ASSESSING THE PRACTICES OF GENETIC COUNSELORS REGARDING HEAD CIRCUMFERENCE MEASUREMENT IN HEREDITARY CANCER ASSESSMENT

by

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Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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ABSTRACT

PTEN, a tumor suppressor gene, has been identified as an overgrowth susceptibility gene causing Cowden syndrome. Cowden syndrome is characterized by an increased risk for breast cancer and other malignancies, mucocutaneous lesions, and macrocephaly. Macrocephaly is a hallmark of Cowden syndrome, is considered a major criterion for the clinical diagnosis, and is present in an estimated 80% of individuals diagnosed with Cowden syndrome. However, it is unknown what percentage of genetic counselors routinely measure head circumference when evaluating patients for hereditary cancer assessment. This study queried National Society of Genetic Counselors (NSGC) members about current practices and opinions regarding head circumference measurement. A questionnaire was dispersed electronically to all members of NSGC, and those who have practiced cancer genetic counseling in the last six months were eligible to respond. The data from 216 surveys was analyzed using descriptive statistics and qualitative methods including thematic analysis. Eighty-four percent of genetic counselors are not measuring head circumference on every patient presenting for hereditary cancer assessment, nor those who are specifically presenting for hereditary breast cancer assessment. Thematic analysis revealed these individuals feel head circumference measurement should not be standard in a cancer assessment, but reserved for those who are suspicious of Cowden syndrome based on personal or family history. Additionally, some genetic counselors expressed they have not received appropriate

training in head circumference measurement. However, the 29% of genetic counselors who believe head circumference should routinely be measured felt it is a quick and easy measurement that is helpful in assessment and is good clinical practice. Thematic analysis also revealed mixed responses about the value of head circumference measurement with the increasing use of next generation sequencing panels.

Although macrocephaly is a major diagnostic criterion for Cowden syndrome, there have been diverse outcomes on the exact incidence, ranging from 40-100%. Identification of Cowden syndrome has significant public health implications. Because Cowden syndrome is associated with increased lifetime risks of cancer of multiple organ sites, and because increased screening and consideration of risk-reducing surgery, it is important that health care professionals identify cases of Cowden syndrome in their patient population.

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PREFACE

I would first like to acknowledge Ms. Emily James, my thesis advisor, for allowing me to work on this project with her on such short notice. I want to thank her for her hard work, patience, guidance, and support with this project. I next want to thank Dr. John Shaffer for being my official University of Pittsburgh “mentor”. Without his approvals of the IRB and survey, I would not have been able to do this work. I would also like to thank my thesis committee for their support and assistance with this project in the short time frame that I gave them. Thank you all for being the sounding board for all my ideas and helping to mold them into something interesting and meaningful.

I want to thank my classmates for their constant support these past two years at the University of Pittsburgh. I would not have made it to this point without them and I will be forever grateful for that. I would also like to thank the program directors for allowing me to have the opportunity to be a part of this program and helping me reach my goals.

Last, but not least, I want to thank my husband and family for their love and support the last two years and all the years before that. I would not be here without them and I want to especially thank my husband for moving to Pittsburgh with me to allow me to follow my dream.

1.0 INTRODUCTION

Cowden syndrome is an autosomal dominant condition that affects approximately 1/200,000 individuals, however, this is most likely an underestimate due to the variability in expression of symptoms. It is caused by germline mutations in the *PTEN* tumor suppressor gene. Individuals with Cowden syndrome are at an exceptionally high risk for breast cancer, mucocutaneous lesions, and a predisposition to hamartomas.[1] A clinical diagnosis is made from a combination of mucocutaneous features, major criteria, and/or minor criteria. One of the clinical hallmarks and major diagnostic criterion of Cowden syndrome is macrocephaly, which is defined as a head circumference greater than or equal to the 97th percentile (58 centimeters for adult women and 60 centimeters for adult men).[2] Mucocutaneous lesions in the form of trichilemmomas, acral keratosis, and papillomatous lesions also contribute to the major diagnostic criteria. Another major criterion almost exclusively seen in Cowden syndrome is adult-onset Lhermitte-Duclos disease. Other major criteria are breast carcinoma, non-medullary thyroid carcinoma (especially follicular), and endometrial carcinoma. Several minor criteria are also concerning for Cowden syndrome, and all criteria are discussed in detail below.

Due to the variability in expression, individuals, particularly women, who might benefit from *PTEN* gene testing could be missed if head circumference is not measured. Occipital-frontal head circumference is a physical feature that is relatively easy to measure accurately and reproducibly in routine clinical care. However, we hypothesize that the clinical approach to an individual at high risk for breast cancer often does not include head circumference measurement. Practices of genetic counselors regarding head circumference measurement in a cancer genetic counseling setting has not yet been assessed in the literature. It seems reasonable that cancer genetic counselors would be the health care professionals to implement the measurement due to their experience in cancer risk assessment based on personal and family medical histories. Because of this, assessing the attitudes of genetic counselors towards head circumference measurement may give a better understanding of the perceived benefits and limitations of head circumference measurement. Routine screening for Cowden syndrome clinical features could increase detection with substantial implications for a patient's care.

1.1 BACKGROUND AND SIGNIFICANCE

1.1.1 Head Circumference

1.1.1.1 Birth to 18 years

Head circumference in children has been well studied and established since 1948, but the first graphs providing head circumference past the first few years of life were not published until 1968. These graphs were prepared by using the world data obtained since 1948, and the grand means and standard deviations for age and sex were calculated from the pooled variances.[3] The participants were stated or considered to have been full term infants and older children were physically and mentally well.

Two thirds of total head growth from birth to adulthood occurs within the first two years of life, and less than two percent of total head circumference growth occurs after the age of 18 years.[4] Head growth in boys is slightly more rapid in the first two years of life and approximately 0.9 centimeters larger than girls overall.[3] There is no appreciable difference in head circumference for race in either sex. Nellhaus et al. concluded that head circumference measurement should be as much a part of a physical examination as obtaining the height and weight. Nellhaus et al. also noted that head circumference measurements graphed routinely may lead to an early diagnosis of certain conditions.

A similar study was conducted 20 years later[2] and reached the same conclusions as previously reported[3]. However, Roche et al. noted that the head circumference in their sample was larger from birth to six months and at older ages. Roche et al. concluded that this difference may have been due to the low socioeconomic status of the previous study, differences in the method of measurement, or the years in which the data was collected. To create a more uniform reference for head circumference, the World Health Organization (WHO) released head circumference growth charts in 2007 that are intended for international use.[5] However, the standards are limited to age 5 years, causing a need for more standard charts beyond this age.

1.1.1.2 Adulthood

While investigating a child with an apparently isolated abnormal head circumference, the parents should also be measured since studies have shown that up to 50% of normal variation in head size is familial.[6] However, until 1992, head circumference charts for adults past the age of 18 years were non-existent. The first adult head circumference charts were published at this time using a British cohort.[7] Bushby et al. concluded that height should be taken into account when graphing the head circumference of adults. They also noted that due to the later pubertal development of males, head circumference continues to grow into early adulthood which is not true for females.

Head circumference appears to be a useful parameter for a variety of different reasons. It can be used when pediatricians search for familial syndromes with parental microcephaly or macrocephaly. Head circumference can also be a measurement for brain size and cognitive reserve that is associated with severity of impairment in Alzheimer's disease.[8] Graves et al. indicated that patients with probable Alzheimer's disease who had smaller head circumference had lower scores on a global cognitive test than those with larger head circumference. The findings suggest that brain size may be important in determining reserve capacity. This could potentially modify the clinical presentation of that process. Other studies have found similar results and the research continues to improve in this area.

Head circumference in adults has also been identified as a marker for genetic syndromes that may not be present in childhood or adolescence. Genetic syndromes are often defined by different physical findings that are frequently seen in individuals with a certain condition. It has been generally accepted that the definition of normocephalic includes those that are within two standard deviations of the mean.[2; 3] Any measurement below two standard deviations is considered microcephalic and above is considered macrocephalic. This corresponds to below the third percentile and above the 97th percentile, respectively. The most well-known genetic syndrome associated with macrocephaly is Cowden syndrome, a *PTEN* hamartoma tumor syndrome, which is associated with an increased risk for breast cancer, as well as other cancers and skin manifestations.

1.1.1.3 Macrocephaly

Macrocephaly is a common cause of genetic evaluation, especially when associated with developmental delay or autism spectrum disorders. There are various genetic syndromes associated with macrocephaly, including Neurofibromatosis 1 (NF1), Fragile X syndrome, Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome, and metabolic disorders.[9] Evaluation for macrocephaly associated with a developmental disorder often includes a physical examination, brain CT or MRI, chromosome analysis including karyotype and/or microarray, Fragile X testing, and metabolic screening. *PTEN* screening has also been suggested in the case of familial macrocephaly over 3 standard deviations when the first screening methods are negative.

1.1.2 Features of Cowden Syndrome

Cowden syndrome is considered to be part of the spectrum of *PTEN* hamartoma tumor syndromes (PHTS), which also includes Bannayan-Riley-Ruvalcaba (BRRS), Proteus, and Proteus-like syndromes.[10] It was first described in 1963 and the prevalence of PHTS is estimated to be about 1 in 200,000, but this is suspected to be an underestimate due to the variability in expression and the subtlety of skin findings. Cowden syndrome is inherited in an autosomal dominant fashion. Cowden syndrome is associated with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Renal cell carcinoma and colorectal carcinoma have also recently been shown at increased risk for individuals with *PTEN* mutations. Affected individuals usually present with macrocephaly and mucocutaneous lesions that usually present by the late twenties. More than 90% of individuals with Cowden syndrome have some clinical manifestation,[11] and by the third decade of life, 99% of affected individuals develop the mucocutaneous lesions. There are several different features, both malignant and non-malignant, that are associated with Cowden syndrome that will be discussed.

1.1.2.1 Head Circumference

In a clinical setting, there are no established guidelines that include head circumference measurement for individuals with breast cancer. It has been estimated that the current incidence of macrocephaly among women who meet the PHTS criteria to be at least 80%.[10] Until recently, head circumference measurement had not been studied clinically to determine if it is a useful clinical feature for the diagnosis of Cowden syndrome. It appears that macrocephaly is in fact a useful feature contributing to the clinical diagnosis of Cowden syndrome, given its high sensitivity.[12] However, the presence of macrocephaly alone will not identify all *PTEN* mutation carriers, even in a high risk population. Although this may be true, routine head circumference measurement offers a clinical advantage for identifying those with PHTS in high-risk breast cancer clinics.

Macrocephaly is known to be associated with Cowden syndrome, but the reported frequencies very widely in the literature. The frequency was initially reported to be 40% in early reports, but has been found to be 80-100% in more recently published studies.[13-15] It has been suggested that *PTEN* screening also be performed in the case of familial macrocephaly over three standard deviations when the first macrocephaly screening, such as physical examination, brain CT or MRI, or chromosome analysis is normal.[16]

1.1.2.2 Malignant Findings

The most common cancer associated with Cowden syndrome is breast cancer. The lifetime risk for women with Cowden syndrome is 25-50%,[17-19] compared to the general population at 8-12%.[20] However, a more recent study that prospectively collected and followed families with a *PTEN* pathogenic variant revealed the lifetime risk to be 85%.[21] The average age of diagnosis is usually between 38 and 46 years of age, which is ten years younger than women with sporadic breast cancer. There have only been two reported cases of male breast cancer associated with Cowden syndrome[13] and no reported cases in the largest cohort of patients with *PTEN* testing to date[18]. Cowden syndrome associated breast cancers, along with other hereditary breast cancers, are also more likely to be multifocal and bilateral compared to sporadic breast cancers.

