5-2010

Attitudes of Parents at risk of inheriting Li-Fraumeni Syndrome towards predictive genetic testing in their minor-aged children.

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A THESIS

Presented to the Faculty of

The University of Texas

Health Science Center at Houston

and

The University of Texas

M.D. Anderson Cancer Center

Graduate School of Biomedical Sciences

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

By

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Houston, TX

May 2010

ACKNOWLEDGEMENTS

Dr. Louise Strong, my advisor for her continued support, guidance and inspiration. I began my experience at the Texas Medical Center with you three years ago, and feel honored that I have been able to learn from you each step of the way. This thesis would not have been possible without you.

Dr. Susan Peterson, for providing her expertise and extensive experience in this subject matter. Your input has been invaluable. Dr. Christopher Amos for introducing me to the world of statistics.

Kate Wilson and Michelle Jackson for their sense of humor and excitement about this project. Thank you for letting me know that I was never alone in this process.

The Department of Cancer Genetics at MDACC. I wish each one of you could have been on my committee. You have guided me through so many steps and given me unbelievable support when I needed it most. I could not have gotten through IRB without you!

The University of Texas Genetic Counseling Program faculty and staff. Each one of you made the program my "home away from home". You have provided enormous support, patience and encouragement throughout my training these past two years. The education I have received and experiences you have given me are irreplaceable, as are each one of you.

To my classmates. Never have I met a more the special set of people who understand my love of and excitement about genetics as much as the five

of you. I cannot imagine having gone through the past 2 years with anyone else. I truly love you and will miss you immensely.

To my parents, Ron and Cindy Newman, and my sister and brother in law, Bailey Newman-Lanier and Adam Lanier. Your love and support has gotten me through so many hard times in my life. Thank you for always believing in me and my abilities. And thank you for putting up with me when I was in crazy thesis mode.

To the brave families with Li-Fraumeni Syndrome who participated in the study. Without your thoughtful responses, none of this would have been possible.

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Publication No. _____

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Li-Fraumeni Syndrome (LFS) is a hereditary cancer syndrome which predisposes individuals to cancer beginning in childhood. These risks are spread across a lifetime, from early childhood to adulthood. Mutations in the p53 tumor suppressor gene are known to cause the majority of cases of LFS. The risk for early onset cancer in individuals with Li-Fraumeni Syndrome is high. Studies have shown that individuals with LFS have a 90% lifetime cancer risk. Children under 18 have up to a 15% chance of cancer development. Effectiveness of cancer screening and management in individuals with Li-Fraumeni Syndrome is unclear. Screening for LFS-associated cancers has not been shown to reduce mortality. Due to the lack of effective screening techniques for childhood cancers, institutions vary with regard to their policies on testing children for LFS. There are currently no national guidelines regarding predictive testing of children who are at risk of inheriting LFS. No studies have looked at parental attitudes towards predictive p53 genetic testing in their children. This was a cross-sectional pilot study aimed at describing these attitudes. We identified individuals whose children were at risk for inheriting p53 genetic mutations. These individuals were provided with surveys which included validated measures addressing attitudes and beliefs towards genetic testing. The questionnaire included qualitative and quantitative measures. Six

individuals completed and returned the questionnaire with a response rate of 28.57%. In general, respondents agreed that parents should have the opportunity to obtain p53 genetic testing for their child. Parents vary in regard to their attitudes towards who should be involved in the decision making process and at what time and under what considerations testing should occur. Testing motivations cited most important by respondents included family history, planning for the future and health management. Concern for insurance genetic discrimination was cited as the most important "con" to genetic testing. Although limited by a poor response rate, this study can give health care practitioners insight into testing attitudes and beliefs of families considering pediatric genetic testing.

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Background

Li-Fraumeni Syndrome (LFS) is a hereditary cancer predisposition syndrome which predisposes individuals to a large range of cancers beginning in childhood. Individuals with LFS have up to a ninety percent lifetime risk of developing cancer. Originally discovered through bedside clinical observations and epidemiological studies, LFS has an estimated birth prevalence of 1 in 5,000 (Lalloo, Varley, Ellis, O'Dair & Pharoah, 2003).

In the general population, cancer was the second leading cause of death in 2006, preceded by heart disease (American Cancer Society, ACS, 2009). Men have a one in two lifetime cancer risk, while a woman's lifetime risk is one in three (ACS, 2009). These risks increase exponentially with age. Most cancers occur sporadically throughout a person's life-time, however, five to ten percent of cancers can be attributed to a hereditary cause (Schneider, 2002).

Greater than 200 hereditary cancer predisposition syndromes have been identified (Schneider, 2002). As a group, hereditary cancer syndromes confer an increased risk to individuals of developing certain cancer types in their lifetime, often at younger ages than the general population. Individuals with hereditary cancer syndromes often have a significant family history of cancer with multiple generations and individuals affected with cancer. Sometimes these individuals will have a personal or family history of a rare cancer type such as male breast cancer, ovarian cancer or adrenocortical carcinoma. It is crucial to recognize these syndromes in an individual as there are established guidelines in regard to management, prevention and treatment

for most hereditary cancer syndromes. Once an individual has been identified to have a hereditary cancer syndrome, it is important to notify other at risk relatives and facilitate testing. It is often helpful for these individuals to meet with a professional such as a physician or a genetic counselor to facilitate education and testing (Schneider, 2002).

Established guidelines have been created regarding testing individuals for several hereditary cancer syndromes. The main theme in these guidelines is a risk/benefit analysis. In general, if the benefit of testing will not manifest until adulthood, genetic testing is postponed until the age of 18 (American College of Medical Genetics (ACMG) & American Society of Human Genetics (ASHG), 1995). Hereditary cancer syndromes, such as Li-Fraumeni syndrome, that confer a cancer risk in childhood but have no established management, are more controversial. Testing for cancer syndromes such as LFS is often at the discretion of the physician facilitating the testing since there is currently a lack of guidelines regarding when to test an individual for these conditions. It is also unclear what kind of management should be implemented in hereditary cancer syndromes like LFS. The American Society of Clinical Oncology (ASCO) recommends that physicians and parents participate together in the decision making process (ASCO, 2003). Few studies have examined the interest parents have regarding having their minor-aged child tested for a hereditary cancer syndrome in which management in childhood is limited (Patenaude, Basili, Fairclough & Li, 1996). In 1969, Li and Fraumeni reported four families who appeared to have autosomally dominant inherited cancers, including childhood cancers, soft

tissue sarcomas and breast cancer. This collection of cancers was termed Li-Fraumeni Syndrome, after the investigators who initially described it. In 1988, Li and Fraumeni searched the Cancer Family Registry of the National Cancer Institute. They discovered twenty four individual families who had a similar pattern of cancers. From this study, it became apparent that individuals with Li-Fraumeni Syndrome had increased risks for brain tumors, leukemia, breast cancer and adrenal cortical tumors. The researchers noted that these cancers typically occurred before the age of 50 (Li et al., 1996).

Meanwhile, in 1978, Lynch observed several families with apparent hereditary segregation of cancer which was consistent with Li-Fraumeni Syndrome. He too noted that these families had a predominance of sarcoma, breast cancer, leukemia and adrenal cortical tumors. Lynch referred to the collection of these specific cancers in one family as SBLA syndrome (sarcoma, breast/brain, leukemia/laryngeal/lung cancer and adrenal cortical carcinoma). A genetic segregation pattern was established for this hereditary pattern of cancers which was compatible with autosomal dominant inheritance. The study concluded that the reported kindred had a rare, deleterious autosomal dominant aggregation of cancers (Lynch, Mulcahy, Harris, Guirgis & Lynch, 1978). This mode of inheritance was then confirmed by segregation analysis of 159 childhood soft tissue sarcoma patients in 1992 (Lustbader, Williams, Bondy, Strom & Strong, 1969).

The gene responsible for Li-Fraumeni Syndrome was discovered in 1990 (Malkin et al., 1990). Linkage analysis was not possible due to the rarity of Li-Fraumeni Syndrome and its deleterious nature. Therefore, a candidate

gene approach was taken. Investigators were interested in p53 because of the gene's known involvement in the tumorigenesis of many sporadic cancers (it is estimated that p53 is mutated in fifty percent of all sporadic tumors) (Levine, 1997). In 1990, five families with LFS were analyzed. All of these kindreds were found to have p53 mutations (Malkin et al., 1990). Soon, another family which fit clinical criteria for LFS was tested. Several members in this family tested positive for a mutation in p53 (Srivastave, Zou, Pirollo, Blattner & Chang, 1990).

P53 is a tumor suppressor gene that is commonly mutated in sporadic cancers. Termed "the guardian of the genome", p53 is key in cell cycle regulation (Lane, 1992). It has several functions including activation of DNA repair, arresting the cell cycle and initiating apoptosis (Lane, 1992). This explains why individuals with a germ line p53 mutation have a significantly increased cancer risk. Tumor formation in individuals with p53 mutations is most often consistent with Knudson's "two-hit" hypothesis, in which cancer develops in individuals that inherit the "first hit" or mutation and cancer occurs in cells that acquire a "second hit" or mutation (Levine, 1996)(Knudson, 1971). Therefore, it is important for individuals with a germ line p53 mutation to avoid oncogenic environmental factors such as radiation.

Initially, it was thought that germ line mutations in another gene, CHEK2, could account for other cases of LFS. Lee et al. (2001) and Varley (2003) reported on several families with germ line CHEK2 mutations who satisfied the LFS clinical criteria (Lee et al., 2001) (Varley,2003). Currently, CHEK2 mutations are generally not considered a part of Li-Fraumeni

Syndrome. Rather, they are thought to be low penetrant tumor suppressor genes involved in breast cancer (Vahteristo et al., 2002).

Li-Fraumeni Syndrome is an autosomal dominant and highly penetrant hereditary cancer syndrome. Greater than seventy percent of individuals with Li-Fraumeni Syndrome have a p53 germ line mutation (Chompret, 2000). Mutations in the p53 tumor suppressor gene are known to cause the majority of cases of LFS (Malkin, 1994). Commercial molecular testing consists of direct sequencing of the p53 coding region, the first non-coding exon , promoter, all splice site junctions, and the 3'-untranslated region, rearrangement and large duplication/deletion testing (Varley, 2003).

Unlike other cancer susceptibility syndromes, which may predispose individuals to site-specific tumors, LFS increases an individual's risk of developing a variety of tumor types (Hartley, Birch, Kelsey, Marsden, Harris and Teare, 1989) (Varley, 2003). The malignancies which dominate this condition include soft tissue sarcoma, osteosarcoma, brain tumors, adrenal cortical carcinoma and premenopausal breast cancer. Additional data suggests that Li-Fraumeni Syndrome may also be associated with other diverse neoplasms including pancreatic cancer, leukemia, Wilms' tumor and neuroblastoma(Li et al., 1988) (Birch et al., 2001) (Nichols, Malkin, Garber, Fraumeni and Li, 2001). Other cancers have been seen in individuals with Li-Fraumeni Syndrome including renal, gonadal germ cell, melanoma, colon, ovarian and lung cancer (Nichols et al., 2001) (Bougeard et al., 2008). Individuals with LFS are clearly predisposed to tumor formation in a large range of tissues and tissue types.

