts Cancer Registry, 2020) Thus, the frequency of pediatric cancer in MA is similar to that in PA in the USA. Among the pediatric cancer cases, the frequency is slightly higher in males (57%) than females (43%), again similar to the frequencies in

Pennsylvania (58% vs. 42% respectively). In addition, 64% of pediatric cancer cases were white and 6% were black; the frequencies of pediatric cancer cases in Pennsylvania, is slightly higher among whites (78%), but similar among blacks (9%). BCH investigators conducted a study on their patient population to determine the prevalence and scope of medical and psychosocial needs. The investigators reported that the frequency of males in their population was higher than females (58.9 versus 41.1%, respectively). In addition, they reported that more whites than blacks were seen: whites 80.8%; African Americans 17.8%; and other 1.4%)(Groves et al., 2019), These results are similar to the results from the Cancer Predisposition Clinic. Again, the reasons for the substantially higher frequency of males than females, are unclear.

In summary, results of my study demonstrate the usefulness of a screening tool to refer pediatric patients to a multidisciplinary cancer predisposition clinic. Development of a standardized screening tool and referral process have increased the number of pediatric patients who are seen by the clinic. Given the advances in genetic knowledge and treatment of syndromes, identification of specific mutations for a cancer predisposition syndrome will enable earlier detection of the syndrome and better long-term management of the child's and/or family member's health.

However, several disparities were noted. First, a higher proportion of males are referred to the clinic and a lower proportion of blacks are referred, especially in comparison to the reported frequency of pediatric cancers in these groups in Pennsylvania. Intriguingly, similar results were seen in the BCH study. Additional studies to confirm these disparities and to determine the causes of these disparities need to be done.

5.0 Limitations

This study has several limitations. First, almost all of the patients are from Western Pennsylvania. Although the BCH program reported demographics among patients seen in their clinic, that is, higher proportion of males and lower proportions of blacks than expected, these results may not be representative of the whole United States or their respective communities. Second, most of the information regarding most of variants associated with cancer susceptibility has been derived from white populations. This bias is likely to result in an underrepresentation of positive test mutations in other ethnicities. e screening tools developed by BCH and UPMC (which are very similar) were used to analyze patients from other geographical regions and/or comprised of predominantly non-white populations.

A second limitation was the inability to obtain the total number of patients who were referred to the predisposition clinic. This number would be the equivalent to the 562 patients in the retrospective study. In other words, the proportions of males versus females, ethnic/racial composition, and geographic location in the retrospective study may not be equivalent between the two studies, especially if the dropout rate differed by sex, race/ethnicity, or location. Furthermore, the baselines differed between the retrospective study and the clinic with regards to identification of mutations. The retrospective study contained a small subset (31%) of the patients who met the criteria referral, whereas in the clinic study, more patients who met the screening criteria were assumed to be referred. If the patients in the retrospective study who were referred to the clinic represented a biased subset of the at-risk population, the frequency of identified mutations would differ. For example, if only patients with a strong family history of risk were referred, the probability of identifying a risk allele may be increased.

Appendix A Cancer Predisposition Clinic Screening Tool

Patient name: Patient date of birth:

1. Family history of the child with cancer:
    - ≥ 2 malignancies in childhood (individuals with multiple primary tumors)
    - A first degree relative (parent or sibling) with cancer < 50 years of age
    - ≥ 2 second degree relatives with cancer < 50 years of age on the same side of the family
    - Several affected generations in the same bloodline
    - Unusual tumors
    - Clustering of cancer in a family
    - Parents of the child with cancer are related (i.e., consanguineous)

2. A person with one of these tumors in childhood:
    - Adrenocortical carcinoma
    - Aggressive fibromatosis
    - Atypical teratoid malignant rhabdoid tumor
    - Cancers of adult age that are extremely rare in the pediatric age group (i.e., colorectal cancer, ovarian cancer, pheochromocytoma, basal cell carcinoma)
    - Cerebellar gangliocytoma
    - Choroid plexus carcinoma
    - Desmoid tumor
    - Endolymphatic sac tumors
    - Gangliocytoma
    - Hemangioblastoma
    - Hepatoblastoma
    - Hepatocellular carcinoma
    - Juvenile myelomonocytic leukemia
    - Low hypodiploid acute lymphoblastic leukemia
    - Malignant melanoma
    - Malignant peripheral nerve sheath tumor
    - Malignant Schwannoma
    - Medullary thyroid carcinoma
    - Medulloblastoma
    - Meningioma
    - Myelodysplastic syndrome
    - Nephroblastoma (Wilms tumor)

- Optic pathway/optic nerve glioma
- Ovarian Sertoli-Leydig cell tumor
- Pheochromocytoma
- Pineoblastoma
- Pituitary adenoma
- Pituitary blastoma
- Pleuropulmonary blastoma
- Retinoblastoma
- Renal carcinoma
- Rhabdomyosarcoma
- Skin carcinoma
- Spinal ependymoma
- Subependymal giant cell astrocytoma
- Thyroid carcinoma
- Vestibular schwannoma

3. 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).
4. Child with one of the following inherited conditions:
    - Ataxia-Telangectasia
    - Beckwith-Wiedemann Syndrome / Isolated Hemihypertrophy
    - Bannayan-Riley-Ruvalcaba Syndrome
    - Biallelic mismatch repair gene mutations
    - Bloom syndrome
    - Carney complex
    - Constitutional mismatch repair deficiency
    - Costello Syndrome
    - Cowden Syndrome
    - Denys-Drash
    - *DICER1*-related Pleuropulmonary Blastoma Family Tumor and Dysplasia Syndrome (DICER1 syndrome)
    - Familial Adenomatous Polyposis
    - Familial paraganglioma/pheochromocytoma syndrome
    - Hereditary Leiomyomatosis and Renal Cell Cancer
    - Hereditary melanoma
    - Hereditary neuroblastoma
    - Hereditary Paraganglioma-Pheochromocytoma Syndrome
    - Hyperparathyroid-jaw tumor syndrome
    - Li-Fraumeni Syndrome
    - Lynch syndrome
    - Multiple Endocrine Neoplasia, Type 1
    - Multiple Endocrine Neoplasia, Type 2

- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Nevoid Basal Cell Carcinoma (Gorlin) Syndrome
- Nimegen breakage syndrome
- Noonan syndrome/rasopathies
- Peutz-Jeghers Syndrome
- PTEN Hamartoma syndrome
- Retinoblastoma
- Rhabdoid Predisposition Syndrome
- Simpson-Golabi-Behmel
- Tuberous Sclerosis Complex
- Von Hippel-Lindau Disease
- WAGR (Wilms tumor syndromes)
- Paraneoplastic syndromes with concern for occult malignancy

5. 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	

6. A child with excessive treatment toxicity

Appendix B

Table 5 County Incidence Rates (Number of Patients)

County	Population	PA Cancer registry (2013-2017)	Retrospective (2012-2017)	Predisposition Clinic (2017-2020)
Adams	120,134	14	-	1
Allegheny	1,329,047	253	77	58
Armstrong	71,860	18	2	6
Beaver	182,307	35	7	13
Bedford	54,422	13	-	2
Blair	143,754	28	9	9
Butler	220,673	37	17	10
Cambria	151,391	29	9	7
Clarion	44,414	6	-	3
Clearfield	83,205	22	1	1
Clinton	49,171	11	-	2
Crawford	105,129	13	1	6
Elk	33,816	10	2	1
Erie	348,269	56	22	10
Fayette	142,532	18	9	2
Fulton	16,533	3	-	1
Greene	41,872	12	3	2
Indiana	101,082	22	6	7

Jefferson	52,266	4	3	7
Lawrence	99,197	23	8	9
McKean	48,813	13	4	3
Mercer	130,846	18	6	8
Mifflin	57,037	14	-	1
Potter	19,875	3	-	1
Somerset	76,113	18	7	4
Venango	58,496	14	4	3
Warren	43,534	9	2	-
Washington	232,213	50	18	16
Westmoreland	374,197	80	22	18

**These data were provided by the Pennsylvania Department of health. The department specifically disclaims responsibility for any analyses, interpretations, or conclusions.*

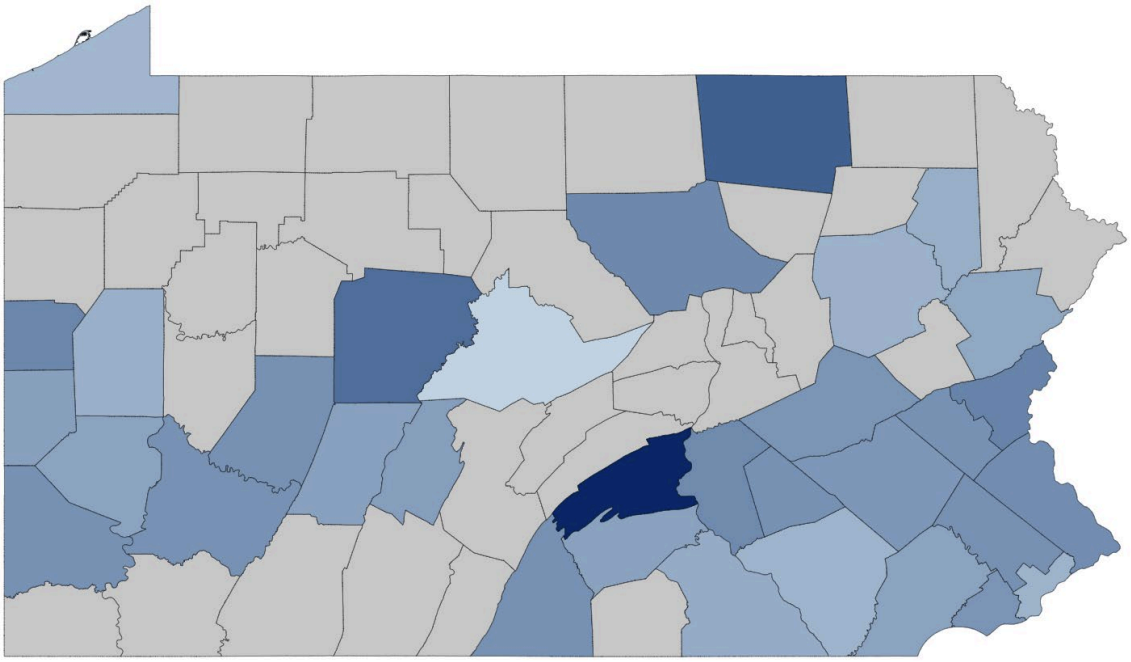

Figure 4 Age-Adjusted Incidence Rate, by County, All Cancer Sites, Pennsylvania Residents Aged <20 Years, Invasive, 2013-2017

**These data were provided by the Pennsylvania Department of health. The department specifically disclaims responsibility for any analyses, interpretations, or conclusions.*

Appendix C Tables

Table 6 Chi-Squared Test for Gender of Patients in Study Populations

	Retrospective	Predisposition Clinic
Males	106 (38%)	121 (56%)
Females	174 (62%)	95 (44%)
Total	280	216

A chi-squared test of independence was performed to examine the relationship between the two study populations and the proportion of the genders seen in the clinic. The relationship between these variables was significant, X^2 (1, N = 496) = 16.2036, p = .000057.

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