Endometrial cancer has been reported to be the second most common cancer in individuals with Cowden syndrome. The lifetime risk in women with Cowden syndrome has been estimated to be 19-28% at age 70 years,[21] compared to the general population lifetime risk of 2.5%.[18; 22] However, this evidence may be an under or overestimate for the following reasons: These studies did not censor endometrial cancer incidence rates for previous hysterectomy, causing an underestimation, and the studies contain ascertainment bias, leading to an overestimation.

The chance of developing non-medullary (follicular or papillary) thyroid cancer is approximately 3-10% in individuals with Cowden syndrome, compared to a lifetime risk of less than 1% in the general population.[23] Papillary thyroid cancer accounts for 80-85% of the non-medullary cancer in the general population, while follicular cancer accounts for only about 15%. Medullary thyroid cancer is not felt to be part of the syndrome. Among confirmed mutation carriers who develop thyroid cancer, both papillary, 56-60% risk, and follicular, 25-45% risk, have been reported.[24] Follicular thyroid cancer appears to be over-represented in mutation carriers compared with the general population and may have greater value in predicting *PTEN* mutation status.

An increased risk for colon cancer has not historically been described in the Cowden syndrome tumor spectrum, however, recent studies have described a risk. These risks have ranged from 9-16%[21; 25; 26] and the individuals were all under the age of 50 years. The risk for other cancers, such a renal cell carcinoma and cutaneous melanoma, has also been suggested to be increased in Cowden syndrome. The lifetime risk for renal cell carcinoma is 35%, and the average age of onset is in the fourth decade of life.[21] A lifetime risk for melanoma has recently been reported to be 6%[21], suggesting it may be associated with Cowden syndrome.

1.1.2.3 Non-malignant Findings

Individuals with Cowden syndrome are also at an increased risk for benign hamartomatous overgrowth in a number of tissues. Historically it has been reported that a majority of individuals with Cowden syndrome have mucocutaneous manifestations, as high as 90-100%[27], and was initially thought to be a primarily dermatological disease.[20] One of the hallmark features of Cowden syndrome is trichilemmomas and is pathognomonic when 3 or more lesions are present. Multiple trichilemmomas are commonly observed on the face, especially on the eyes, mouth, nose, and forehead, and have also been found on the neck, axillae, and hands.[26; 28; 29] Trichilemmomas are clinically significant sign of Cowden syndrome when 3 or more are observed in an individual. However, some individuals have few and relatively insignificant skin manifestations, which could easily be overlooked on a primary exam.

Other mucocutaneous lesions are also prevalent, such as oral papillomas, which are a major criterion and can be seen in abundance on the lips, tongue, buccal mucosa, and gingivae.[20; 23; 26; 30] It has been reported that 100% of individuals with Cowden syndrome will present with this finding by the second decade of life, and this manifestation is typically asymptomatic.[20; 31] Mucocutaneous neuromas (hamartoma of the peripheral nerve sheath), at least three present on the face or elsewhere on the body, should be counted as a major diagnostic feature of PHTS due to reports of more than half of individuals presented with this manifestation.[20] Acral keratoses are located on the palmoplantar surfaces and dorsal hands/feet and are wart-like appearing lesions.[20; 22; 28; 32] They have been noted in both pediatric and adult populations with *PTEN* mutations but further studies are needed to determine the age of onset and penetrance.[33-35] Penile pigmentation is a major criterion in males and has been found in 53% of males with *PTEN* mutations or a clinical diagnosis of Cowden syndrome.[17; 36]

Benign thyroid disease, including goiter, nodules, and adenomas, has been estimated to affect 30-68% of adults and 2-14% of children with Cowden syndrome. [17; 36] Thyroid nodules occur at a range of lifetime frequencies, from 2-6% based on physical exam, 19-35% based on ultrasound, and 65% based on autopsy.[37] Multinodular goiter is present in about 4% of the population[38] and Hashimoto's thyroiditis occurs in 2% of the population[39]. One study looked specifically at Hashimoto's thyroiditis and reported a prevalence of 3-21% in individuals with *PTEN* mutations.[18] However, no studies to date have looked at the likelihood of detecting *PTEN* mutations in individuals presenting only with benign thyroid disease.

Benign breast disease is commonly seen in individuals with Cowden syndrome and presents with varying and often complex histologies. Benign breast disease includes all non-malignant conditions of the breast, fibrocystic disease, intraductal papillomas, and fibroadenomas. Up to 60% of premenopausal women in the general population may develop fibrocystic breast disease[14] and 50% of all breast biopsies are constituted as fibroadenomas[33], making this the most common benign tumor of the breast. The reported frequencies of benign breast disease in women with Cowden syndrome are between 32-64%.[18; 20; 40; 41] In a small study, the pathology of benign breast findings were analyzed[34]. Widespread and complex pathology was noted and the hamartomatous lesions were more diffuse and more often multifocal and bilateral than in patients without Cowden syndrome.

Polyps of the gastrointestinal tract have generally been said to affect about 40% of individuals with Cowden syndrome. However, this may be an underestimate due to the lessened frequency of asymptomatic individuals undergoing endoscopic surveillance.[36] The polyps associated with Cowden syndrome are primarily hamartomatous, but there have been reports that include hyperplastic, inflammatory, juvenile, leiomyomatous, lipomatous, lymphoid, and neuromatous. It has been suggested that GI adenomas reported in individuals with Cowden syndrome are coincidental rather than related to the disease.[10]

It is unclear whether uterine fibroids are seen at an increased frequency in women with Cowden syndrome, even though they are part of the minor diagnostic criteria.[38] The general U.S. population risk for uterine fibroids by age 50 has been reported to be 70% for Caucasian women and 80% for African American women.[42] It seems unlikely that the rate for uterine fibroids in women with Cowden syndrome is dramatically increased.[20]

The precise estimate of the frequency of brain lesions in individuals with Cowden syndrome is not available since brain imaging is rarely done on asymptomatic individuals. Those with Cowden syndrome are known to be at an increased risk for Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum; LDD). Lhermitte-Duclos is a rare, slow growing, non-malignant hamartomatous brain lesion and is usually diagnosed in the second or third decade of life. The prevalence of LDD found in individuals undergoing clinical *PTEN* testing have been found to be 1.8%[41], 6%[18], and 15%[26]. MRI is the preferred diagnostic imaging modality and treatment is through surgical excision. LDD was first recognized to be associated with Cowden syndrome in 1991[40], and since then, 54 more cases have been identified, yet the frequency of LDD in individuals with Cowden syndrome is unknown[28].

Hemangiomas have been seen at increased rates in a number of studies, compared to the general population risk of approximately 5-10%.[10] Arteriovenous malformations (AVMs) seem to be less frequent since they have been noted in only a few case studies. These are both features of BRRS, which is known to be allelic to Cowden syndrome and shows that PTEN plays a role in regulating VEGF-regulated angiogenesis.

Developmental delay and mental retardation have been reported to be associated with *PTEN* mutations in Cowden syndrome, but limited data is available. The number of cases reported range from 12-20% in the literature.[17; 19; 22] Because the rate of mental retardation in the general population is approximately 3%, it appears this should remain a criterion despite the need for additional data.[10]

A recent study[17] consisting of 172 individuals with *PTEN* mutations, the largest single cohort with testing reported, assessed the frequencies of the clinical features of Cowden syndrome, and which features are most predictive of a mutation. The results are listed below and differ significantly than other reports in the literature. This study also led to the development of a mutation-prediction model that should be useful in clinical practice.

- ► Mucocutaneous lesions (77%)
    - Trichilemmomas
    - Acral keratosis
    - Papillomatous papules
- ► Thyroid cancer (7.6%)
- ► Breast cancer (41% of females, 0% of males)
- ► Gastrointestinal cancer (suggested increase)
- ► Macrocephaly (84%)

► Genitourinary abnormalities

- Uterine fibroids (26%)
- Endometrial cancer (17%)
- Renal cell carcinoma (suggested increase)

*Note: given the overall young age of the cohort, and that additional cancers might be diagnosed at later ages, the study may underestimate the lifetime cancer risks.

1.1.2.4 Diagnostic Criteria

Before the gene known to cause Cowden syndrome was elucidated in 1996, the International Cowden Consortium proposed a set of operational diagnostic criteria to ascertain Cowden syndrome families and to assign affected status within families. The first diagnostic criteria were initially proposed in 1983[34] and were later revised by the researches (the consortium) who mapped the gene locus[43]. These criteria have since been adopted by the National Comprehensive Cancer Network (NCCN), whose task is to present evidence based or expert consensus practice guidelines. Modifications to the original criteria have been proposed, including the addition of endometrial cancer as a major criterion[11], renal cell carcinoma as a minor criterion[44], and more recently, adult Lhermitte-Duclos disease be moved into the pathognomonic category.

A study has suggested that the specificity of the Consortium criteria are lower than previously estimated.[17] Only 34% of participants meeting the Cowden syndrome diagnostic criteria had a detectable mutation, which is significantly lower than the 80% previously reported[45]. This suggests that the Consortium criteria are not as robust at identifying individuals with *PTEN* mutations as previously thought.

The clinical diagnostic criterion differs from the genetic testing criteria and is listed here[1]:

Major Criteria

- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- $\geq$3 Gastrointestinal hamartomas (includes ganglioneuromas but excludes hyperplastic polyps)
- Lhermitte-Duclos disease (adult)
- Macrocephaly ($\geq$97th percentile: 58cm for females, 60cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - $\geq$3 trichilemmomas (at least one biopsy proven)
  - $\geq$3 palmoplantar keratotic pits and/or acral hyperkeratotic papules
  - $\geq$3 mucocutaneous neuromas
  - $\geq$3 oral papillomas (particularly on tongue or gingiva) OR biopsy proven OR dermatologist diganosed

Minor Criteria

- Autism spectrum disorder
- Colon cancer
- $\geq$3 esophageal glycogenic acanthuses
- $\geq$3 lipomas
- Mental retardation (IQ $\leq$75)

- ► Renal cell carcinoma
- ► Testicular lipomatosis
- ► Thyroid cancer (papillary or follicular variant of papillary)
- ► Structural thyroid lesions (adenoma, multinodular goiter, etc)
- ► Vascular anomalies (includes multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following):

1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
2. Two major and three minor criteria

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a PTEN mutation:

1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria

1.1.3 Genetics of Cowden Syndrome

Cowden syndrome is caused by germline mutations in the *PTEN* (phosphatase and tensin homolog on chromosome 10) tumor suppressor gene located at 10q23.3.[43] It is a dual specificity phosphatase with multiple and incompletely understood roles in cellular regulation.[46] As a lipid phosphatase, *PTEN* is known to signal down the PI3K/Akt pathway to cause G1 cell cycle arrest and apoptosis. It has also been shown to regulate cell-survival pathways, such as the mitogen-activated kinase (MAPK) pathway. *PTEN* mutations were first reported in individuals with Cowden syndrome in 1997.[32]

Germline mutations in *PTEN* have also been associated with Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus and Proteus-like syndrome, adult Lhermitte-Duclos disease, and autism-like disorders associated with macrocephaly. The penetrance of Cowden syndrome is thought to be nearly complete and approaches 90% penetrance by age 20 years.[20] These figures are based on evidence from older studies that predated the development of the Consortium diagnostic criteria, so accurate penetrance estimates using the criteria are not available.