LFS increases an individual's risk of developing multiple primary tumors. These risks are spread across a lifetime, from early childhood to adulthood, and the risk for early onset cancer in individuals with Li-Fraumeni Syndrome is high. In 2000, Chompret et al. found that individuals with Li-Fraumeni Syndrome have a 15% chance of developing cancer from ages 0 to 15 and a 54% chance of developing cancer between ages 16 to 45 years. Overall, the individuals in this study had up to a 68% lifetime risk of developing cancer (Chompret et al., 2000). Bihan et al. (1995) studied five individuals with p53 mutations and estimated age specific cancer risks. They found that the risk for cancer was 42% in individuals aged 0 to 16, 38% in individuals aged 17 to 45, and above 63% for individuals aged 45 and older. Using segregation analysis, Lustbader et al. (1992) found that individuals with Li-Fraumeni Syndrome had up to a 50% risk of cancer development by age forty, and a 90% lifetime cancer risk (by age 60). By age thirty, nearly 50% of individuals with LFS will develop cancer, in comparison to only one percent of the general population (Malkin et al., 1990). By age seventy, over ninety percent of individuals with a germ line p53 mutation will develop a malignancy (Malkin et al., 1990).

Cancer screening and management in individuals with Li-Fraumeni Syndrome is not well defined. Screening for LFS-associated cancers, however, has not been shown to reduce mortality (Varley, Evans & Birch, 1997). No proven beneficial methods for childhood cancers currently exist. Methods that may be used to detect childhood cancers include blood cell counts and radiographic studies, the predictive power of these tests is not

known. Magnetic resonance imaging (MRI) may be used to scan for cancerous lesions. MRI is desirable because it can detect small lesions without delivering radiation the body. This is important because individuals with LFS are especially sensitive to radiation, which can potentiate tumor development. Unfortunately, MRI is a costly procedure and may not be available to all affected individuals (Varley et al., 1997).

Screening recommendations regarding LFS have been published (National Comprehensive Cancer Network, NCCN, 2010) Screening for children includes annual and thorough physicals,. Based on family history, other forms of organ-targeted surveillance should be implemented. It is important to keep in mind, however, that these screening methods have not been proven to be effective. Screening for adults with LFS includes annual physicals, dermatology evaluations. Women with LFS should have a clinical breast exam biannually beginning at 20-25. They should rotate screening methods between mammograms and breast MRI. All individuals with Li-Fraumeni Syndrome should consider colorectal cancer screening beginning at age 20-25, with subsequent colonoscopies every two to five years. Again, organ targeted surveillance should be practiced based on family history of specific tumors (Varley, 1997) (Evans et al.,1997) (NCCN, 2010).

The use of MRI and PET (position emission tomography) scans in screening for LFS-related tumors is controversial. Clinicians are inconsistent in their attitudes towards the use of this technology in monitoring individuals for cancer. Proponents of the method believe that it will detect lesions that are otherwise undetectable. Others argue that it will subject the patient to many

unnecessary biopsies and procedures (Wertz, Fanos & Reilly, 1994) (Varley et al., 1997) (Goyen & Debatin, 2006).

Management and screening in individuals with LFS is a complicated process since LFS is associated with a wide variety of tumors in several organ systems. Several of the LFS associated cancers are difficult to detect until late stages of its growth, and the later a cancer is detected, the poorer the prognosis. Most importantly, individuals with LFS must be alert to changes in their health and seek medical attention if they experience any symptoms (Wertz, et al., 1994) (Varley, 2003) (Evans et al., 1997).

Due to the lack of appropriate screening techniques for childhood cancers, institutions vary with regard to their policies on testing children for Li-Fraumeni Syndrome. An international consortium of physicians and researchers met in 1992 to develop a consensus towards management of and testing individuals for LFS, and this meeting concluded that genetic testing should not be offered to minors who are at risk of inheriting LFS. There has been no follow-up in the last seventeen years to these recommendations (Li et al., 1992)

Before the molecular cause of Li-Fraumeni Syndrome was discovered, diagnosis was made on the basis of clinical criteria. Three criteria guidelines exist for the diagnosis of Li-Fraumeni Syndrome.

A person who is diagnosed with LFS based on the classic or original criteria must meet all three of the following:

1. A proband with a sarcoma diagnosed before the age of 45

2. A first degree relative with any cancer under the age of 45
3. A first or second degree relative with any cancer under the age of 45 or a sarcoma at any age (Li & Fraumeni, 1969)

Following the creation of these criteria, a new set of guidelines was set forth by Chompret et al. to diagnose individuals with LFS. These criteria are less dependent on family history of cancer and focused more on an individual's personal history. An individual who has a clinical diagnosis of LFS based on the Chompret criteria must meet one of the following:

1. A proband with a tumor belonging to the LFS spectrum (soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer. Adrenal cortical carcinoma, leukemia, lung, bronchoalveolar cancer) prior to the age of 46 years AND at least one first or second degree relative with a LFS tumor (excluding breast cancer if the proband has breast cancer)
2. A proband with multiple tumors (except multiple breast tumors). Two of which belong to the LFS tumor spectrum and the first tumor occurred before age 46
3. A proband with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history (Chompret, 2002)

Currently, Li-Fraumeni Syndrome is diagnosed in two ways: clinically and molecularly. While historically individuals with Li-Fraumeni syndrome were only given a clinical diagnosis, we now have the possibility to perform genetic testing on individuals for molecular confirmation.

Additionally, individuals who are at risk of inheriting LFS can have predictive genetic testing based on the identified p53 mutation in the family.

Molecular testing of the p53 gene is now routinely performed to facilitate the diagnostic process of LFS. Seventy percent of individuals who fit the clinical description of LFS will have a mutation in the p53 gene, and sequencing of the entire gene will detect ninety-five percent of p53 mutations in these individuals (Birch et al., 1994) (Varley, 2003)(Bougeard et al., 2008). The remaining five percent will have a deletion, rearrangement, or unidentified mutation in the p53 gene (Nichols et al., 2001). Between 7 to 20% of p53 mutations are believed to be *de novo* events (Gonzalez et al., 2009).

With new technology come new questions. Issues among debate in the genetics community involve who should be tested for LFS and at what age should testing occur (Li et al.,1992). When these questions are considered, several things must be taken into account. What benefit would genetic testing results have on the patient? At what age do cancer risks begin, and are there affective approaches to manage these risks? These questions are not specific to Li-Fraumeni syndrome and can be applied to all cancer syndromes in general. Several agencies have set forth recommendations and guidelines to help health professionals answer these difficult questions.

The American Society of Clinical Oncology (ASCO) published recommendations regarding testing children for cancer susceptibility in general. ASCO recommends that one should consider several variables when deciding to offer testing to a potentially affected child. First, the child must

be at risk for a pediatric cancer. Also, the test under consideration should be adequately interpretable, and the test results and implications should be clear to the ordering clinician. Test results should be used for diagnosis, or influence the medical management of the child, and evidence based risk reduction strategies should be available (ASCO, 2003). Conditions such as Multiple Endocrine Neoplasia (MEN) and Familial Adenomatous Polyposis (FAP) have appropriate childhood interventions for their associated cancers (Brandi et al., 2001) (Rozen and Macrael, 2006). Because of this, testing in children at risk for these conditions is appropriate. Testing for the adult onset cancer susceptibility syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (HNPCC) is typically not recommended in minors since the benefit that individuals could derive from these tests would not accrue until adulthood. ASCO enforces the belief that the parents or guardian of the child should have the authority to decide whether or not to test (ASCO, 2003).

The American Society of Human Genetics (ASHG) and the American College of Medical Genetics (ACMG) published literature regarding ethical, legal and psychosocial implications surrounding genetic testing in minors (1995). In addition to emphasizing the necessity for a timely medical benefit to the child, these guidelines focus on the need for genetic testing to contribute to the global well-being of the child. Individuals undergoing genetic testing may experience anxiety, altered self- image, and uncertainty. ASHG and ACMG suggest that if the psychological or medical benefits of testing won't occur in childhood, testing should be postponed until

the child is old enough to make an autonomous competent decision. If the balance of benefits and harms related to pediatric genetic testing is unclear, ASHG and ACMG recommend that the provider respect the wishes and decisions of the family, after adequate counseling. In the event that testing is clearly harmful in the child, providers are encouraged to advocate for the best interest of that child (ACMG/ASHG, 1995).

Upon reviewing national agency guidelines regarding predictive testing in minors, one frequently encounters the concept of "best interest". For a genetic test to be justified, it must be in the best interest of the child, both medically and psychologically. One key tenet in all genetic testing is informed consent. Testing minors can be especially sensitive because a minor's informed consent cannot be given. Instead, it is up to the parent or legal guardian to make medical decisions for the child. It is expected that parents know their children better than health care providers and are therefore in the unique position to determine what is in the best interest of their child (Wertz et al., 1994).

As children mature, they are often included in the health care decision making process. The older a child gets, the more likely they are to grasp the intellectual concepts that are key in making these decisions. They are also likely to have increased psychosocial skills as they get older. It is generally accepted that "as soon as children are able to communicate and participate in decisions that affect them, they should be encouraged to participate in all aspects of the decision making process" (Borry, 2009). It is therefore important to involve children as well as their guardians in

counseling and information giving sessions. It would be reasonable for parents to defer genetic testing until their child is old enough to have active participation in the decision.

Multiple issues arise when considering genetic testing in minors. Test results may impact several areas of an individual's life including decision making, reproductive decisions, education, occupation, insurance coverage and overall lifestyle. Genetic test results may impact family dynamic or impose guilt or anxiety on family members (ACMG/ASHG, 1995). Testing in minors denies the rights of these individuals to make an autonomous decision to be tested when they reach adulthood. Individuals lose confidentiality of results from family members when they are tested as minors (Andrews et al., 2006).

Wertz et al. (1994) set forth several reasons against testing pre-symptomatic children for genetic conditions. They claim that children with a positive test may be made a scapegoat of their test results, and the test results could cause adverse effects to that child's self esteem. For example, the test results could cause the child to feel unworthy and the parents to lower their expectations for the child. The authors also speculate that test results could disrupt family functioning, causing disharmony in parent-child and sibling relationships. Finally, the authors are concerned that test results could evoke feelings of guilt (Wert et al., 1994).

Many individuals from a wide range of specialties have voiced their opinions regarding predictive testing in asymptomatic minors. Clarke et al. (1995) have concerns that test results may result in parents feeling

disappointment or rejecting the child. Several individuals have expressed concern that knowing a child had a cancer predisposition syndrome would raise anxiety in both parents and the child (Clarke, 1994) (American Medical Association, AMA ,1995) (Duncan et al., 2001). Other studies, however, have shown that parents are interested in having genetic testing in their children so they can plan for their child's future (Wertz, et al., 1994).

Several studies have looked at many aspects of predictive testing in children. Yet none have examined feelings that parents with Li-Fraumeni Syndrome may have towards genetic testing in their children. Patenaude et al. (1996) interviewed 47 mothers of children who were diagnosed with cancer. Given a scenario of a hypothetical test that could detect cancer susceptibility, 13% of participants reported they would decline having their child tested due to a lack of family history or preventative measures. Mothers were concerned about the anxiety they might encounter from learning that a healthy child carried a cancer susceptibility mutation. Thirty six percent of participants would agree to have their child tested only if knowledge of the results would reduce the risk of cancer development. Fifty-one percent of mothers would wish to have their child tested for the cancer susceptibility gene, despite the lack of potential benefit. Mothers reported that they would feel significantly less depressed or anxious if their child did not have a cancer susceptibility gene. Alternatively, they did report that they would experience depression and anxiety if a healthy child tested positive for a cancer susceptibility syndrome. Eight percent of mothers said they would not test their healthy children. Mothers had several reasons for this, including

their wish to defer the decision to test for their child and fear of insurance and social discrimination (Patenaude et al., 1996).

The researchers then looked at factors that are important mothers' decision to pursue genetic testing in their children. Mothers appeared to be consistent regarding what they valued in a genetic test. The most common aspects of a genetic test that mothers considered include utility of results and their ability to manage health and test reliability. Mothers were also concerned about privacy, insurance discrimination and family disruption. (Patenaude et al., 1996). These themes appear to be similar to other hereditary cancer syndromes.

Few reports have been published concerning clinicians' experience with testing minors for LFS. Evans, Lunt, Clancy and Eeeles (2009) depicted their experience with testing four children in two LFS families. They reported on two families, "Family 1" and "Family 2". Three children were tested in family 1, one set of siblings and the siblings' cousin. The siblings both tested negative for the pathogenic mutation that had been identified in the family. These siblings' parents reported feelings of relief upon hearing the test results. The father of the siblings' cousins was very anxious about that chance that his child could have a pathogenic mutation, especially after several recent deaths and cancer diagnoses in the family. Unfortunately, this child did have a pathogenic mutation. Following the test result, the child's father did report a decline in anxiety despite these results. This child was gradually introduced to Li-Fraumeni syndrome and is now an adult considering preimplantation genetic diagnosis (Evans, et al., 2009).

In "Family 2", the patient was a nine year old girl who had an extensive family history of LFS, including a brother who was diagnosed with a cerebral primitive neuroectodermal tumor at ten and died shortly after. A p53 mutation had been identified in the patient's mother after she had developed three primary tumors. The patient's mother was very anxious regarding her healthy child's genetic status and reported that knowledge of this would help her manage her daughter's health. After several counseling sessions, the patient underwent genetic testing and was negative. The family reported being content with the counseling process. No follow up studies have looked at the children's attitudes towards having been tested at a young age. The authors of this article emphasize the point that until there are proven medical and psychological benefit to the child, genetic testing decisions for LFS should be made carefully on a case by case basis (Evans et al., 2009).

No studies have examined the emotional impact genetic testing for LFS has on children. Familial Adenomatous Polyposis (FAP) is a cancer predisposition syndrome that, like LFS, confers a childhood cancer risk. Unlike LFS, there are proven beneficial screening modalities in minors with FAP. Children with FAP should begin colonoscopy and sigmoidoscopy at ages 10 to 11 to evaluate for polyposis (Rozen & Macrae, 2006). In 2001, Michie et al. studied the emotional impact genetic testing for FAP has on minors. The investigators studied 60 asymptomatic children at risk for FAP who had undergone genetic testing. They looked at factors such as anxiety and depression. Children who received positive results had a normal range of anxiety and depression, although they tended to be more anxious and

depressed than children who received negative results. The study also explored the difference in anxiety and depression between children and adults receiving genetic test results. The group did not find a significant difference in either variable between the two groups (Michie, Bobrow& Marteau, 2001). In this study, children did not appear to have exaggerated adverse emotional impact.

Hereditary Breast and Ovarian Cancer Syndrome (HBOC) is a hereditary cancer predisposition syndrome which predisposes individuals to breast and ovarian cancer (often premenopausal). HBOC does not confer a risk of childhood cancer. Genetic testing is therefore not recommended until adulthood. In 2008, Bradbury et al. surveyed a cohort of parents and offspring with HBOC about their attitudes towards testing minors. Fifty two percent of participants reported that they were opposed to testing minors for HBOC, some participants felt that genetic testing was only appropriate in minors in special scenarios. Individuals who were in favor of testing cited implementation of health management guidelines specific to patients with HBOC. Although HBOC is clearly very different than LFS, it is interesting to see that 48% of these participants are in favor of testing minors, even though HBOC does not confer a childhood risk of cancer (Bradbury et al., 2008).

Li-Fraumeni Syndrome clearly meets the testing criteria of conferring a cancer risk in childhood. However, there are no proven benefits to implementing screening for cancer in children with Li-Fraumeni Syndrome. Due to this discrepancy, testing in children is controversial and not standard of care. Currently, in LFS, there are no data looking at parental

attitudes towards predictive testing in children. Recently, there has been a movement of practitioners testing children for p53 mutations. If the trend in testing minors for p53 mutation continues, it is important to describe parental attitudes and beliefs towards predictive testing in their children.

MATERIALS AND METHODS

This was a cross-sectional pilot study aimed at describing the attitudes of parents of children at risk of inheriting a p53 mutation toward genetic testing in their children. This study was approved by MD Anderson Cancer Center's Institutional Review Board (BS99-038) and the Committee for the Protection of the Human Subjects at the University of Texas Health Science Center (HSC-GEN-09-0415).

Study Population Identification and Recruitment

Individuals who had previously participated in LFS genetics research at the University of Texas MD Anderson Cancer Center (MDACC) were recruited for the study. The recruitment source was a research database that included data from families with Li-Fraumeni Syndrome and was maintained by the Department of Genetics at MDACC. The database includes 73 kindreds, and we identified 371 living individuals who were at 25% or greater risk of carrying a p53 germ line mutation or who were known p53 mutation carriers. Individuals were eligible for the study if they were: 1) a parent of a child younger than 27 years of age who was at risk of inheriting Li-Fraumeni Syndrome or previously diagnosed with a LFS-associated cancer, 2) 18 years of age or older, and, 3) able to speak, read, and write English.

Fifty six individuals were identified as being eligible for the study. Valid mailing addresses were available for 20 of the eligible individuals. We also identified an additional 25 deceased individuals from the database who were confirmed or presumed p53 mutation carriers, whose children met the above eligibility criteria, and who had a surviving co-parent. Of these 25 individuals, 5 mailing addresses were available for surviving co-parents.

Data Collection

Study packets were mailed to 25 eligible individuals and included a cover letter, a consent form, a study questionnaire, and a postage-paid return envelope. The cover letter included a description of the study and an invitation to participate, as well as instructions for completing and returning the questionnaire. In the event that the individual in our LFS database was deceased, the co-parent was instructed to complete the survey. Co-parents were given the same survey packet as LFS-affected parents. Co-parents were defined as a surviving spouse of an individual with LFS who is deceased. Parents were instructed to complete the written informed consent prior to completing the study questionnaire, and to return both the consent form and the completed questionnaire in the return envelope.

The study was conducted from December 2009 to March 2010. Study packets were mailed in mid-December 2009, and follow-up packets were mailed to non-respondents at 3 and 6 weeks after the initial mailing. At 4 weeks post-initial mailing, we attempted to contact non-responders by telephone to follow up and invite them to complete the questionnaire by phone, if they preferred. Three study packets were returned without a forwarding mailing address, and one study packet was returned because the intended recipient had passed away. Thus, our denominator of eligible individuals was reduced to 21.

Measures

The selection of study measures was based on several key domains in pediatric genetic testing, including attitudes towards p53 genetic testing, communication about

testing, stage of change (or readiness) regarding genetic testing, and decisional balance (consideration of pros vs. cons). Measures regarding parental communication about genetic testing as well as attitudes and beliefs related to testing were adapted from existing instruments used in other studies (Andrews et al., 2006)(Peshkin et al., 2008)(Peterson et al., 2008)(Terycak et al., 2001). Additional measures were created specifically for this study based on domains in the pediatric genetic testing literature.

The survey was organized into three sections and encompassed the following six domains: 1) general attitudes, 2) communication, 3) stage of change, 4) decisional balance for parents who have sought testing, 5) decisional balance for parents who have not sought testing, and 6) demographics. We estimated that the study questionnaire took about 30 minutes to complete. No compensation was provided for study participation.

Attitudes toward genetic testing in children

We included three measures regarding attitudes and interest in genetic testing in children. We used the Pediatric Testing Attitudes Scale (P-TAS), an 11-item validated measure developed by Peshkin and colleagues (2008). P-TAS was created to determine the interest of parents with BRCA1/2 mutations towards genetic testing in their children. The P-TAS measures two factors along this dimension: Attitudes and Beliefs (factor 1) and Decision Making and Communication (factor 2). The P-TAS includes 11 statements describing attitudes toward testing children for a BRCA1/2 mutation, and respondents are instructed to rate each item on a scale of 1 to 5 (1=strongly against genetic testing in minors to 5=strongly in favor of it). Participants were also given the option of "unsure" (6). Score are obtained by summing the individual items. "Unsure" responses were not counted in the total P-TAS score. For the present study, we revised the statements to

reflect attitudes towards p53 genetic testing. Higher P-TAS scores were indicative of individuals who were in favor of genetic testing in minors, while lower scores were indicative of individuals who opposed genetic testing in minors. Our second measure was a seven item questionnaire developed specifically for this study. We developed seven scenarios when p53 genetic testing may be considered in minors. The participants were instructed to determine whether in each scenario, they would pursue genetic testing in their child. Participants were given the options of "yes", "no" and "unsure". Finally, we included a single item measure aimed at determining at what age the participant thinks testing should be considered in minors. This item was initially used in a similar study looking at parental attitudes towards testing minors for familial adenomatous polyposis (FAP) (Andrews et al., 2006).

Communication with children regarding p53 genetic testing

We included a measure adapted from Tercyak et al. (2001) to characterize how parents communicated with each child regarding Li-Fraumeni Syndrome and p53 genetic testing. This measure was originally developed to evaluate communication between mothers with BRCA1/2 mutations and their children about genetics and testing. The measure included four topics regarding communication with children about genetic testing. Individuals were asked how frequently they discussed these four topics with their child and how comfortable they felt about it. Items were scored on a scale of 1 to 4 (1= not at all, 4= often) (1= not at all, 4 = very). Lower scores indicated less communication with children about genetic testing, and higher scores indicated greater communication. Two scores were given: 1) communication with child and 2) comfort with communication with child.

Trans-Theoretical Model

The Trans-Theoretical Model (TTM) is a psychological and health behavior tool that measures and individual's readiness to implement a behavior (Prochaska & DiClemente, 1983) (Prochaska, DiClemente & Norcross, 1992)(Prochaska & Velicer, 1997). This model, which focuses on the decision making of an individual, consists of five "core constructs": 1) stage of change, 2) process of change, 3) decisional balance, 4) self- efficacy, 5) temptation (Prochaska & Velicer, 1997). In this study, we utilized "stage of change" and "decisional balance" measures to explain attitudes respondents had towards predictive p53 genetic testing in minors. A consistent pattern has been observed between the relationship of decisional balance and stage of change (Prochaska & Velicer, 1997).

Stage of Change

Stage of change is one of five "core constructs" of the Trans-Theoretical Model (TTM) (Prochaska, Velicer, 1997). It consists of five discrete levels of behavior change or adoption: 1)pre-contemplation 2)contemplation 3)preparation 4) action 5)maintenance. We ascertained the steps each parent had taken towards seeking genetic testing for their child. Scores were based on a 1 to 5 scale. Individuals were given the option of "I have no interest in this", "I haven't thought about it", "I have thought about it", "I am committed to it", and "I have already done it". Low scores were indicative of individuals who have taken no or few steps towards obtaining genetic testing in their child while high scores correlated with individuals who have been active in seeking genetic testing for their children.