Although germline mutations in *PTEN* are generally reported to be found in about 80% of individuals with Cowden syndrome, detection rates using DNA sequencing have ranged from 11-80% in individuals who have met the Consortium criteria.[10] More recently in a much larger cohort, *PTEN* mutations have been found in 30-35% of patients meeting the diagnostic criteria.[17] This same study also concluded that 37% of individuals with mutations did not meet diagnostic criteria for Cowden syndrome or BRRS. More recent studies have been testing individuals with no detected mutations in *PTEN* to determine if there is a deletion or rearrangement of the gene. One study examined 95 individuals and found no evidence of large gene deletions or rearrangements.[47] However, in another report, 80 unrelated individuals clinically diagnosed with Cowden syndrome but negative for a *PTEN* mutation were tested, and four individuals, or five percent, were found to have deletions.[48]

Because Cowden syndrome is rare and the diagnosis is difficult due to highly variable expressivity, data regarding genotype-phenotype correlations are limited and mostly based on a collection of case series. Most studies have failed to demonstrate a consistent genotype-phenotype correlation, but all have found an increased risk for associated cancers.[45; 49-51]

1.1.3.1 Genetic Testing

The National Comprehensive Cancer Network (NCCN) has used the Consortium criteria to serve as a basis for the list of *PTEN* mutation testing criteria which is included in the NCCN guidelines. Based on the literature and expert consensus, the panel recently revised the list of criteria associated with Cowden syndrome as well as the combinations of criteria that establish which individuals are candidates for *PTEN* mutation testing. The following is that criteria:

- ► Individual from a family with a known *PTEN* mutation
- ► Individual meeting clinical diagnostic criteria for Cowden syndrome/PHTS
- ► Individual with a personal history of:
    - Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
    - Adult Lhermitte-Duclos disease (cerebellar tumors) or
    - Autism spectrum disorder and macrocephaly or
    - Two or more biopsy-proven trichilemmomas or
    - Two or more major criteria (one must be macrocephaly) or
    - Three major criteria, without macrocephaly or
    - One major and ≥3 minor criteria or
    - ≥4 minor criteria
- ► At-risk individuals with a relative with a clinical diagnosis of Cowden syndrome/PHTS or BRRS for whom testing has not been performed
    - The at-risk individual must have the following:
        - ▪ Any one major criterion or
        - ▪ Two minor criteria

As mentioned previously, Cowden syndrome is known to have wide variability in the clinical presentation between individuals, even within the same family. Because of this, it can be difficult to determine which individuals are appropriate candidates for *PTEN* genetic testing. It has been suggested that individuals meeting or coming close to meeting the Consortium diagnostic criteria should be tested.[10] All individuals with Lhermitte-Duclos disease or multiple trichilemmomas should be tested, and those with macrocephaly, along with other significant Cowden syndrome findings, are also appropriate candidates. It is unclear, however, how much weight the minor criteria should be given since several of the criteria are common in the general population, and the dermatologic features may also be less obvious than implied in the literature.

There are also a number of studies that have suggested that individuals with features of Cowden syndrome should not be tested for *PTEN* mutations. These would include isolated cases of early onset breast cancer[52], BRCA-negative familial breast cancer[53], and isolated cases of endometrial cancer[54]. Testing may also not be of value to families with no signs of Cowden syndrome, other than breast and thyroid cancers and breast and brain cancers in the same individual or family[41], and women with double primary cancers[55].

1.1.3.2 Cancer Gene Panels

New genetic testing panels use next-generation sequencing that are intended for individuals who have tested negative for high penetrance genes and for those whose family history is suggestive of more than one cancer syndrome. The testing laboratories include somewhat different, but often overlapping, genes, and included in most of these panels is *PTEN*. The recent Supreme Court decision in June 2013 has allowed all testing companies to include *BRCA1/2* in their panels.[56] This decision has enabled companies to offer panels with more cancer predisposing genes, as well as reduce the cost of the panel. It has been suggested that multiplex panels will be both clinically useful and cost-effective for patients with near-equivalent risks for Hereditary Breast and Ovarian Cancer (HBOC) syndrome and PHTS or other conditions.[57] It has also been suggested that these panels should only be ordered in consultation with a cancer genetics professional due to the complexity and limited data available regarding their clinical utility. Table 1 shows that there are several advantages and disadvantages to panel testing.[58]

Table 1. Advantages and disadvantages of panel testing

Advantages	Disadvantages
Greater sensitivity for assessing cancer risks	Insurance coverage still in question
	Limited data on risks for less penetrant genes
Cost-effective for some patients (just about the same as an individual gene)	Difficulty interpreting risks when mutations in more than one gene occur
	Explanation of negative results can be more confusing for patients
Extend genetic risk assessment to a wider population	Lack of established management guidelines for lower penetrance genes
	Difficulty defining the target population for testing
Determine who is at risk for highly penetrant cancers, moderate risk due to lower penetrance, or average population risk	Increased chance of detecting a variant of unknown significance (limited information available on impact of VUS on risk)
Broaden number of gene targets used to assess risk	More complex results – false positive rates increase with increasing number of tests and when testing low risk population

1.1.4 Management and Treatment

Management guidelines for individuals with Cowden syndrome have been adopted by the NCCN and should be followed for all individuals with germline *PTEN* mutations. Individuals who have an operational diagnosis but not mutation are followed based on family history. Those guidelines are listed below:

Women

- ► Breast
    - Awareness starting at age 18 years
    - Clinical breast exam, every 6-12 months starting at age 25 years or 5-10 years before the earliest known breast cancer in the family
    - Annual mammography and breast MRI screening starting at age 30-35 years or based on earliest age of onset in the family
    - Consider risk-reducing mastectomy
        - Includes counseling regarding degree of protection, extent of cancer risk, and reconstruction options
        - Address psychosocial, social, and quality of life aspects
- ► Endometrial
    - Patient education and prompt response to symptoms
    - Consider annual random endometrial biopsies and/or ultrasound beginning at age 30-35 years
    - Risk-reducing hysterectomy (discussion same as mastectomy)

Men and Women

- ► Annual comprehensive physical exam starting at age 18 years or 5 years before the youngest age of diagnosis of an associated cancer in the family (whichever comes first)
- ► Thyroid
    - Particular attention to thyroid exam during physical
    - Ultrasound starting at age 18 years or 5-10 years before earliest known thyroid cancer in family (whichever is earlier)

- ► Colon
    - Colonoscopy, starting at age 35 years, every 5 years or more frequent if patient is symptomatic or polyps found
    - Consider renal ultrasound starting at age 40 years then every 1-2 years
- ► Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
- ► Education regarding signs and symptoms of cancer

<u>Risk to Relatives</u>

- ► Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
- ► Recommend genetic counseling and consideration of genetic testing for at-risk relatives

1.1.5 Genetic Counseling

Cancer genetic counseling in general is geared to identify individuals with cancer predisposition gene mutations as well as those family and personal histories that affect the overall risk for development of cancer. However, only about 7-10% of cancers are associated with heritable conditions, leaving a majority of individuals left without a single gene cause. Cancer genetic counseling has become an imperative part of the risk assessment process in order to identify those with mutations in cancer genes as well as to reassure those who have not inherited a specific mutation but may still be at increased risk for developing malignancies.

Counselors can us a variety of qualitative and quantitative risk assessments to determine an individual's risk for possessing a deleterious mutation in a cancer gene and for developing cancer. Qualitative risk assessment primarily uses family and personal medical histories to determine an individual's risk, and incorporates environmental factors, such as toxic substances, use of medications, and lifestyle issues. An accurate assessment includes a detailed personal and family history, including, but not limited to, age of patient and family members, reproductive history, causes of death, lifestyle issues, such as obesity and oral contraceptive use, age and type of cancer diagnosis, and years of survival. Quantitative risk assessment uses risk assessment models to determine an individual's risk to carry a deleterious mutation. Most models are geared toward assessing risk for breast cancer, so the combination of qualitative and quantitative assessment is necessary.

To date, there are only two risk assessment tools for Cowden syndrome, the Cleveland Clinic *PTEN* calculator and the Ohio State University calculator. The Cleveland Clinic risk assessment tool is based on the patient's medical history and physical findings. It has been shown to outperform the NCCN Cowden testing criteria.[18] It was developed from a prospective series of 3,042 probands who, at minimum, met the relaxed Consortium diagnostic criteria. After comparing age-related prevalence within mutation positive and negative participants to expected community frequencies from published literature, a weighted score was given for each studied phenotype. The weight was adjusted where referral bias was evident, mostly for cancer diagnoses, and then totaled to calculate a total *PTEN* risk score. This score correlates with percent risk for finding a germline *PTEN* mutation. The tool was developed with the thought that it would be easy to use for clinicians who would be able to inquire about the different features from the checklist provided.

The Ohio State University is home to the primary clinical laboratory in the United States to offer *PTEN* gene testing, having tested the most patients. Because of this, they were able to assemble the world's largest reported series of clinically tested, mutation positive patients (802 subjects) on which to assess clinical features and performance of the Consortium criteria.[17] Besides determining the prevalence of the phenotypic features of Cowden syndrome in the cohort (discussed in a previous section), a model was developed to predict the likelihood of a *PTEN* mutation for a patient based on their clinical features. It was also determined that the Consortium criteria is not as robust at identifying patients with mutations as previously thought, due to the fact that only 34% of subjects meeting the criteria had a detectable mutation, which is significantly lower than the 80% previously reported.[47]

Psychosocial assessment is also important during the counseling process since individuals frequently face emotional stress and psychological upset based on the findings of counseling and/or genetic testing. It is pertinent to obtain information from individuals before counseling and risk assessment concerning their expectations for the counseling session, the personal impact of the cancer in question, the potential clinical outcomes, their relationship with relatives, the desire to initiate preventative measures in case an increased risk for cancer is determined, and the personal and familial implications of a positive or negative genetic test result. This information is important to consider so counselors are aware of and work with these issues so they can provide effective counseling and empower their patients to obtain all the information in order to make the best decision for them.

1.2 SPECIFIC AIMS

A topic that has not yet been explored is the question of implementing head circumference measurement in a cancer genetic counseling session. Head circumference growth charts are presumably used on a daily basis in a pediatric setting, at least in a clinical genetics department, but the implementation of head circumference measurement in an adult setting is not well understood, especially in a cancer genetics consultation. If head circumference is measured in a clinical cancer genetics consultation, the question of how this decision was made is also an area of interest since once again, it is not well studied. These questions will attempt to be answered by implementing specific aims to facilitate assessment of genetic counselors' attitudes towards head circumference measurement.