Decisional Balance

The decisional balance measure is one of five "core constructs" of the TTM (Prochaska, Velicer, 1997). The items were aimed at determining decisional balance (pros and cons) regarding desire to obtain genetic testing in their children. Items were adapted from past studies (Vernon et al., 1999)(Peterson et al., 2008) looking at genetic testing attitudes. These items were initially created based on patient and health care professional experience (Vernon et al., 1999). Individuals who have and have not had their children tested for p53 mutations were asked to rank the important four "pros" and "cons" in their decision to pursue/decline predictive p53 genetic testing in their children. Answers were based on a 1 to 5 point Likert scale (1= not important, 5= very important). We aimed to determine how each participant prioritized the positive and negative components of predictive p53 genetic testing in minors.

Demographics and Family History

We assessed participants' demographic characteristics including gender, marital status, education, occupational status and household income. Additional demographic and family history information such as age, race, ethnicity and family history of LFS-related cancer and death was obtained through existing information in the MDACC database.

Data Analysis

Data were entered into an excel spreadsheet. Descriptive statistics were run on the data. We first analyzed each individual participant's responses. The participants were then analyzed as a group. Next, we divided the participants in two groups: those who

have tested their children and those who have not tested their children. As our sample size is small (n=6), we did not feel it was appropriate to perform statistical tests of association or other analyses.

RESULTS

Demographics

Of the 21 potentially reachable participants, 6 returned the survey, with a response rate of 6/21 (28.57%). Two of the participants were co-parents, while the other 4 belonged to our original Li-Fraumeni Syndrome cohort. Three participants (50%) were male and three (50%) female. Four individuals were married (66.67%), while the other two were widowed. Education level of the participants varied with one completing some high school, two completed some college, two were college graduates and one had an upper level degree. Most individuals held either full or part time employment, while one participant was unemployed and seeking a job. Of note, one participant was disabled from a diagnosis of terminal cancer Annual household income ranged from $25,000-$50,000 per year (50%), to >$75,000 per year. Table 1 summarizes participants' demographic profiles.

Table 1b describes characteristics of each respondent and/or co-parent. Three respondents were co-parents of individuals with p53 mutations who have passed away. Of the remaining 3 participants, 2 had a p53 mutation, while 1 did not. Ages of the respondents/ co-parents ranged from 35-52 years.

Data from 6 families with 12 children were available for study. Five of the individuals who completed the survey had children (Table 2). The sixth participant did not have children. On average, the families had 2.4 children, with ages ranging from 15 to 22 years. Three children from 2 families were deceased at ages 6, 9 and 23. All of these children were reported to have died from cancer. Of the offspring reported in the survey responses, 8 (66.67%) were female, and 4 (33.33%) male.

Table 1. Demographic Characteristics of Participants					
	Number	**%**		**Number**	**%**
Total Participants (N)	6		**Occupation**		
			Employed (full time)	2	33.33%
Gender			Employed (part time)	2	33.33%
Male	3	50%	Unemployed (seeking job)	1	16.67%
Female	3	50%	Disabled	1	16.67%
Marital Status			**Annual Household Income**		
Married	4	66.67%	$25,000 – $50,000	3	50%
Widowed	2	33.33%	$50,000 - $75,000	1	16.67%
			>$75,000	2	33.33%
Education					
Some high school	1	16.67%			
Some college	2	33.33%			
College graduate	2	33.33%			
Upper level degree	1	16.67%			

Table 1b. Respondent characteristics					
Family	Vital	Age/Age of Death	Gender	Genotype	Respondent
1	Living	50	Male	Mutation	Self
2	Living	50	Female	Wild type	Self
3	Deceased	37	Male	Mutation	Co-parent
4	Deceased	43	Female	Mutation	Co-parent
5	Deceased	35	Female	Mutation	Co-parent
6	Living	52	Female	Mutation	Self

Table 2. Child information					
Family	**Child**	**Vital**	**Age**	**Cause of death**	**Gender**
1	1	Deceased	9	Unspecified cancer	Female
	2	Deceased	23	Unspecified cancer	Female
2	1	Alive	22	NA	Female
	2	Alive	21	NA	Female
	3	Alive	20	NA	Female
3	1	Alive	20	NA	Male
	2	Alive	18	NA	Male
4	1	Alive	20	NA	Male
	2	Alive	16	NA	Female
	3	Alive	15	NA	Female
5	1	Alive	16	NA	Female
	2	Deceased	6	Unspecified cancer	Male

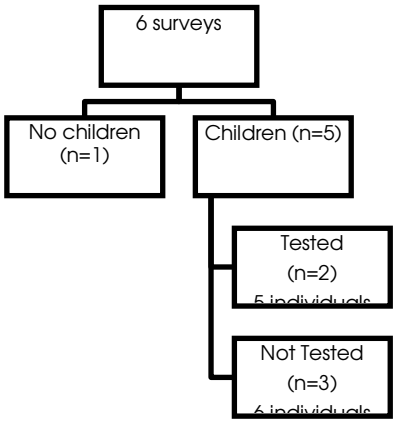


Figure 2. Survey response dichotomization

Questionnaire Response

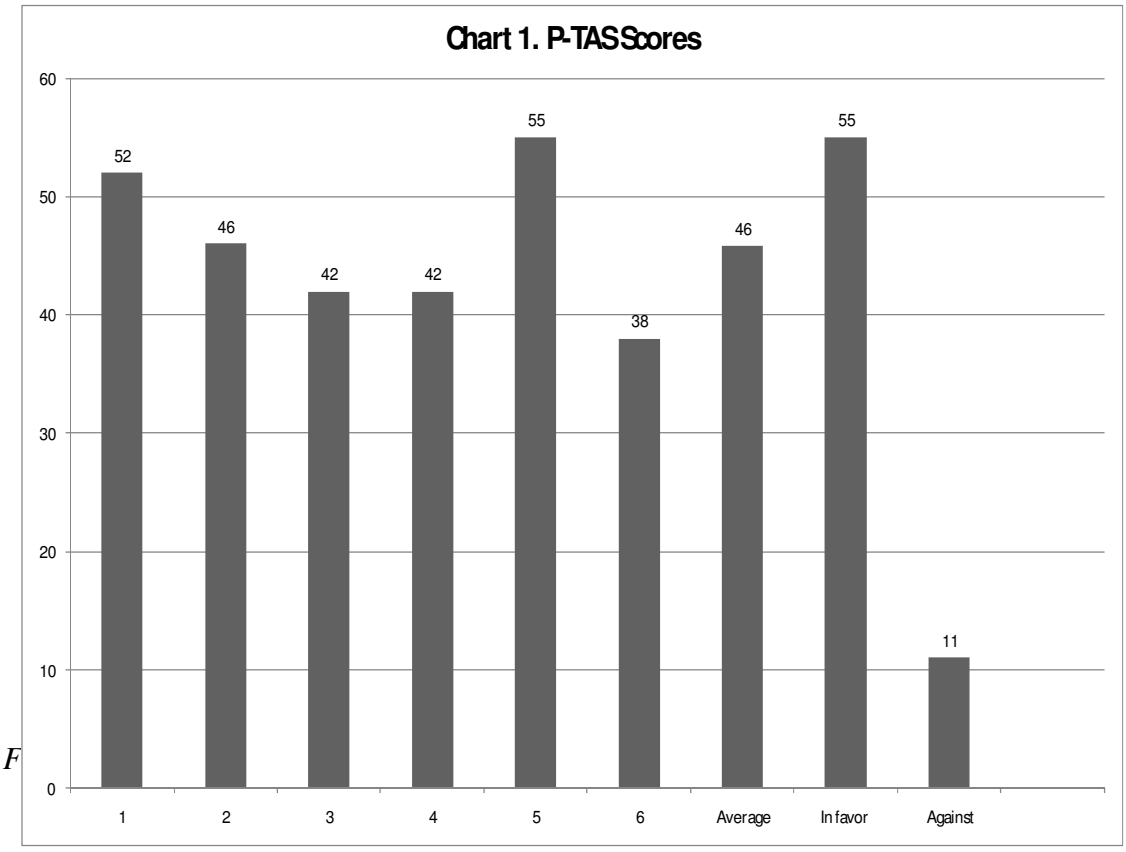
P-TAS (Pediatric Testing Attitudes Scale)

All six participants completed section one of the questionnaire. P-TAS scoring is based on a 1-5 scale, with lower scores indicating attitudes against testing and higher scores indicating attitudes in favor of testing. This was an 11-item scale, scores could potentially range from 11 (strongly against testing) to 55 (strongly in favor of testing). The P-TAS scores from this survey ranged from 38-55, with an average of 45.833, indicating strong attitudes towards p53 testing in children (Table 3). The creators of the P-TAS model further divided the questionnaire into two factors, 1) attitudes and beliefs and 2) decision making and communication. These factors are believed to assess parents' attitudes in pediatric p53 testing. The average scores were 4.42 and 4.22 for factors 1 and 2, respectively. Scores for factor 1 ranged from 3.2 to 5, while factor 2 scores ranged from 3 to 5 (Table 4).

Table 3. P-TAS responses

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	Unsure
1. Children under age 18 should be given the opportunity to be tested for the p53 mutation				2 33.33%	4 66.67%	
2. Parents should decide if their children are allowed to have a p53 test or not, even if a doctor disagrees				1 16.67%	4 66.67%	1 16.67%
3. Even though some of the cancers associated with p53 mutations do not affect children until they reach adulthood, children should still be offered p53 testing			1 16.67%	1 16.67%	4 66.67%	
4. Children should be involved in making the decision about whether or not they participate in p53 testing	1 16.67%		1 16.67%	1 16.67%	3 50%	
5. If children are tested and they carry a p53 mutation (that is, they test positive), they should be told about their test result immediately	1 16.67%		2 33.33%	2 33.33%	1 16.67%	
6. Even if there is no known prevention, treatment, or cure for the cancers associated with p53 mutations, children should be offered p53 testing				3 50%	3 50%	
7. If children are tested and they turn out to carry a p53 mutation (that is, they test positive), then this information should be shared with the child's pediatrician.				2 33.33%	4 66.67%	
8. I want my child to be tested for a p53 mutation before age 18 *		1 20%		1 20%	3 60%	
9. If children are tested and they do not carry a p53 mutation (that is, they test negative), they should be told about their test result immediately *	1 20%		1 20%	1 20%	2 40%	
10. The benefits of children participating in p53 genetic testing outweigh the risks			2 33.33%	1 16.67%	3 50%	
11. I am in favor of p53 gene testing for children		1 16.67%			4 66.67%	1 16.67%

Table 4. P-TAS and Factor Analysis			
Family	*Total P-TAS*	*Factor 1 (average)*	*Factor 2 (average)*
1	*52*	*5*	*4.4*
2	*46*	*4.5*	*4.75*
3	*42*	*3.83*	*3.75*
4	*42*	*5*	*3*
5	*55*	*5*	*5*
6	*38*	*3.2*	*4.4*
Average	*45.833*	*4.42*	*4.22*



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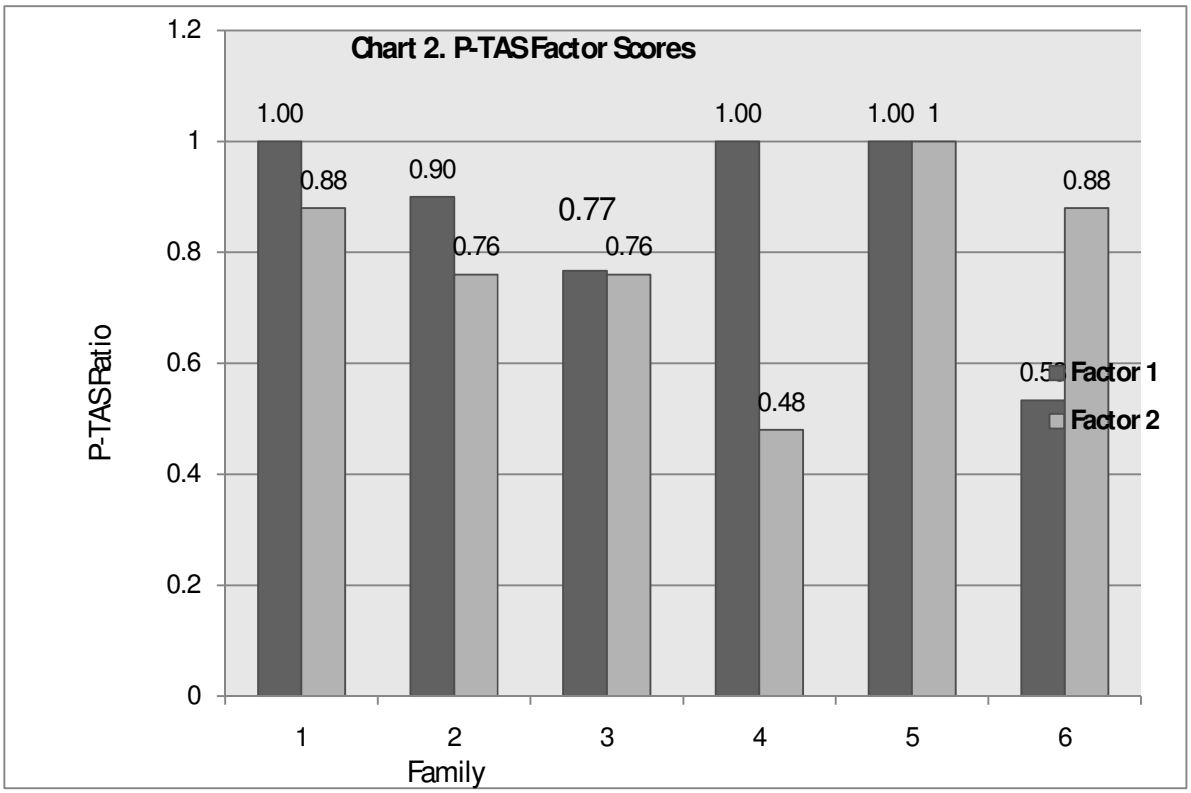


Scenario Decision Making

Participants were given a scenario and asked if they would be in favor of p53 gene testing for their child. All participants indicated that they would be in favor of testing if any of their children had developed cancer, if the results would help manage the health of that child or help another family member in any way. Most individuals (n=4, 80%) would be in favor of testing if the child agrees to or requests testing, while one was unsure. Table 5 summarizes these results.

Participants varied when asked at what age it is appropriate to test a child for a p53 mutation. Responses included numerical responses such as 13, 18 or 21.

Others made comments such as “ASAP” and “As early as possible without child knowing, one or above”. Table 6 summarizes these results.

Table 5. Scenario Decision Making

	Yes		Unsure	
	n	%	n	%
My child has developed cancer	5	100%		
One of my other children has developed cancer	5	100%		
He/She agrees to have testing	4	80%	1	20%
He/She requests testing	4	80%	1	20%
He/She is older than ten	3	60%	2	40%
If the results would help manage my child’s health	5	100%		
If results would help other family members	5	100%		

Table 6. Age of testing responses	
Family	At what age do you feel it is appropriate to test an individual for a p53 mutation?
1	ASAP
2	No answer
3	Should be based on the individual child. Too many variables to establish one specific age.
4	As early as possible without child knowing. One or above.
5	13
6	18 or 21, depends on the child (adult)?

Communication

Communication was characterized by a model created by Tercyak et al. (2004). Individuals were asked how frequently they discussed topics pertaining to p53 mutations and genetic testing and how comfortable they were with this discussion (or lack thereof). Five individuals completed this section for a total of 11 children (Table 7). Three parents reported sometimes talking to their children about p53 genetic testing, while 2 parents have never had this discussion. Of the individuals who have spoken with their children about this issue, all of them felt either mostly or very comfortable with it. Only two parents have asked children how they felt about genetic testing often, one individual reported having this discussion sometimes, while two parents never have had this conversation. All of the individuals who have asked their child their feelings towards p53 testing felt either mostly or very comfortable with the discussion. Most participants' responses did not vary

between children. One participant (4) did vary their responses between his/her three children. It is unclear why these results are discrepant.

Stage of change

Five participants with a total of 11 children completed the stage of change questionnaire. Participants varied regarding the steps they have taken towards seeking genetic testing for their child. Two individuals have reportedly had p53 genetic testing on all of their children (n=3) and shared the child's results with him/her. Others have thought about (n=2) or are committed to (n=1) discussing p53 genetic testing with their child and seeking more information about the subject. One individual has reportedly not thought about seeking information or meeting with someone to discuss p53 genetic testing. One individual is committed to have their child tested for a p53 mutation, while two individuals have thought about it. Individuals gave consistent answers for each of their children. Table 8 reviews these responses.

Testing motivations – child tested

Two of the five participants have sought genetic testing for their children (n=3). Table 9 depicts their responses to the testing motivation questionnaire. Family number one reported testing both of their children prior to their death. Family 1 reported that the possibility of relief to know that their child did not have a p53 mutation was "important", while family number two ranked it as "very important". Both families ranked their family's experience with cancer and the level of concern about their child it has caused as "very important". Likewise, both families ranked the possibility of their child undergoing preventative measures or planning for their future as "very important". Participants' responses did not vary between children.

Testing motivations- child not tested

The three families whose children have not had p53 genetic testing answered similar questions about what their motivations would be towards seeking testing (table 10) Family 3 ranked relief from knowing their child does not have a mutation as "slightly important", while families four and five ranked it as "very important". Family 3 said that their family's experience with cancer making them more concerned is "somewhat important", while families 4 and five ranked family experience with cancer as "very important". The chance that their child could do something to lower his/her risk was "somewhat important" to family 3, "important" to family 4, and "very important" to family 5. Family 5 thought that the possibility that they or their child could plan for the child's future was "very important", family 3 thought it was "somewhat important", and family 4 thought it was "slightly important". Participants' responses did not vary between children. Family 6 did not complete this questionnaire because they do not have children.

Table 7. Communication								
How often have you:					**How comfortable were you with this?**			
	Not at all	**Rarely**	**Some-times**	**Often**	**Not at all**	**A little bit**	**Mostly**	**Very**
Talked with this child about genetic counseling and testing for p53?	3,4		1,2,5		4(2,3)*		3,5	1,2
Asked this child how he/she felt about genetic testing?	3,4		2	1,5	4(2,3)*		2,3,4(1)*	1,5
Tried to reassure this child that he/she would be OK? **	4			1,2,5	4(2,3)*		4(1)*	1,2,5
Tried to reassure this child YOU would be ok?	4	3		1,2,5	4(2,3)*		3,4(1)*	1,2,5

*Parenthesis indicate instances when individuals responded differently for each child. Numbers inside parenthesis represent which child each response was intended.
** Participant 3 did not respond to this item

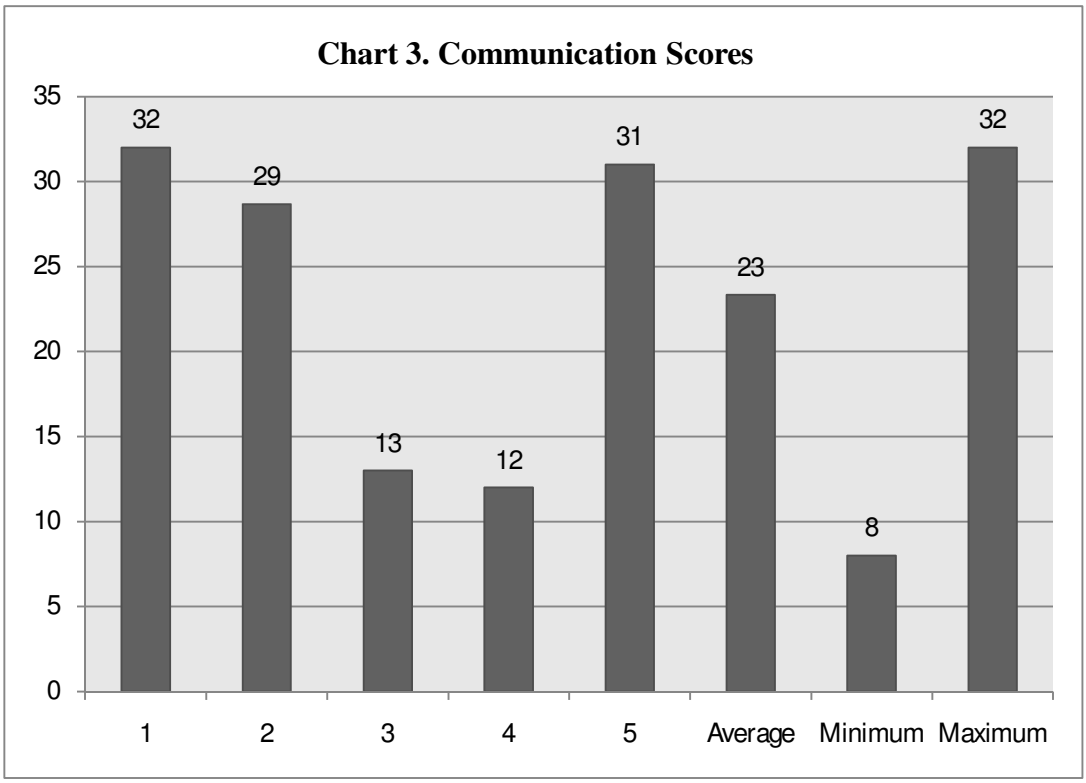


Table 8. Stage of Change

n= 5 families (11 children)	I have no interest in this		I haven't thought about it		I have thought about it		I am committed to it		I've already done it	
	n	%	n	%	n	%	n	%	n	%
Discussed genetic testing with this child					2	40%	1	20%	2	40%
Sought information regarding testing for a p53 mutation in this child			1	20%	1	20%	1	20%	2	40%
Made an appointment with a doctor/genetic counselor			2	40%	1	20%			2	40%
Met with a doctor/genetic counselor			1	20%	2	40%			2	40%
Had this child tested for a p53 mutation					2	40%	1	20%	2	40%
Shared these results							1	33.33%	2	66.67%

Testing concerns

Five families with a total of eleven children completed the "testing concerns" section of the questionnaire. Participants were asked to rank the importance each factor was/is when considering pediatric genetic testing (Table 11). Most individuals (n=4) stated that the concern that they or their family would get too upset about test results was "not important", while one individual ranked it as "somewhat important". The concern that their child would get too upset was somewhat important to three individuals and slightly important to two individuals. The majority of participants (n=4) cited concern about insurance discrimination and test results affecting their child's future as "very important". Participants responses regarding the lack of management or prevention techniques for individuals who have p53 mutations varied from "not important" (n=1), "somewhat important" (n=1) and "very important" (n=2). Most of the participants' responses did not vary from child to child. One individual did vary their responses between children.