1.2.1 Specific Aim 1

Specific Aim: To determine whether head circumference is currently being measured clinically in hereditary cancer assessment

Hypotheses: Head circumference is not being measured for every patient who presents for hereditary cancer assessment.

Half of the patients who present for hereditary *breast cancer* assessment will receive a head circumference measurement.

1.2.2 Specific Aim 2

Specific Aim: To assess the attitudes of genetic counselors concerning the clinical implementation of head circumference measurement for any patient with a Cowden syndrome associated cancer.

Hypotheses: Most counselors will use a variety of techniques to determine which patients should receive head circumference measurement and information on other clinical symptoms is also elicited with all patients who present for cancer genetic counseling.

Half of the genetic counselors surveyed will believe head circumference measurement is a beneficial tool for all patients and the other half will not think it is necessary for all patients.

2.0 EXPERIMENTAL DESIGN AND METHODS

2.1 PARTICIPANTS

Study participants were recruited through an e-blast maintained by the National Society of Genetic Counselors (NSGC), including dissemination to all members, including full, associate, and student members. The invitation to participate (Appendix C) and the electronic questionnaire (Appendix D) were disbursed to approximately 3,000 members of the NSGC. Approximately 25%, or 740 individuals, of these members are thought to specialize in cancer genetics. However, it is assumed that not every practicing cancer genetic counselor is a member of the NSGC. Therefore, the target sample size was 250 individuals but the actual number of participants was 216. The participants were both male and female and of all ethnic backgrounds. All participants were over the age 18 years. The participants were not mentally incompetent or members of any other legally restricted group. The participants were reminded that the questionnaire is completely voluntary and can choose to stop participation at any point. All participants who completed the questionnaire had the option to enter a random drawing for a $25 Amazon gift card donated by the study investigators. Contact information for the drawing was entered separately from the study using an option at the end of the questionnaire by providing the email address of the co-investigators. If participants elected to be entered for the drawing, they sent an email to the co-investigator with their name and email address in order to be contacted if they are the winner of the drawing.

2.2 QUESTIONNAIRE

The questionnaire used for this study was created by the co-investigators at the University of Pittsburgh and Allegheny Health Network, and approved for research purposes by the Institutional Review Boards of the University of Pittsburgh and Allegheny Singer Research Institute (ASRI) in Pittsburgh, Pennsylvania (see Appendices A and B for approval). The questionnaire, designed through Qualtrics, included 14 multiple choice and short answer questions for the participants. The first six questions pertained to the participant demographic information in order to determine the details of the study population. These included questions such as gender, age range, number of years practicing cancer genetic counseling, and primary credentials. The last eight questions were designed based on the review of current literature and the specific aims of this study. These questions include current clinical practices and beliefs about the clinical readiness of head circumference measurement. Multiple opportunities existed throughout the questionnaire for participants to elaborate on their answers and provide personal comments. The open-ended questions were also taken into consideration during data analysis, as described below.

2.3 DATA COLLECTION

Data was collected in April and May of 2014. The questionnaire took approximately ten minutes to complete. Data from a total of 216 participant questionnaires was used for analysis. All participants were contacted two weeks after the initial e-blast was sent, whether they completed the questionnaire or not, as a reminder for their voluntary participation in this study. Information was gathered on the participants demographic information, including gender, age range, credentials, and number of years providing cancer genetic counseling. Information was also collected about the current clinical practices and beliefs about head circumference measurement, which included multiple choice and short answer responses. All of this information was obtained through Qualtrics Survey Software, a system that allows results to be read in real-time, analyzed, and presented in a user-friendly fashion. A user ID and password were required to access the data.

2.4 DATA ANALYSIS

2.4.1 Descriptive Statistics

The results of this study were analyzed using descriptive statistics, qualitative data interpretation, and thematic analysis. The descriptive statistics method was used because it is a quick way to display and interpret the data. Because there were several demographic and multiple choice questions, this is the best mode of analysis to use. This method allows researchers to notice trends, if any, which may warrant a more detailed look for future research studies. Data was collected and quantified to evaluate individual question trends or overall trends with multiple questions. For both specific aims, a Z test for proportions was used in order to determine if the results were different than half, or 50%. This was also used to determine the difference between the current practices and beliefs of the participating counselors. Because this is a preliminary study, the data analysis aimed to summarize the results for an information-gathering study.

2.4.2 Qualitative Data

Qualitative research aims to study from the perspective of the acting individual by applying interpretive and naturalistic approach to its subject matter.[59] Qualitative research aims to capture the empirical reality of social life, meaning researchers much give careful attention to the range of contextual issues and the variety of perspectives that exist in society. This type of description is usually gathered from minimally to moderately open ended questions, as is the case for this study. It can be effective in obtaining and understanding how various perspectives create and sustain particular understandings of empirical reality. However, collection and analysis of qualitative data is typically more time consuming, labor intensive, and intimate as compared to quantitative data collection and analysis. Analysis of qualitative data is a dynamic process and is data-derived by generating themes in the course of the study. This methodology is a large part of this study in order to determine the beliefs of genetic counselors towards head circumference measurement.

2.4.3 Thematic Analysis

Analysis of the qualitative data involves the identification, analysis, and reporting of patterns, or themes, within the data. A theme is defined as a pattern that captures something important about the data in relation to the research question and represents some level of meaning within the data set. Detecting these themes involves a process of coding and interpreting the data. The thematic analysis used in this study was conducted in an inductive manner by coding the data without any preconceived ideas devised by the investigators. On the other hand, theoretical thematic analysis involves a more explicitly analyst-driven approach and provides a more detailed analysis of some aspect of the data in contrast to a less rich description of the data overall.

Data from the open-ended responses in the electronic questionnaire were exported to Microsoft Excel. Thematic analysis was used to analyze the open-ended response data using guidelines proposed by University of Wisconsin Planning Council for Health and Human Services (2011) (Table 2).

Table 2. Phases of Thematic Analysis

Phase	Description of Process
Read through all responses	Reading through all the responses will enable a sense of emerging themes
Develop categories	Develop categories to include the themes that emerged during initial review
Assign each response to a category	Known as coding, each response will be assigned a category or categories
Check your categories	Check to see if categories are actually appropriate. Some categories may be broken into subcategories.
Review for major themes	Review to see which categories have the most responses and therefore represent major themes. Think about what the themes are really saying.
Identify patterns and trends	Identify which categories are related and where patterns and trends can be identified
Write-up analysis	Summarize in order effectively communicate the findings. Use descriptive text incorporating some of the comments that exemplify major themes. Themes may complement or clarify the quantitative data to tie it all together.

3.0 RESULTS

3.1 DEMOGRAPHICS

A total of 216 NSGC members participated in this study. Only data from those who have practiced cancer genetic counseling in the last six months were used. A majority of the participants were female (94%) and aged 21 to 30 years (50%). Most individuals (62%) identified their primary credentials as having a Master's of Science (MS) in Genetic Counseling and being a Certified and/or Licensed Genetic Counselor (CGC/LGC). It is assumed that those who stated only CGC/LGC (25%) also have a MS in Genetic Counseling. It is also assumed that those who stated as only having a MS in Genetic Counseling (10%) have not taken the Certification Exam or they practice in a state that does not require licensure. A majority of the participants have been practicing cancer genetic counseling for one to five years (60%), as well as work in a primary clinical counseling work setting (98%). Table 3 illustrates the full characteristics of the participants.

Table 3. Questionnaire Demographics

	Participant Categories	Total
Gender	Female	203 (94%)
	Male	10 (5%)
	No Response	3 (1%)
	Total	**216**
Age	21-30	109 (50%)
	31-40	65 (30%)
	41-50	18 (8%)
	51-60	18 (8%)
	>60	5 (2%)
	No Response	1 (0.5%)
	Total	**216**
Primary Credentials	MS in Genetic Counseling Only	21 (10%)
	CGC/LGC Only	55 (25%)
	MS in Genetic Counseling + CGC/LGC	134 (62%)
	MS in GC, CGC/LGC, other*	2 (0.9%)
	CGC/LGC + other*	1 (0.5%)
	Other* only	2 (0.9%)
	No Response	1 (0.5%)
	Total	**216**
Years Providing Cancer Assessment	1-5	130 (60%)
	6-10	51 (24%)
	11-15	19 (9%)
	16-20	9 (4%)
	>20	5 (2%)
	No Response	2 (1%)
	Total	**216**
Primary Work Setting	Clinical Counseling	212 (97%)
	Lab	0
	Research	3 (1%)
	No Response	1 (0.5%)
	Total	**216**

*Those who chose other stated their primary credentials as:

1. CCGC (Canadian)
2. Also have other Master's degree
3. Credentialed Advance Practice Nurse Genetics (APNG)
4. 2nd year genetic counseling student
5. MPH genetic counselor

3.2 SPECIFIC AIM 1

Specific aim 1 was designed to determine whether head circumference is currently being measured in a clinical setting. Certain questions were developed in order to provide information for this aim, specifically questions seven, eight, and nine (see Appendix D). Both descriptive statistics and qualitative data analysis were employed to determine whether head circumference is currently being measured.

3.2.1 Descriptive Statistics

Study participants were asked if they measure the head circumference on every patient that presents for a hereditary cancer genetics assessment and also if they measure on every patient that presents for a hereditary *breast cancer* assessment. Both questions were asked in a ‘yes or no’ fashion, with an opportunity to elaborate following the question. If a participant answered ‘yes’ to measuring on all individuals who present for hereditary cancer assessment, another question was asked. This question was asked in order to determine if the reason for the head circumference measurement being taken was explained to the patient. The results are displayed in Figure 1. As seen in this figure, the majority of participants for questions seven and nine answered ‘no’, they do not measure on every patient and/or every breast cancer who presents for hereditary cancer assessment. However, there were six individuals who do not measure on every patient but explained that this is part of routine clinical care for their patients. These participants do not personally measure, but the nurses or oncologists in the clinic will. It is also noted that, in the majority of cases, if head circumference is measured, an explanation is given to the patient.

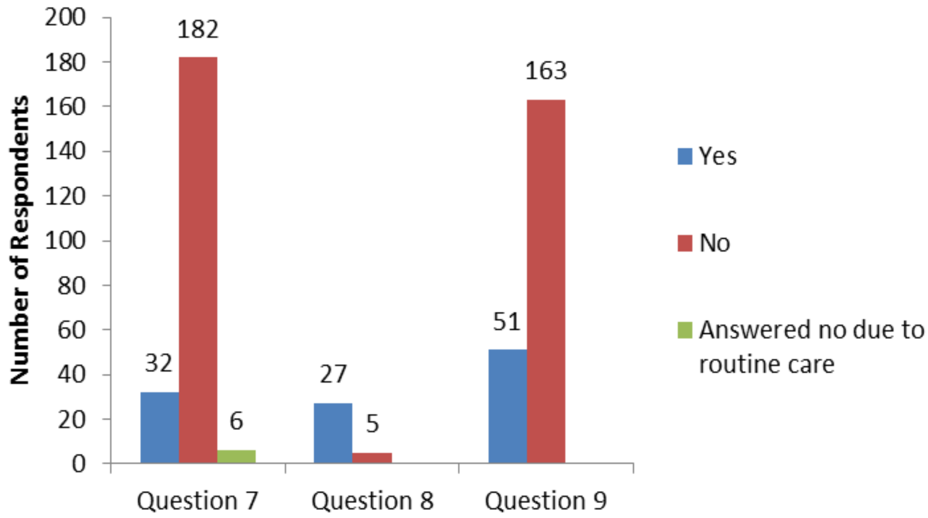

Figure 1. Head circumference measurement on all and breast cancer patients
The questions state:
Question 7: Do you measure head circumference on every patient who presents for cancer genetic counseling?
Question 8: Since you do measure head circumference on every patient, do you explain to them why you take this measurement?
Question 9: Do you measure head circumference on every patient *with breast cancer* who presents for cancer genetic counseling?