In addition to the quantitative results previously discussed, our questionnaire included several opportunities for respondents to provide additional comments. Table 11 consists of comments the respondents shared with us in open-ended opportunities.

Table 9. Testing motivation (tested)			
	n=2 families , 5 children	Important	Very Important
	I would have been relieved to know that my child did not have a p53 mutation	Fam. 1	Fam.2
	My family's experience with cancer made me more concerned about my child's own risk for the disease		Fam. 1 Fam.2
	My child could do something to lower his/her cancer risk		Fam. 1 Fam.2
	I / My child could plan for the future		Fam. 1 Fam.2

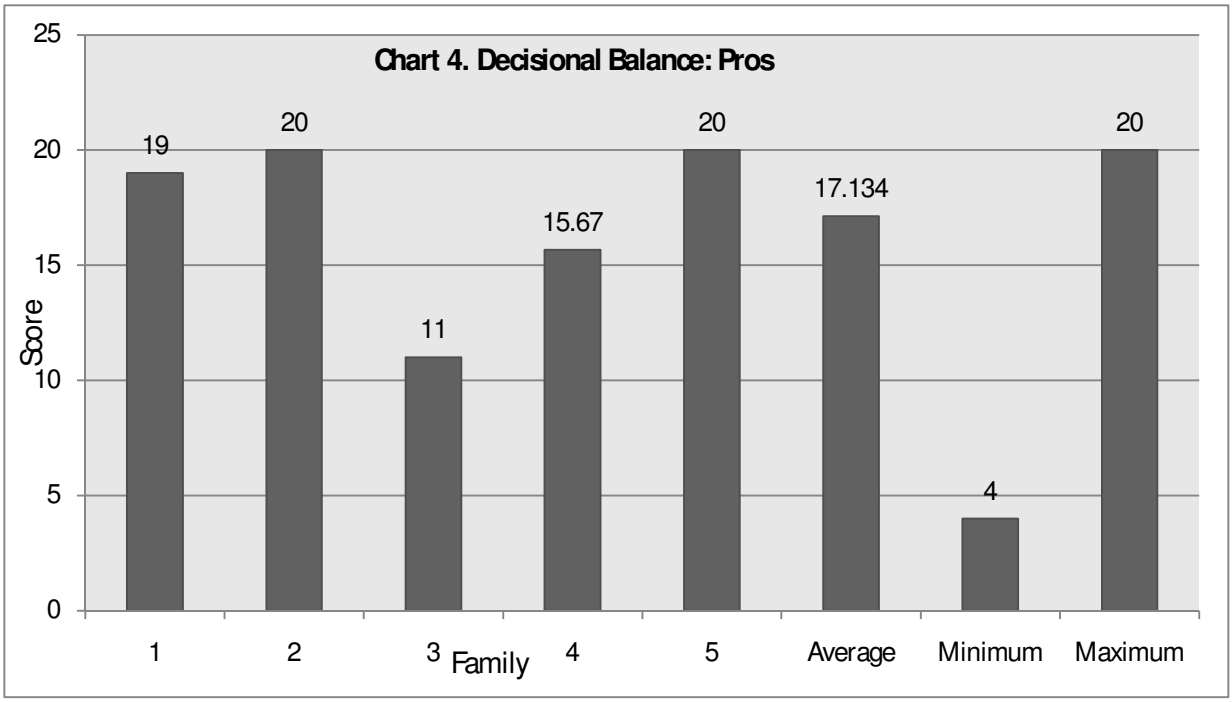
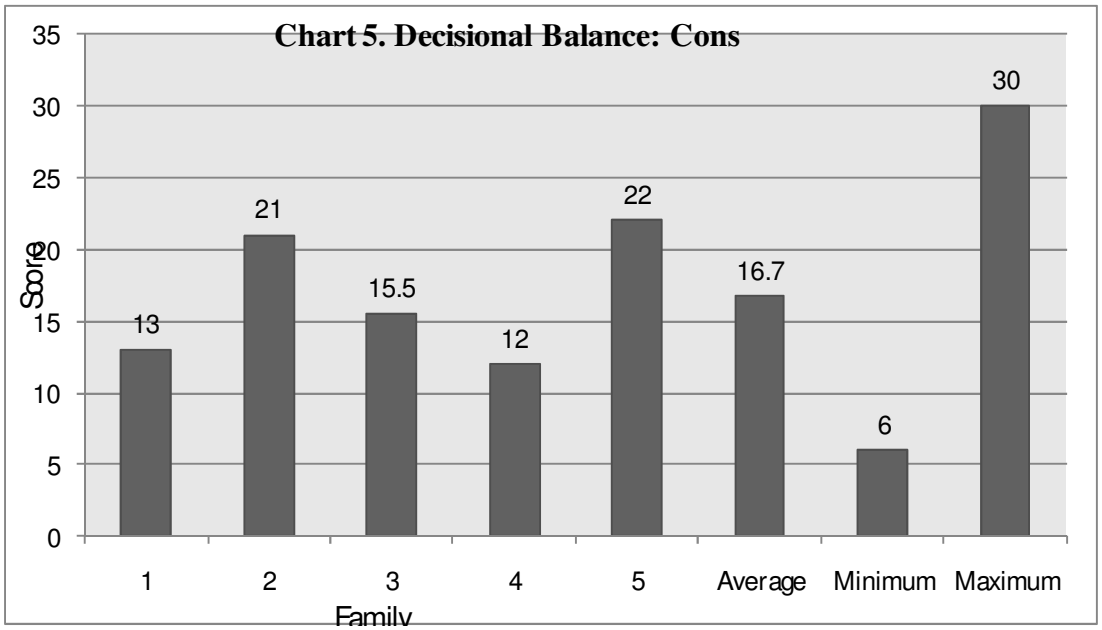


Table 10. Testing motivations (not tested)								
	Slightly Important		Somewhat Important		Important		Very Important	
n=6 children from 3 families	n	%	n	%	n	%	n	%
I would have been relieved to know that my child did not have a p53 mutation	3	33.33%					4, 5	66.67%
My family's experience with cancer made me more concerned about my child's own risk for the disease			3	33.33%			4, 5	66.67%
My child could do something to lower his/her cancer risk			3	33.33%	4	33.33%	5	33.33%
I / My child could plan for the future	4	33.33%	3	33.33%			5	33.33%

Table 11. Testing concerns										
n=5 families, 11 children	Not Important		Slightly Important		Somewhat Important		Important		Very Important	
I'm afraid I would get too upset	1,2,3,4	80%			5	20%				
I'm afraid my child would get too upset			1,3	40%	2,4,5	60%				
I am concerned that having the test might cause problems with my child's insurance					1	20%			2,3,4,5	80%
There is nothing my child can do about getting cancer	1,4	40%			3	20%			2,5	40%
I am concerned about my family's reaction	1,3,4,5	80%	2	20%						
I am worried about how it could affect my child's future					3(1)*	10%	3(2)*	10%	1,2,4,5	80%

- Parenthesis indicate instances when individuals responded differently for each child. Numbers inside parenthesis represent which child each response was intended.



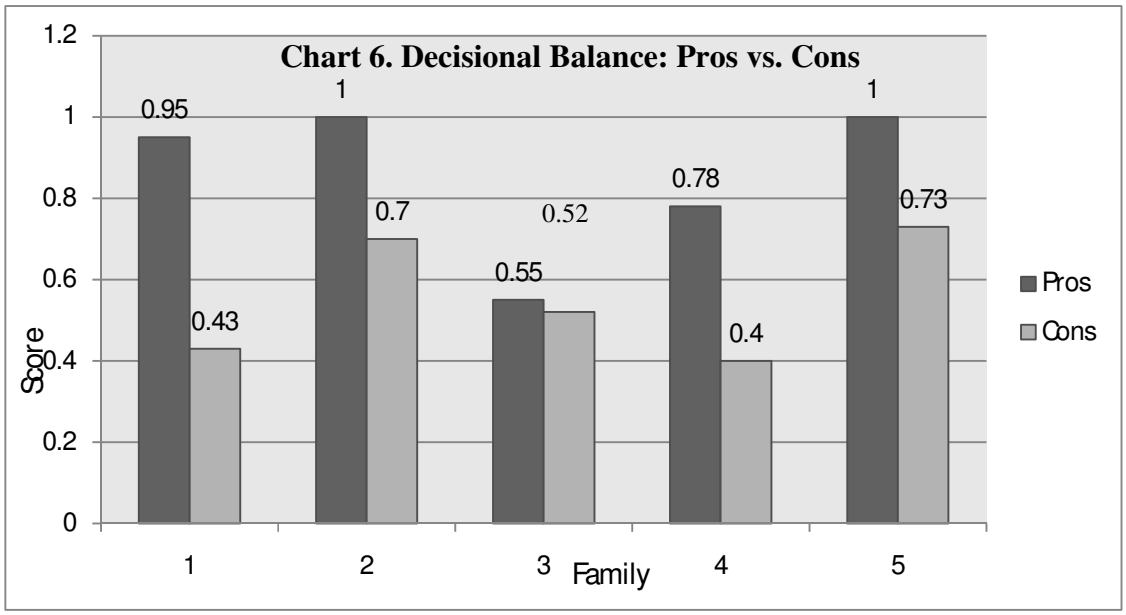


Table 11. Additional Comments	
Family	Comment
1	Info is power
3	I have not had my children tested because their father's opinion/request was not having them tested. He felt that being aware of the risks and having regular checkups would be a better option. He feared if they were tested positive, it could have adverse affects. I.E. ability to get health or life insurance, psychological since their father lost his battle with cancer, etc. As young adults I need to educate them with their options and allow them the choice at some point
4	I want to know as a parent. My kids already know they are at a greater risk because of being related to my wife's family. I do not want them to know results until all 3 are ready as adults. I do want their doctors to know.
	I do not want my kids to know results or even what the test is looking for until all 3 are adults or if one develops cancer. If one finds out, the others will worry.
	I don't want my kids to know results or even the real reason for the test other than testing them is for research. Would prefer if draw made by family doctor as "routine" blood work. I do want to know and I also want my family doctor to know (verbally).
	It would justify testing that could give early detection, allowing better odds on treatment.
5	We have recently been discussing with (proband's)15 year old daughter about getting her tested for (LFS).
	We are living with the effects that losing a mother and a brother because of (LFS), has on a child. The worries and the fears that are created when she is ill or just doesn't feel good. (Daughter) is constantly worried about developing cancer and it has created a major impact on all of our lives.

Discussion

Pre-symptomatic testing for p53 mutations is clinically available and the choice to test a child for these mutations is typically left to the parents and physician of the child. The decision whether to have a minor-aged child tested for a cancer predisposition gene such as p53 is composed of several factors (Patenaude et al., 1996). This study looks at parental attitudes towards testing children for p53 mutations. We looked at factors such as basic attitudes towards genetic testing, communication with children and used the Trans-theoretical model to assess decisional balance and stage of change. This is the first study to examine the attitudes of parents towards testing their children for p53 mutations.

Demographics and family characteristics

The demographic characteristics of our participants appear to be unremarkable. Among the six respondents, there is no clear pattern in terms of gender, marital status, education, employment our annual household income. Age of respondents also appeared to be insignificant. Of note, the survey was sent to households with children who are a variety of ages. All of the participants with living children who responded had children between 15 and 23 years of age. It is interesting that no individuals with younger children chose respond to the study. The average age of living children to individuals who did not respond to the survey was 17.4 years with ages ranging from 1 to 35 years.

Questionnaire

Pediatric Testing Attitudes Scale (P-TAS)

The pediatric testing attitudes scale (P-TAS) is a measure developed my Peshkin et al. (2009) to ascertain parental attitudes towards testing minors for BRCA1/2 mutations. This eleven-item scale was divided by its creators using principal components extraction method with rotation of factors in two factors: 1) attitudes and beliefs (six items), and 2) decision making and communication (five items). Scores from each factor were summed to give the total P-TAS score for each participant with a minimum of 11 and maximum of 55. Higher scores were indicative of parental attitudes more strongly in favor of pediatric p53 genetic testing, while lower scores indicated parents who were more opposed to testing their children for p53 mutations.

Scores from our six participants ranged from 38 to 55 with an average of 45.833. These scores indicate that parents were mostly in favor of obtaining p53 genetic testing for their children, although scores varied. When scores are divided into their two factors, an interesting observation can be made. Factor 1 is composed of 6 items regarding attitudes and beliefs about p53 genetic testing in minors, with a minimum and maximum score of 6 and 30, respectively. The average factor 1 score from our six participants is 26. Respondents seem to be consistently "in favor of", or "strongly in favor of" most items regarding minors having the opportunity to be tested for p53 mutations. Sample items from factor 1 include: "children under age 18 should be given the opportunity to be tested for the p53 mutation", and "even if there is no known prevention, treatment, or cure for the cancers associated with p53 mutations, children should be offered p53 testing". Only one individual reported that they did not want their children tested for p53 mutations before the age of eighteen, although they appeared to believe that children and parents should be given the opportunity to make that decision. In total, parents seemed to agree that all

children should have the right to be tested for p53 mutations, although not all would personally test their child or children.

Factor 2 pertains to decision making and communication (Peshkin et al., 2009). Sample items from factor 2 include statements such as: "Children should be involved in making the decision about whether or not they participate in p53 testing" and "If children are tested and they turn out to carry a p53 mutation, they should be told about their test result immediately. Factor 2 consisted of five items which were totaled to make a minimum and maximum score of 5 and 25, respectively. Respondents' factor 2 scores ranged from 12 and 25 with an average of 19.83. Individual responses to these items varied. While most people believed that parents should be able to make the decision to test their child for a p53 mutation, respondents did not agree whether children should be involved in the decision making process. One individual strongly disagreed that children should take a part in this decision, while others were either unsure or agreed. That same individual was strongly against sharing the child's genetic testing results with him/her regardless of if the testing identified a mutation. This respondent did, however agree that the information should be shared with the pediatrician. While some individuals would apparently readily involve their child in the testing decision, others would prefer to make a decision on behalf of their child.

Testing Scenarios

All participants reported that they would test their child for a p53 mutation if that child had developed cancer, or if the child's sibling developed cancer. Other studies have demonstrated that parents would be more likely to test a child who has already developed cancer for a cancer susceptibility gene, than a healthy child (Patenaude et al., 1996). The

question of pre-symptomatic testing in minors becomes more complex. Four individuals would test their child if the child consented to or even requested testing, while one was unsure. Three individuals would test their child if he/she was over the age of ten, while others were unsure. Finally, all individuals would test their child for a p53 mutation if results would help manage that child's health or help other relatives. Although the option of "no" was given, respondents never chose it for any of the seven scenarios. Parents most likely recognize that the decision to test their child for a p53 mutation is composed of several factors which must all be considered in light of each child/family's unique situation.

Age

Parents varied in their response regarding the appropriate age would be to test children for a p53 mutation. Family 1, who had two children die from cancer related issues reported that he thought children should be tested for p53 mutations as early as possible. Family 4 agreed that children should be tested as early as possible but added that the child should not know about the test or results. Family 4 is consistent throughout the survey in their attitude about not wanting their children to know the results of the test. Family number five believes children should be tested at age 13. At this age, minors are often thought to be able to make their own meaningful decisions, and it may therefore some may consider it reasonable to allow these children to participate more in their healthcare decisions. Family 3 reported that the age to test a child for p53 mutations "should be based on the individual child" and that there are "too many variables to establish one specific age". This statement may refer to the fact that children, regardless of age have varying

cognitive abilities, maturity, and decision making capabilities. Some mature adolescents may have the same mental capacities that are associated with autonomous agents (Kon, 2006), while others may not. Other factors such as health of the child and their siblings, family history and other psychosocial characteristics that are unique to that child may also play a role in a parent's decision of when to test their child. Family 6 stated that individuals should be tested for p53 mutations at the age of 18, or 21, depending on the individual. This individual seems to be taking a more conservative stance on genetic testing and believes that it should be postponed until the child has reached the age of majority (18 in most states) or age of license (varies) . The age of majority refers to the age at which a child transitions to an adult and assumes responsibility of his or her own self, decisions and responsibilities. At this age, the child is no longer under jurisdiction of their parent or guardian. Age of license refers to the age at which an individual gains certain privileges. For instance, 21 is often the age of license for consumption of alcoholic beverages and participation in gambling activities. Family 6 appears to associate these ages with the ability of an individual to make reasonable and well thought decisions about their healthcare.

Communication

Past studies indicate that the frequency of communications parents have with their children about family history of cancer, genetic testing and general child and parental health correlates with interest in genetic testing and disclosure of results (Terycak et al., 2002)(Tercyak et al., 2006). Overall, families varied in regard to how frequently they communicated with their children about these issues. Families 3 and 4 were consistent non-communicators. They do not appear to have open communication with their children with regard to genetic testing and parental/child health. Family 4 appears to be fairly

consistent in their attitudes about not wanting to involve their children in any of the decision making processes of genetic testing. While family 3 did not make any other revealing comments about not wanting to involve their children in the decision to test, they do not appear to be having active discussions about the issue.

Other families reported that they sometimes spoke with their children about genetic counseling and testing for p53 mutations and felt mostly or very comfortable with it. These individuals also sometimes or often asked their child how he/she felt about genetic testing and seemed comfortable with those discussions. These families seem to have open communication with their children about p53 genetic testing and most likely their child's input. Most individuals report frequently reassuring their child about their own health and that child's health. Those who have this discussion appear to be fairly comfortable with it. Although our sample size is small, the results are consistent with research done by Tercyak et al. (2002). The two families who have already had their child tested for p53 genetic mutations appeared to be very open with their children about p53 genetic testing. Others who reported less frequent communication with their children have not taken steps towards seeking testing in their children.

Trans-theoretical Model

The trans-theoretical model (TTM) has been used extensively in health-related studies looking at intentional behavior change (Prochaska & DiClimente, 1983) (Prochaska, DiClemente & Norcrow, 1992) (Prochaska & Velicer, 1997). The model is composed of five core constructs: 1) stages of change, 2) processes of change, 3) decisional balance, 4) self-efficacy and 5) temptation (Prochaska & Velicer, 1997). In our

study, we used the stage of change and decisional balance measures to explain attitudes towards p53 genetic testing.

Stage of Change

The stage of change measure is composed of a series of five changes: 1) pre-contemplation, 2) contemplation, 3)preparation, 4) action and 5) maintenance (Prochaska & Velicer, 1997). Pre-contemplation refers to the stage when individuals do not intend to make an action in the next 6 months (Prochaska & Velicer, 1997). In our questionnaire, the pre-contemplation stage is represented by two items: have individuals discussed testing with their children and have they sought information regarding testing. All of the respondents have at least considered talking with their children about genetic testing. Some answers to this section were not consistent with respondents' answers to the communication measure. Only two individuals reported that they have already discussed genetic testing with their child, while three individuals reported that they have sometimes talked with their child about genetic testing in the communication measure. It is not clear why these responses are discrepant. Individuals who are in the contemplation stage are intending to change in the next six months (Prochaska & Velicer, 1997). In most cases, they have thought seriously about the decision to change, such as the pros and cons. Individuals who are in the contemplation stage in obtaining p53 genetic testing for their children have presumably sought information or made an appointment with a physician or genetic counselor. Most families have at least thought about seeking information and making a counseling appointment. Two families reported that they had not thought about seeking information about testing, while one has not thought about making a genetic counseling appointment. These individuals do not appear to be seriously considering genetic testing in their children, although in previous sections of their survey, they

appeared to be in favor of pediatric genetic testing in minors. The preparation stage refers to the stage when people plan on taking action in the immediate future (Prochaska & Velicer, 1997). In our study, individuals who have met with a physician or genetic counselor were in the preparation stage. Only two individuals reported that they have met with a physician/genetic counselor, while the rest have either not thought about it, or have thought about it and not acted on it.

Only two individuals (families 1 and 2) have had their children tested for p53 mutations, thus completing that action stage (the stage in which people have implemented a change or action) (Prochaska & Velicer, 1997). One family is committed to this, while two have thought about it. Both individuals who tested their children have disclosed the results to those children. Another individual is committed to sharing genetic results with their child once that child gets tested. Overall, only two individuals have gone through all of the stages of change and even disclosed results to their children. Others appear to be still in the pre-contemplation stage. Among those in the pre-contemplation stage, some individuals seem to be more interested in genetic testing than others, by saying that they are committed to having their child tested for a p53 mutation and disclosing those results. Other families do not appear to have contemplated to subject.

Decisional Balance

Decisional balance refers to the weighing of pros vs. cons of implementing a behavior or change (Prochaska & Velicer, 1997). How an individual weighs the pros and cons of a decision is thought to predict their stage of change. For instance, a person who is only in the contemplation stage might rate the pros and cons equally, while someone who is in the action stage might rate the pros higher than the cons. If this is true, individuals

who have tested their children for p53 mutations should have higher "pros" scores than "cons" scores. In fact, this is the case. The pros scores for families 1 and 2 are 0.95 and 1.0, respectively, while the cons are 0.52 and 0.84. Both families seemed to value the pros more than the cons. Likewise, individuals who are still considering p53 genetic testing should have a near balance of "pros" and "cons". Families 3,4 and 5 had "pros" scores of 0.55, 0.8, and 1.0, respectively and "cons" scores of 0.62, 0.64 and 0.84. With the exception of family 5, families 3 and 4 and lower "pros" scores than the two families who tested their children. It is possible that they have not pursued p53 genetic testing in their children because they do not see value in results. Family 5 has "pro" and "con" scores identical to family 2, but has not tested their child for p53 mutations. They did, however, indicate that they are committed to testing their child for p53 mutations and disclosing those results to that child. The decisional balance appears to be a predictable indicator of stage of change in this small sample.