3.2.2 Narrative Responses

Questions seven and eight were designed to assess Specific Aim 1 by including open-ended responses to elaborate why the participant chose their answer. Thematic analysis was used in order to analyze the qualitative data from the responses. Out of the 214 individuals who answered question seven, 192 gave an open-ended response. Although not all respondents who answered the question gave a narrative response, 90% did answer which allowed the thematic analysis to occur. For the 32 individuals who measure head circumference on everyone, 27 gave an open-ended response.

3.2.2.1 Head circumference measurement on all individuals

Participants were asked in a free response format to explain how their clinic made the decision to measure or not to measure head circumference on all individuals who present for hereditary cancer assessment. After reviewing all responses, each response was arranged into a category and coded to determine the major themes that arose from this question. Table 4 provides the themes identified within the responses.

Table 4. Themes derived from Question 7

Category #	Theme from Analysis	Number of Participants
1	Suspicious of Cowden syndrome[1]	120
2	Routine in clinical care or based in a pediatric setting	9
3	Measurement on everyone unless individual is coming in specifically for a non-*PTEN* site-specific testing[2]	5
4	No formal decision has been made or it has been that way since starting at the clinic	22
5	Feel that it is not part of the training for genetic counselors or the measurement is used solely as an estimate	8
	Multiple themes involved	23

[1]Includes cancers and/or features of Cowden syndrome elicited from family and/or personal history
[2]For example, *BRCA1/2* genetic testing

The theme with the most amounts of responses was category one, 'Suspicious of Cowden syndrome'. Counselors felt that a suspicion of Cowden syndrome included one or more cancer(s) and/or other benign findings associated with the condition in the family and/or personal history of the patient. One participant wrote in regard to only measuring when suspicious of Cowden syndrome:

We base this off of reported personal and family history – if there is any indication of Cowden syndrome in the patient or family members, we'll take a head circumference to document on the family history and to see if they do in fact, meet criteria for PTEN testing

Another commented:

We measure based on family history…if it is suggestive of a PTEN mutation, we will measure. This decision was made based on the clinical presentation of typical PTEN mutations

One other participant stated:

I take OFC's on patients with a personal history of cancers associated with PTEN (breast, CRC, renal)

Another theme involved several individuals feeling it was outside the scope of practice for genetic counselors to be measuring head circumference. Some measure head circumference but it is only used as an estimated measurement. A participant commented:

I do not feel qualified to take an accurate head circumference

There were also individuals who had the opposite opinion and thought head circumference should be measured on everyone, unless the individual was specifically presenting for non-*PTEN* genetic testing, such as *BRCA1/2*. One participant stated:

I do not measure OFC only for patients who are presenting for non-PTEN site-specific testing. Everyone else gets a head measurement. ☺

Along the same beliefs, another participant stated:

We had multiple patients that had negative BRCA1/2 testing and we were considering PTEN and kicking ourselves that we didn't have a head circumference so we started measuring it for all patients seen at our institution.

There were also individuals who work in a setting where head circumference measurement is routine in clinical care, in addition to weight, height, and blood pressure, and may also include working in a pediatric setting. In these cases, a nurse would measure the head circumference, not the genetic counselor. One individual noted that:

It is part of their physical evaluation along with weight, height, and blood pressure. I think it was originally for the purpose of assessing candidates for PTEN testing.

A select few individuals work in a pediatric setting but have counseled for hereditary cancer assessment. The practices in this case were similar to those who measure due to routine clinical care, stating:

I see only pediatric patients and if they present with adenomatous colon polyps, I do not measure an OFC. For almost any other type of polyp, especially hamartoma or juvenile, I do recommend an OFC.

The rest of the individuals who gave a response simply stated that there was no formal decision or the decision was made before they started working at the clinic. A participant stated:

I joined an established clinic where it wasn't standard to measure head circumference

Only a few participants brought up the subject of panel testing, which most often includes *PTEN*, and ordering the testing for those who present for hereditary cancer assessment. They felt it was unnecessary to measure head circumference when ordering a panel. In particular, one participant commented:

For my patient that we suspect PTEN, we will order a NGS panel that includes PTEN analysis. The only time head circumference is measured is if PTEN alone is suspected, and there is no panel that the patient would be eligible for that includes PTEN and PTEN analysis only is going to be pursued

Others, however, felt that measuring head circumference, in addition to ordering a panel, was the best approach for their clinic. One participant stated:

It was fairly common practice prior if there was a suspicion of Cowden syndrome. Since the advent of panel testing it was decided that it should be routine for all patients

Some of the responses from the participants encompassed multiple themes, most of which identified measuring when suspicious of Cowden syndrome, plus another theme. Examples of the multiple themes expressed are described in Table 5.

Table 5. Multiple themes expressed in a single statement

Category #	Statement
1 & 4	*No formal decision has been made. I measure a patient's head circumference when Cowden syndrome is a concern based upon personal or family history information, and only when the patient consents. We do not have a medical geneticist and so I ask patients before doing that measurement.*
1 & 5	*We measure heads when there is a suspicion of Cowden syndrome. Also, we don't always have an Medical Geneticist in clinic to do this and I'm not confident about all my measurements.*
2 & 3	*Our clinic began as primarily pediatric/general genetics and over the years has expanded to include cancer genetics. Measuring head circumference has always been a requirement for our general genetics patients; therefore it is now a requirement for all cancer genetics patients. As we have expanded our program to include off-site cancer specific clinics, those patients also received head circumference measurement as this is a helpful measurement for PTEN risk assessment*

All of the participants who responded with an open-ended comment fell into at least one of the themes described above.

3.2.2.2 Explanation of Head Circumference Measurement

Participants were asked in a free response format to describe why or why not an explanation is given to patients as to why head circumference measurement is taken. After reviewing all responses, each response was put into a category and coded to determine the major themes that arose from this question. Table 6 provides the themes identified within the responses.

Table 6. Themes derived from Question 8

Category #	Theme from Analysis	Number of Participants
1	Explain that large head size is associated with a cancer syndrome	16
2	Nurses do the measuring as part of routine clinical care	1
3	Explain only if the patient asks	3
4	Explain everyone gets the measurement done	2
	Multiple themes involved	5

A majority of the participants commented that they do explain to a patient why the measurement was taken and explain that large head size is associated with a cancer syndrome. One participant responded:

I give a very brief explanation that occasionally a feature of a hereditary cancer syndrome is a larger head size. I only elaborate if the patient asks.

Another participant commented:

I've noticed that patients are more accepting if they understand why questions or measurements are being taken. It helps them to feel a part of the process.

Some have a different approach and explain that all patients have their head circumference measured as part of their assessment. A participant stated:

We explain that as part of a genetic evaluation we often take many measurements.

In other clinics, the nurses do the measuring as part of routine clinical care, which is explained to the patient, either by the nurses or the genetic counselors if the patient asks. One participant responded to this decision by stating:

I do not do the measurement myself. I have told the medical assistants that if a patient asks, they should tell them that it is done on all patients coming for genetic counseling since sometimes the genetic counselor uses the measurement in her assessment.

The respondents who answered ‘no’ to this question all fell into the theme that an explanation is given only if the patient asks. One participant stated:

Only if they ask or if we are suspicious of PTEN mutations.

All of the responses were clear and fit into only one theme. No overlapping of themes was included in any of the responses.

3.3 SPECIFIC AIM 2

Specific aim 2 was designed to assess the attitudes of genetic counselors concerning the clinical implementation of head circumference measurement for any patient with a Cowden syndrome associated cancer. The rest of the questions in the questionnaire were directed at answering this aim (see Appendix D). Some of the questions were skipped if a certain answer was chosen and was designed this way on purpose. For example, if the answer to question nine was ‘yes’, question ten would be skipped. If the answer to question 11 was ‘no’, question 12 was skipped. This mechanism was built into the survey so if a question was skipped, the respondent did not see the question nor have the chance to answer. Both descriptive statistics and qualitative data analysis were employed to determine the beliefs of genetic counselors in implementing head circumference measurement.

3.3.1 Descriptive Statistics

Study participants were asked about their beliefs on implementing head circumference measurement on all patients who present for hereditary cancer assessment. The questions directed at these beliefs were either asked in a 'yes/no' or multiple choice fashion. Question 13 enabled participants to elaborate on their answer. If a participant answered 'no' to question nine, they were given the option to answer question 10. Of the 163 people who answered 'no' to question nine, 160 responded to question 10. Question 10 had the option for 'other' to be selected, in which the participant was asked to specify why they chose that answer. Unfortunately, question 10 did not give the option to select multiple choices so the 'other' category included some or all of the choices. Because of this, it was easy to categorize these responses, similar to the thematic analysis, and to incorporate multiple answers instead of just one. Figure 2 displays the multiple choice answers. The legend signifies how many participants chose just one answer or how many times participants included a choice. For example, nine participants chose A, but choice A was selected 25 times in conjunction with choices B, C, D, and/or E. Most respondents would have chosen all of the above and taken multiple factors into consideration when deciding which patients should have their head circumference obtained.

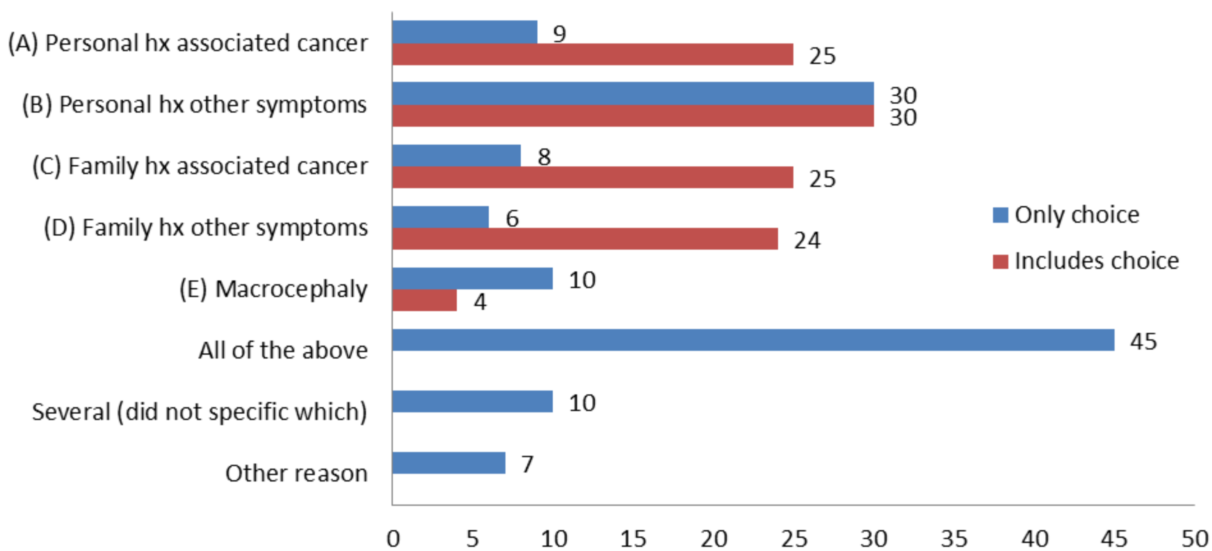

Figure 2. Reasons for determining when to measure head circumference
The question states: Since you do not measure head circumference on every patient, how do you determine which patients should have their head measured?

The next set of questions aimed to determine if genetic counselors elicit information on other clinical symptoms of Cowden syndrome with every patient, and if so, how they elicit the information. Figure 3 shows that just over half of genetic counselors elicit information on other clinical symptoms of Cowden syndrome with every patient who presents for counseling. Of the counselors who do, Figure 4 shows that most counselors elicit information from review of systems questions, directed questions about Cowden syndrome, and from medical records. Most other counselors are eliciting information from directed questions about Cowden syndrome only, or review of systems questions and directed questions or medical records.

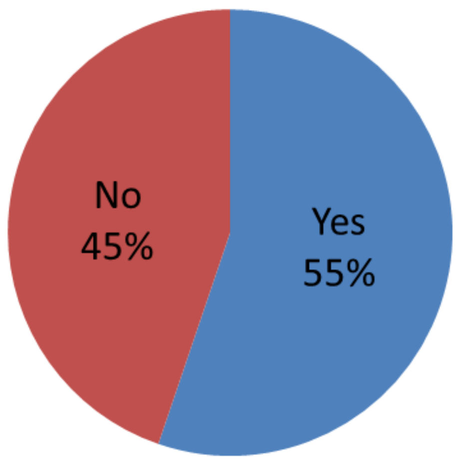

Figure 3. Eliciting information on other clinical features of Cowden syndrome
The question states: Do you elicit information on other clinical symptoms of Cowden syndrome with every patient who presents for cancer genetic counseling?

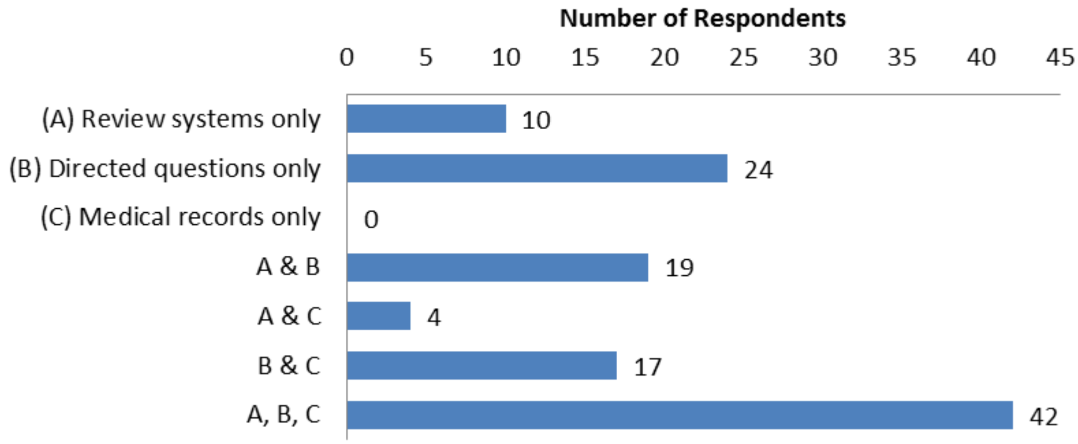

Figure 4. How information is elicited about Cowden syndrome

The next question aimed to decipher the professional opinions of counselors to determine if they believe head circumference should be measured for every patient who presents for cancer counseling. As shown in Figure 5, a majority of the counselors believe head circumference should not be measured in every patient, but should be reserved only for those that are suspicious of Cowden syndrome.

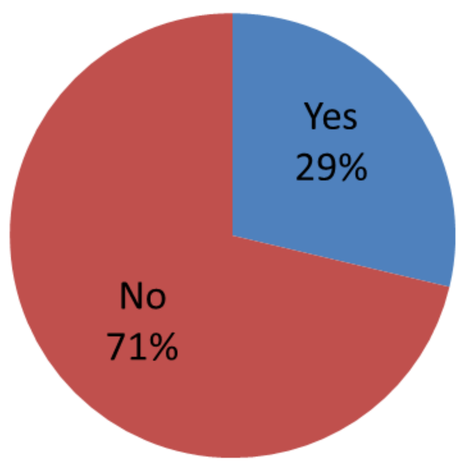

Figure 5. Should head circumference be measured on every patient

The last questioned aimed to also decipher the professional opinions of the counselors to determine the percentage of cases they feel are undiagnosed due to head circumference not being measured. Figure 6 shows that 31% of counselors believe between one and two percent of Cowden syndrome cases are undiagnosed while 18% believe more than 5% are missed.

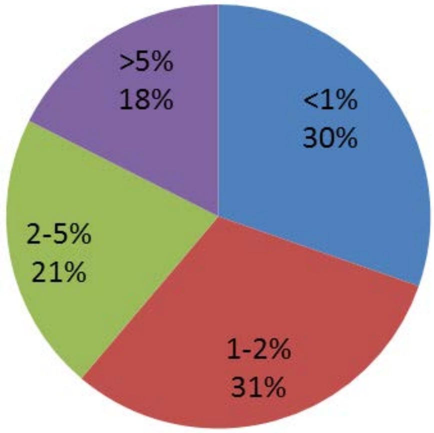

Figure 6. Percentage of Cowden syndrome cases believed to be undiagnosed

3.3.2 Narrative Responses

Question 13 was designed to assess Specific Aim 2 by including an open-ended response to elaborate why the respondent chose their answer. Thematic analysis was used in order to analyze the qualitative data from the responses. Out of the 216 individuals who answered the question, 209 gave an open-ended response. Although not all respondents who answered the question gave a narrative response, 87% did which allowed for the thematic analysis.

Participants were asked in a free response format to explain why they believe head circumference should be measured for every patient who presents for hereditary cancer assessment or why they do not believe this should be standard practice. After reviewing all responses, each response was put into a category and coded to determine the major themes that arose from this question. Table 7 provides the themes identified within the responses.

Table 7. Themes derived from Question 13

Category #	Theme from Analysis	Number of Participants
1	Cowden syndrome is rare and likely not helpful in assessment	44
2	Only if suspicious of Cowden syndrome	73
3	Easy measurement to help in assessment	12
4	Good clinical practice and/or essential in assessment	29
5	Moving towards panels so it is not necessary	7
	Multiple themes involved	12

The theme with the most amounts of responses was category two, ‘Only if suspicious of Cowden syndrome’. One participant wrote in regard to the clinical practice of only measuring head circumference on those that are suspicious of Cowden syndrome:

Anyone with a remote chance of Cowden in the differential should have their head circumference measured. I suppose you could do it on everyone, but I don’t think it is necessary

Another participant noted:

I think it is best to measure OFC in patients who seem Cowden-like. If I am seeing a woman for a history of breast and ovarian cancer, a large head circumference will not change my decision to pursue BRCA testing first (in the absence of other Cowden-related symptoms in the patient’s personal or family history)

While most identified with only measuring when there is a suspicion for Cowden syndrome, the next largest group of participants believed that Cowden syndrome is rare so measuring head circumference on all patients would not necessarily be helpful. One participant commented:

Although I understand our incidence may be underestimated, it is still rare, and it is not necessary on every patient.

On the other hand, other counselors believed it is good clinical practice to measure head circumference on all patients and/or is essential in hereditary cancer assessment. One participant believes that:

Macrocephaly is considered a major criterion for Cowden syndrome, and many times the other features can be subtle or considered "common" (i.e. fibrocystic breasts, uterine fibroids, thyroid problems), therefore it is my professional opinion that measuring head circumference for every patient who presents for cancer genetic counseling is good clinical practice and an essential part of the cancer genetics evaluation.

Another participant responded in such a way because of a particular patient, stating:

You may not know if a patient meets criteria for PTEN testing without doing so. I actually had one patient that was identified as having a PTEN mutation only because I made a point to measure every breast cancer patient's head. Otherwise, this would not have been known.

Similarly to the respondents above, other participants thought measuring head circumference is quick and easy and can aid in hereditary cancer assessment. One participant responded:

It's an easy, quick thing to do. Typically there are other things in addition to macrocephaly that make us think about PTEN testing but why not, more information is better

The last category involved genetic counselors believing cancer genetic testing is moving towards panels and not individual *PTEN* testing. Some felt that measuring head circumference may not be necessary in this case since the genetic testing includes *PTEN*, the only gene associated with Cowden syndrome. One participant wrote:

Since we are shifting more towards panel testing each year, I think PTEN will be performed on many more patients, and head circumference will not necessarily be a determining factor.

A few counselors' comments encompassed more than one category. Although there were very few comments like this, a few interesting examples are noted. One participant encompassed the rarity of Cowden syndrome, measuring when there is a suspicion, and head circumference being an easy measurement with the statement:

Cowden syndrome is rare, and most patients, even with associated features do not have this condition. Macrocephaly should only be evaluated for if other Cowden syndrome features are present. However, since it is a fairly simple and non-invasive procedure, I don't feel strongly that it shouldn't be done, just that it's not necessary.

Another participant encompassed measuring when there is a suspicion and panel testing by stating:

That was usually reserved for suspicion of Cowden cases, however with the new cancer panels, and "surprising" result, maybe obtaining head circumference would not be a bad idea for clinical correlation.

Another participant encompassed head circumference measurement as good clinical practice as well as panel testing by commenting:

Cowden syndrome is underdiagnosed and with the advent of panel testing I think we are also going to start seeing broader phenotypes so it will be helpful to have as much information as possible to help correlate.

All of the participants who responded open-endedly fell into at least one of the themes described above.

4.0 DISCUSSION

The practices, attitudes, and beliefs of genetic counselors regarding the measurement of head circumference for patients who present for hereditary cancer assessment has, to the best of our knowledge, not yet been documented in the literature. The goal of this study was to assess these practices, attitudes, and beliefs about implementing head circumference measurement in a cancer genetic counseling appointment. Specific aims were developed in order to sufficiently explore this topic, along with hypotheses for each aim. An aspect of this study that may be different from others like it is the fact that it is more of an informational or preliminary study and is the starting point for many other studies that will be discussed in this section. The bulk of the analysis came from the qualitative data which gave an interesting insight into the attitudes and beliefs of genetic counselors on measuring head circumference measurement in hereditary cancer assessment.

4.1 SPECIFIC AIM 1

Specific Aim 1 was focused to determine whether head circumference is currently being measured clinically in a hereditary cancer assessment setting. It is widely accepted that macrocephaly is associated with Cowden syndrome, but the exact prevalence is still being elucidated, falling somewhere between 50-80%. However, whether health care professionals are measuring head circumference in an oncology setting is unclear. The literature has provided essential information on head circumference measurement for Cowden syndrome, including diagnostic and genetic testing criteria, but this study was intended to determine if and how those guidelines are being followed. Centered on this specific aim, hypotheses were formed based on the literature.

The results for specific aim 1 were obtained and analyzed through descriptive statistics, qualitative data, and thematic analysis. A majority of the counselors (85%, see Figure 1) are not measuring on every patient, but their reasons for doing so were also analyzed. These results are consistent with the first hypothesis, that head circumference is not being measured for every patient who presents for hereditary cancer assessment. This is not a surprising result given the fact that the only cancer syndrome associated with macrocephaly is Cowden syndrome.

There were several themes that developed through the narrative responses to the question of measuring head circumference on every patient. As noted before, a majority of genetic counselors stated that their clinic, whether it is a group of individuals, one or two people, or just themselves, decided to only measure head circumference on those patients that were suspicious of Cowden syndrome. Of these counselors, most agreed that they base their judgment off the diagnostic and genetic testing criteria guidelines. Despite their reasoning, we can conclude that most counselors are not measuring head circumference on every patient, only those who are suspicious for Cowden syndrome. Macrocephaly is a major criterion for the diagnosis of Cowden syndrome, so it is interesting to note that most genetic counselors are measuring head circumference when there is other testing criteria present in an individual or family. Genetic counselors rely heavily on the data that is published regarding Cowden syndrome, but those guidelines have not been officially updated since 1996. Several changes have been suggested as previously noted so it might be beneficial to review and modify the diagnostic and testing criteria.

An interesting set of responses that arose as a theme was the fact that some genetic counselors feel it is outside their scope of practice to measure head circumference on their patients. These genetic counselors felt they were not trained or not trained properly to take head circumference measurements on patients. Because of these narrative responses, it might be beneficial to implement training for genetic counselors so they are able to measure head circumference and feel confident in doing so.

Additional information on head circumference measurement was gathered from those individuals who measure on all patients who present for cancer genetic counseling. A majority of counselors (84%, see Figure 1) explain to their patients why they are taking the head circumference measurement or if the patient asks and the counselors feel it is not necessary to explain since it is part of their vitals assessment before the appointment. This is not a surprising result since the major role a genetic counselor plays in sessions is giving the patient information so they can make the decision that is best for them. In certain situations it may not be beneficial to give a patient more information, but giving an explanation for head circumference measurement will hopefully limit the confusion as to why this is being done, as well as allow the patient to feel satisfied with the information provided. It seems the genetic counselors who answered this question appreciate that an explanation is in the best interest of their patients.

The second hypothesis for specific aim 1 states that half of the patients who present for hereditary *breast cancer* assessment will receive a head circumference measurement. A majority of genetic counselors (76%, see Figure 1) are also not measuring on patients who present specifically for breast cancer genetic counseling due a personal and/or family history. These results are statistically significant (p-value = 1.63×10^{-17}) and are not consistent with the second hypothesis, but it is interesting to note the differences between measuring on all patients and measuring on those presenting for breast cancer. Although the majority of counselors are not measuring for either group, there are more measuring on those presenting with breast cancer (24%, Figure 1) compared to all patients presenting for cancer genetic counseling (15%, Figure 1). The difference between these two groups could be the fact that breast cancer is a major criterion on the list of diagnostic criteria. Because of this, Cowden syndrome may appear more on a list of differentials for these patients rather than those who are not presenting specifically for hereditary breast cancer assessment.

4.2 SPECIFIC AIM 2

Specific Aim 2 was directed to assess the attitudes of genetic counselors concerning the clinical implementation of head circumference measurement for any patient with a Cowden syndrome associated cancer. After determining that most genetic counselors are not measuring head circumference in a clinical setting, unless there is a suspicion for Cowden syndrome, specific aim 2 allowed us to assess whether genetic counselors believe this should change or not. Asking certain questions about their current practices and their professional opinions allowed us to obtain results directed at this aim and analyze the hypotheses associated. Centered on this specific aim, hypotheses were formed based on the literature.

The results for specific aim 2 were obtained and analyzed through descriptive statistics, qualitative data, and thematic analysis. Those participants that do not measure head circumference on all patients were given a list of different ways one might determine which patients should have their head circumference measured. Those results are described completely in Figure 2. Most of the participants chose ‘other’ (61%) since they were unable to choose multiple determining aspects. This was a flaw in the questionnaire since the question was originally designed to allow participants to choose more than one answer, but this did not translate to the questionnaire online. However, of the participants that chose ‘other’, new categories were created within this option and all participants fell into a single category. Most participants chose ‘all of the above’ (46%) which signified they use information from personal and family history, as well as macrocephaly to determine when they measure head circumference on a patient. The other participants chose two or more options that included A, B, C, D, and/or E, which are also described in Figure 2. The participants use a combination of personal and family history for Cowden syndrome associated cancers and features. A large part of a cancer genetic counselor’s job is to elicit information from the personal and family histories to determine if there is a concern for a hereditary cancer syndrome. All counselors surveyed seem to be doing just that in assessing who should have their head circumference measured.

Along this same line, the counselors were asked if they elicit information specifically on other clinical symptoms of Cowden syndrome with every patient. More than half (55%) replied that they do elicit this information, as shown in Figure 3. The specific aim also sought to determine what format counselors are eliciting information, if at all. Participants were able to answer with any of combination of the three options given, general review of systems, directed questions about Cowden findings in the review of systems, and medical records. Most participants (36%) chose all three, that they use the combination of all the resources to elicit information specifically about Cowden syndrome. These results were expected since it is thought genetic counselors use all the tools at their disposal to elicit information from their patients in order to better assess their situation.

Based on the above results, we can conclude that genetic counselors use a variety of different techniques and questions to determine which patients should have their head circumference measured, as well eliciting information on other clinical symptoms associated with Cowden syndrome. Although not all counselors use all or the same techniques or questions, a majority of the information about head circumference measurement and Cowden syndrome symptoms are being elicited for a high percentage of patients. This relates back to the first specific aim in that counselors are using the NCCN diagnostic criteria as a guideline for gathering information and using their best judgment based on this information.

The second hypothesis for specific aim 2 states that half of the genetic counselors surveyed will feel head circumference measurement is a beneficial tool for all patients and the other half will not think it is necessary for all patients. A majority of the counselors (71%, Figure 5) feel measuring head circumference on every patient who presents for cancer genetic counseling should not be standard. This is statistically significant (p-value = 7.62×10^{-17}) and although these results are not consistent with hypothesis, the narrative responses obtained give insight into why these results occurred.

There were several themes that developed through the narrative responses about measuring head circumference on every patient who presents for cancer genetic counseling. As noted before, a majority of genetic counselors stated that the only patients that should have their head circumference measured are those in which there is a suspicion for Cowden syndrome, exactly what is currently being practiced based on this study. The percentage of counselors currently not measuring head circumference on every patient (85%, Figure 1) is slightly different from those who *believe* head circumference should not be measured on all patients (71%, Figure 5) and is statistically significant (p-value = 0.00179) It seems that while a majority of those who are currently practicing this way also believe it should not be the standard, there are some that have opposite practices and beliefs. It is interesting to note this difference because this questionnaire may have helped counselors realize what their stance is on measuring head circumference, whether it is their current practice to do so or not. Some counselors may not currently measure head circumference on every patient, but may reevaluate this decision after taking this questionnaire. Although this was not a direct specific aim of this study, it is still beneficial for counselors to understand their own practices, attitudes, and beliefs on head circumference measurement, as well as others.

Probably the most interesting theme coming from this question was genetic counselors believing every patient should have their head circumference measured because it is good clinical practice and/or essential in assessment. This theme is the complete opposite of the themes already discussed and shows the diagnostic and genetic testing criteria in a different light. When taking all of the comments into consideration, it may be beneficial to begin taking head circumference measurements on all patients, or at least those who present for breast cancer assessment. It is possible that some individuals with a *PTEN* mutation may be overlooked because their head circumference was not measured. It seems that since this measurement is quick, easy, and could be considered another vital along with height and weight, it would be an easy way to give each patient the most complete assessment possible. It is something to consider and could aid in the detection of a *PTEN* mutation when one was not originally expected.

Another interesting theme derived from this question involved panel testing, which is becoming more and more relevant in the present day. Most counselors in this category felt that since cancer gene panels are becoming more readily available, head circumference measurement will not be a determining factor if *PTEN* is captured by the panel. In the advent of more cancer gene panels, it does seem unnecessary to measure head circumference due to the fact that no other information, besides family and personal history, is necessary to order a panel. However, it may be beneficial to measure head circumference on those patients who choose to be tested through a panel with *PTEN* coverage in order to better understand the phenotype of Cowden syndrome. This relates back to macrocephaly as a major criterion and the incidence associated with Cowden syndrome. Macrocephaly has been noted to associated with a majority of cases of Cowden syndrome, but this percentage could become higher or lower if we are able to better correlate macrocephaly to Cowden syndrome. This could be established by obtaining the head circumference on those who choose the cancer gene panel including *PTEN*.

The last part of this hypothesis involved asking the professional opinion of the genetic counselors to determine what percentage of individuals they believe to be undiagnosed because head circumference was not measured. A majority of counselors (61%) felt that either less than 1% or 1-2% of cases is missed, or undiagnosed, due to head circumference not being measured. However, 18% of counselors believe more than 5% of cases are undiagnosed, as shown in Figure 6. That number is rather surprising given the other results of this study. The current practices, attitudes, and beliefs toward measuring head circumference on all patients of most counselors do not include obtaining the measurement, but 18% believe more than 5% of Cowden syndrome cases are going undiagnosed. Over 5% is a rather high number given the low incidence of Cowden syndrome. However, a majority of the counselors (61%) did believe that less than 2% of cases are undiagnosed which is expected given the current practices, attitudes, and beliefs. The wording of this question may have skewed the results slightly since there was some confusion about what the question was actually asking. Some participants felt there should be a clarification to the question since the wording made it seem as if macrocephaly is the only reason Cowden syndrome cases are not being diagnosed. If this study is continued in the future, the wording of the last question should be more specific by asking "Out of the total number of Cowden syndrome cases (diagnosed and undiagnosed), what percentage do you believe to be undiagnosed due to head circumference not being measured?".

4.3 LIMITATIONS

The results presented in this study are preliminary and several limitations are present. The first limitation comes from the individuals to which the questionnaire was distributed. The individuals surveyed were genetic counselors who presumably have similar backgrounds and training. Assuming that the genetic counselors represent a relatively homogenous group of people with similar backgrounds and training, the results of the study could be biased and difficult to extend to other groups, such as oncologists, nurses, or even primary care physicians. It is possible that genetic counselors providing cancer risk assessment are measuring/not measuring head circumference because this population better understands the features associated with Cowden syndrome. Genetic counselors are not the only health care professionals performing hereditary cancer assessment. It is possible that other oncology professionals may not fully be aware of the features associated with Cowden syndrome and therefore neglect head circumference measurement.

Because online questionnaires are an easy way to obtain information, they are numerous studies in the genetic counseling community that implement this study tactic. The individuals contacted for this study may feel there is abundance and therefore choose not to participate. Although this particular questionnaire was believe to only take 10-15 minutes to complete, the participants may have felt they had an inadequate amount of time to complete another questionnaire, and therefore not respond, or not respond completely. This limitation falls under the responder-bias term, which is the idea that individuals who did not respond differ from those who did respond. The attitudes of the genetic counselors who did respond may differ from those who did not. This would result in skewing of the overall results and not be a true representative sample. For example, the individuals who responded to the questionnaire may have thought it is beneficial to measure head circumference during a hereditary cancer assessment, while those who did not respond felt the opposite. This may have occurred for a variety of reasons and would be interesting to assess why individuals did *not* respond, but was not part of this particular study.

A similar limitation includes the possibility that the same participants responded more than once. This could have occurred because all NSGC members were contacted two weeks after the questionnaire was distributed as a reminder to complete the questionnaire. Some members may have forgotten they participated in the questionnaire when it was first distributed and participated again. Unfortunately, there is no way to track this information in the Qualtrics survey system.

There are also limitations that are associated with the questionnaire itself. First, the individual questions essentially were arranged in a standard ‘yes’ or ‘no’ answer fashion, with an open-ended response or multiple choice question to follow. For the ‘yes’ or ‘no’ questions, all asked for a reason (open-ended response) as to why the respondent chose that answer in order to better understand the attitudes of the genetic counselors. This enabled the study to incorporate qualitative analysis which was a primary goal of this study. However, a participant may have chosen to respond to the initial question, but did not elaborate on his or her response. Therefore, this would leave the open-ended response blank, resulting in reduced qualitative analysis and potentially an inaccurate portrayal of the results. Some of the multiple choice questions included 'other' in which case the participant was asked to specify their response. Once again, a respondent may have chosen this answer, but not specified with an open-ended response. In order to eliminate these restrictions in data analysis, the questionnaire through Qualtrics could have been set up differently. Instead of giving the respondents an option to fill in the open-ended response, the questionnaire would not enable the respondent to move to the next question until an answer was given. This would essentially force the participant to answer the open-ended question, but may lead to a decrease in the number of participants who fully complete the questionnaire.

4.4 FUTURE STUDIES

This study is intended to be a stepping stone towards larger studies with different goals. An extended recruitment period could enroll more genetic counselors in this study. Extending this study to cancer genetic counselors not registered with the National Society of Genetic Counselors would increase the number of participants and contribute more to the results already obtained in this study. In doing so, a more representative sample would hopefully be achieved.

Similarly, the questionnaire could be extended to oncologists, nurses, and other health professionals who work in an oncology setting. By extending this questionnaire to other individuals who work in an oncology setting, a more detailed and robust data analysis could be determined. It would be beneficial to determine how other oncology professionals handle measuring head circumference, if at all. The study could then focus on the attitudes of oncology health professionals outside of genetic counselors and compare the opinions from the different groups in a quantitative and qualitative analysis.

Another future direction based on this study would include a clinical approach by measuring head circumference on patients who present for hereditary cancer assessment. The current study would serve as Phase 1 understanding the practices currently employed by genetic counselors. The information obtained from other oncology professionals as mentioned before could also be considered in the Phase 1 study. The new study, essentially Phase 2, could initially be investigated at a select few institutions and then expanded to include several other institutions across the country. Measuring head circumference on individuals who come in for cancer risk assessment could determine the number of Cowden syndrome individuals, or families, which may be missed if head circumference was not measured. This could essentially determine the percentage of individuals that would have originally not been offered *PTEN* genetic testing, but would have if macrocephaly was noted during the assessment. Advancing even further with a Phase 3 could eventually lead to a proposition to revise the diagnostic or genetic testing criteria that the NCCN has employed.

5.0 CONCLUSION

The specific aims of this study were designed to determine whether head circumference is currently being measuring clinically in hereditary cancer assessment and to assess the attitudes of genetic counselors concerning the clinical implementation of head circumference measurement for all patients for hereditary cancer assessment. Overall, most genetic counselors are not measuring head circumference on all patients who present for cancer counseling nor those who are presenting for breast cancer assessment. However, if the measurement is taken on patients, an explanation is given. Most genetic counselors are eliciting information on Cowden syndrome in a variety of ways, but most do not feel head circumference measurement should be standard for every patient. Most feel only those patients who are suspicious for Cowden syndrome based on other clinical features should have their head circumference measured. This study gathered much insight into the practices of genetic counselors on this particular topic and may be the initial information to creating a more uniform process for measuring head circumference in hereditary cancer assessment.

APPENDIX A

ASRI IRB APPROVAL LETTER

ALLEGHENY-SINGER
RESEARCH INSTITUTE

West Penn Allegheny Health System

320 East North Avenue, Pittsburgh, PA 15212-4772
412.359.3156

Institutional Review Board 01
FWA00015120

Certification of Exemption

March 19, 2014

Emily James, MS, CGC
Department of Oncology

RE: **RC-5858** "Assessing the Practices of Genetic Counselors Regarding Head Circumference Measurement in Hereditary Cancer Assessment"

Dear Ms. James:

The ASRI-WPAHS IRB (Institutional Review Board) is in receipt of the above-referenced study.

The IRB has reviewed this information and finds it qualifies for exempt status according to the following category in the Code of Regulations: 45 CFR 46.101 (b) Category (2), and with a "*Waiver of HIPAA Authorization.*"

Please retain this letter as evidence of IRB review and determination of exempt status for this research. Annual review of this research is not required provided the research is conducted as proposed. If there are modifications or changes to this study, the Investigator must have the IRB review the study prior to initiating the changes.

If you have any questions, please contact the IRB office.

Sincerely,

Farrel Buchinsky, MD
Vice Chairman
Institutional Review Board

FB/gh

APPENDIX B

UNIVERSITY OF PITTSBURGH IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Amanda Matchette

From: Christopher Ryan, Vice Chair

Date: 4/2/2014

IRB#: PRO14010179

Subject: Assessing the practices of genetic counselors regarding head circumference measurement in hereditary cancer assessment

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section 45 CFR 46.101(b)(2)

Please note the following information:

- If any modifications are made to this project, use the "**Send Comments to IRB Staff**" process from the project workspace to request a review to ensure it continues to meet the exempt category.
- Upon completion of your project, be sure to finalize the project by submitting a "**Study Completed**" report from the project workspace.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX C

INVITATION FOR PARTICIPATION

Dear Genetic Counselor,

You are invited to participate in an anonymous online survey investigating the current practices of genetic counselors regarding head circumference measurement in hereditary cancer assessment. You were selected as a possible participant because you are registered in the NSGC Familial Cancer Risk Counseling SIG or follow the general NSGC discussion board. This survey is part of an ASRI-WPAHS and University of Pittsburgh Institutional Review Board approved research project titled,

Assessing the practices of genetic counselors regarding head circumference measurement in hereditary cancer assessment

We ask that you read the following information and contact us with any questions you have before beginning the survey.

If you agree to participate in this study, we would ask you to do the following:

- Complete the online survey about your current experience as a genetic counselor
- To connect to the survey, please click on this link: https://pitt.co1.qualtrics.com/SE/?SID=SV_4UWZ7Tbs9z5S46N

Participants will have the option to enter a draw to win a $25 Amazon gift card upon completion of the survey.

Participation in this research project is completely voluntary. We estimate that the survey will take 10-15 minutes to complete. Answers to all of the provided questions would be greatly appreciated; however, you may choose to not answer any question(s) within the survey. If you decide to participate, you have the right to withdraw at any time. It will not be possible to connect any response to any one participant. The records of this study will be kept private. In any report that we might publish, any information that will allow for identification of you as a participant will not be included. Research records will be stored securely and only researchers of this study will have access to the records. There are no identifiers and data will be stored on a password protected computer.

Contacts and Questions:
If you have any questions about the research study, please contact Amanda Matchette (asb102@pitt.edu) or Emily James (ejames@wpahs.org or 412-359-8254).

If you would like to talk to someone other than the researchers, you may want to contact the ASRI-WPAHS (412-359-3156) or University of Pittsburgh (412-383-1480) Institutional Review Boards.

Thank you for your time and consideration.

To connect to the survey, please click this link:
https://pitt.co1.qualtrics.com/SE/?SID=SV_4UWZ7Tbs9z5S46N

APPENDIX D

QUESTIONNAIRE

Demographics

1. **What is your gender?**
   Female
   Male

2. **What is your age? (select one)**
   21-30 years
   31-40 years
   41-50 years
   51-60 years
   >60 years

3. **What are your primary credentials? (multiple selections)**
   MS (genetic counselor)
   CGC (certified genetic counselor)/LGC (licensed genetic counselor)
   MD (board certified in genetics)
   MD (non-geneticist)
   Genetics Clinical Nurse
   Advanced Practice Nurse
   Other (please specify) ____________________

4. **How many years have you provided cancer risk assessment and counseling? (select one)**
   1-5

6-10
11-15
16-20
>20

5. **Have you provided cancer risk assessment and counseling in the last 6 months?**
   Yes
   No
   (If no – survey stops)

6. **Which of the following describes your primary work setting (spend >50% of your time)? (select one)**
   Clinical counseling
   Lab (commercial, non-profit, testing lab)
   Research

Cowden Testing

7. **Do you measure head circumference on every patient who presents for cancer genetic counseling?**
   Yes
   No
   (If no, skip question 8)

   Please explain how your clinic made the decision to measure or not to measure head circumference.
   (Open-ended question)

8. **If you do measure head circumference on every patient, do you explain to them why you take this measurement?**
   Yes
   No

   Please explain why you answered YES or NO.
   (Open-ended question)

9. **Do you measure the head circumference on every patient *with breast cancer* who presents for cancer genetic counseling?**

Yes
No
(If yes – skip question 10)

10. If you do not measure the head circumference on every patient, how do you determine which patients should have their head measured? (select one)
Personal history of Cowden syndrome associated cancer
Personal history of other clinical symptoms of Cowden syndrome
Family history of Cowden syndrome associated cancer
Family history of other clinical symptoms of Cowden syndrome
Appears to have macrocephaly or reports macrocephaly
Other (please specify) _____________

11. Do you elicit information on other clinical symptoms of Cowden syndrome with every patient who presents for cancer genetic counseling?
Yes
No
(If no – skip question 12)

12. How do you elicit information on other clinical symptoms of Cowden syndrome? (select one)
General Review of systems
Directed questions about Cowden findings in review of systems
Medical records from previous centers/institutions

13. In your professional opinion, should head circumference be measured in every patient who presents for cancer genetic counseling?
Yes
No

Please explain why you answered YES or NO.
(Open-ended question)

14. In your professional opinion, how many cases of Cowden syndrome are undiagnosed due to head circumference not being measured?
<1%
1-2%
2-5%
>5%

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