Regardless of whether their children have undergone genetic testing, most individuals (n=4, 80%) ranked that their family's experience with cancer increasing their concern about their child's risk as "very important". Likewise, most (n=4,80%) ranked the relief they would feel if their child did not have a p53 mutation as "important" or "very important". It is interesting to note that those who tested their children for p53 mutations ranked the possibility that test results could manage their child's health or help plan for the child's future as "very important", while only one of the individuals who have not tested their children chose the same ranking. This is the same individual who is committed to testing their child. Other families ranked it as "somewhat important" and "important". It appears that individuals who have not had their children tested for p53 mutations see a lack

of potential benefit for the child's health or planning for the future. How families perceive the utility of testing appears to influence how they weigh the "pros" and "cons".

Families uniformly ranked the possibility that they would have a negative reaction to test results as "not important" or "somewhat important". Likewise, individuals were not concerned about their family's reaction, indicating that it was either "not important" (n=4, 80%), or "slightly important" (n=1, 20%). Families seem more concerned about the reaction of the individual child being tested for a p53 mutation, ranking concern about the child's reaction as "slightly important" (n=2, 40%) and "somewhat important" (n=3, 60%). These families appear to be taking a protective role in being concerned about their child's reaction over their own.

Eighty percent (n=4) of respondents ranked concern about insurance discrimination as "very important". This is consistent with other studies which cite concerns about insurance discrimination as major deterrents to pre-symptomatic genetic testing. Individuals do not appear to feel protected by the Genetic Information Non-discrimination Act (GINA), which was implemented in the fall of 2009 (Erwin, 2009). GINA protects pre-symptomatic individuals from discrimination by health insurance companies and employers (Slaughter, 2008) (Erwin, 2009). GINA does not protect pre-symptomatic individuals from life or long term disability insurance (Slaughter, 2008). It remains to be seen whether the country's health care reform will change how individuals feel about insurance discrimination.

There were no clear patterns between the families who have tested their children and those who have not in how they ranked the "cons", with the exception of one item. One item (there is nothing my child can do about getting cancer) was particularly varied,

with answers ranging from “not important” to “very important”. Family 1, who tested their child, and family 4, who did not test their child ranked it as “not important”. Families 2 and 5 ranked this item as “very important”. Family 2 tested their child while family 5 is committed to it. Interestingly, these families ranked the “pro”: my child could do something to lower his/her cancer risk as “very important”. These responses appear to be contradictory.

Other Comments

Respondents were given several opportunities throughout the questionnaire to provide qualitative responses. These comments were especially revealing. While some responses reinforced the themes which have presented themselves in the quantitative data, others introduced new issues which would be interesting to address in future studies.

Family 1 indicated that “info is power”. This family tested their children for p53 genetic mutations. The respondent had two daughters, who both passed away from cancer-related issues. Additionally, the respondent has a diagnosis of a terminal cancer. This family has quite a significant history of cancer diagnoses and subsequent deaths. It is possible that this individual feels that knowing whether his children had the cancer susceptibility gave him some kind of control, although both his children presumably had p53 mutations. Power can be translated in a number of ways. While power can mean that knowing genetic results may benefit the child’s health management, it may also mean that it can allow the family to plan for the future, make lifestyle choices, etc.

Respondent 3 provided the following statement:

> *" I have not had my children tested because their father's opinion/request was not having them tested. He felt that being aware of the risks and having regular checkups would be a better option. He feared that if they were tested positive, it could have adverse affects. I.E. ability to get health or life insurance, psychological since their father lost his battle with cancer, etc. As young adults I need to educate them with their options and allow*

This response highlighted several key issues. This is a co-parent whose spouse had passed away from cancer-related issues. First, this individual is respecting her partner's wishes. It is clear that the couple had put a lot of thought into this topic before the father passed away, and that they had made a choice together to defer testing until the children had reached adulthood. The couple appeared to be concerned about several issues. Insurance discrimination is a theme which continues to present itself both here and in other studies related to pre-symptomatic testing for cancer susceptibility (Patenaude et al., 1996). The couple also feared that watching a parent with LFS die from cancer would cause the children more anxiety when going through genetic testing themselves. It appears that this individual is very knowledgeable about LFS and associated risks. She is making it her responsibility to be vigilant about the health of her children and to share information and help facilitate decision making when the children get older.

Respondent 4 provided comments:

> *"I want to know as a parent. My kids already know they are at a greater risk because of being related to my wife's family. I do not want them to know results until all 3 are ready as adults."*
>
> *"I do not want my kids to know results or even what the test is looking for until all 3 are adults or if one develops cancer. If one finds out, the others will worry."*
>
> *"I don't want my kids to know results or even the real reason for the test other than testing them is for research. Would prefer if draw is made by family doctor as "routine" blood work. I do want to know and I also want my family doctor to*

In previous sections, this individual indicated that he was in favor of predictive p53 genetic testing in children. However, he was strongly against involving children in the decision making process and disclosing results to them. These qualitative comments are consistent with the quantitative responses. This individual appears to believe that testing would benefit the health of the child in some way but feels the need to play the role of gatekeeper with this information. The children of this individual are ages 15, 16 and 20. This individual's responses are especially interesting considering the ages of his children, one of which is considered to be past the age of majority, and is legally able to request his/her own testing without parental permission. The other children may be considered to be at the age of "assent". It would likely be difficult to find a physician or genetic counselor willing to test children of these ages without their assent.

The issue of genetic testing in minors is becoming increasingly prevalent. One key component is the concept of "assent". For minors in healthcare, assent refers to the minor understanding and agreeing to the proposed procedure or test (De Lourdes, Larcher & Kurz, 2003).

In his comments, respondent 4 appears to have concerns about insurance discrimination. He reports that he would want his childrens' doctor to know test results "verbally". This individual presumably does not want genetic results to be documented in their child's medical record, which health insurance companies or other potentially discriminating persons could access. Once again, fear of insurance discrimination appears to color individuals' view of pre-symptomatic testing.

Respondent 5 was a co-parent to an individual who had recently passed away from cancer-related issues. The couple had one living daughter, age 15, and a son who died at age 6 from cancer related causes. In e-mail correspondence, respondent 5 included the following information:

> "We have recently been discussing with (child) about getting her tested for (LFS)".
>
> "We are living with the effects that losing a mother and a brother because of (LFS), has on a child. The worries and fears that are created when she is ill or just doesn't feel good. (Child) is constantly worried about developing

Throughout the questionnaire, this respondent appeared to be strongly in favor of pediatric testing. His P-TAS score was 55, which is the maximum value. During the stage of change questionnaire, the individual was still in the pre-contemplation stage, but reported that he was committed to obtaining p53 genetic testing for his daughter and disclosing the results.

This individual brought up an interesting point that many parents most likely consider. His 15-year old daughter could potentially have up to a 20% risk of cancer before she turns 18. She has seen her younger brother and mother suffer from their cancer diagnoses and eventually pass away. This child may be experiencing excessive cancer-related anxiety by not knowing whether she has the same cancer risks as her mother and brother. If she did not inherit the p53 mutation from her mother, then this child has the general population cancer risk. The estimated cancer for a female of the general population to develop cancer before the age of 20 is 0.32% (Ries, Kosary, Hankey, Miller, Clegg & Edwards, 1998). Alternatively, if she did inherit the p53 mutation, the complaints and health concerns of this child may be taken more seriously.

Strengths of Study

As no research has examined parental attitudes towards testing children for p53 mutations, this is a pilot study. Other studies have looked at parental feelings and beliefs regarding pre-symptomatically testing children for other cancer predisposition syndromes such as Familial Adenomatous Polyposis (FAP), Von-Hippel Lindau disease (VHL) and Hereditary Breast and Ovarian Cancer syndrome (HBOC) (Andrews et al.,2006) (Peshkin et al., 2009) (Rasmussen et al., 2010). Patenaude et al. (1996) questioned parents about their attitudes regarding testing children for a theoretical cancer predisposition gene. One of the largest strengths of this study is that it is the first to focus specifically on parents whose children are at risk of inheriting

p53 mutation and to ascertain parental attitudes toward testing children for p53 genetic mutations.

Another strength of this study is its use of several validated measures in pediatric genetic testing and health-related behavior (Tercyak et al., 2002),(Andrews et al., 2006),(Peshkin et al., 2009), (Peterson et al.,2009). The pediatric testing attitudes scale (P-TAS) has recently been validated and is expected to play an integral role in future studies looking at parental attitudes towards testing minors for cancer susceptibility (Peshkin et al., 2009). The communication questionnaire has been used in several studies and is shown to be reliable (Terycak et al., 2002, Terycak et al., 2006). The trans-theoretical model has also been extensively used in health related research and is a measure that is believed to accurately measure stage of change and decisional balance (Prochaska & Velicer, 1997). Additionally, individuals were given the opportunity to provide qualitative responses. We were therefore able to collect both qualitative and quantitative responses from most respondents. The tools used were appropriate for the study.

Limitations of Study

The major limitation to the study is our small sample size. Only 6 out of 25 potentially reachable participants returned the questionnaire, giving a response rate of 28.57%. We are unable to draw explicit conclusions about our population given this small response rate. In this study, non-response may be attributed to a number of factors. A previous study using the same population of participants showed a response rate of near 70% (Peterson et al., 2008). Surveys were conducted over the telephone, while ours were

mailed-out. Past studies have shown that mail-out surveys were more revealing than telephone, yet showed a lower response rate (Morrissey, 1995) (Erhart, Wetzel, Krugel & Ravens-Sieberer, 2009). Although telephone reminder calls are believed to strengthen response rate (Traina, MacLean, Park & Kahn, 2005), our attempt to do so did not appear to be successful. Due to time constraints, we were not able to conduct the survey over the telephone. If we had used the telephone to conduct the survey, it may have been possible to probe participants for more qualitative responses, as those appeared to be the most revealing in our study.

Low response rate may also be attributed to the timing of the initial survey distribution. Our survey was initially mailed in mid-December, near the winter holidays. Two reminder surveys were then mailed out. It is possible that the timing of initial survey distribution contributed to the poor response rate. We are therefore unable to generalize our results towards a greater population.

Another potential limitation of the study is that parental attitudes towards testing children for cancer predisposition likely have many more factors which we did not inquire about. Such factors may be child's current and past health, health of parent(s) and siblings, child's maturity level and cognitive ability of the child. These are all factors which could potentially play a large role in a parent's decision whether to test their child for a p53 mutation.

Conclusion

Although clinical genetic testing has been available for Li-Fraumeni syndrome, little is known about parental attitudes towards testing children for p53 mutations. This is the first study to address this issue. In general, parents

seem to be in favor of childrens' rights to be tested for p53 mutations. Although most people appear to agree that children should have the opportunity to be tested, they vary in regard to their attitudes towards who should be involved in the decision making process and when it should occur. While some individuals believe that children should be tested as soon as possible, others reported that it should occur later in adolescence or when the child reaches the age of majority. Parents also varied in communication with their children. Some reported having open discussions about genetic testing and general health frequently, while others have reportedly never had these conversations.

Using the health psychology trans-theoretical model, we ascertained the decisional balance and stage of change of each individual. Decisional balance appeared to be a reliable predictor of stage of change. Individuals who favored the "pros" in decisional balance are either committed to test their children for p53 genetic mutations or have already done it. Individuals who ranked the "pros" and "cons" more equally appear to be in pre-contemplation stage of testing their children.

Perhaps most revealing were the qualitative comments that the participants provided us. These thoughtful responses highlighted several key issues in considerations for pediatric genetic testing including concerns about insurance discrimination and pediatric assent to genetic testing.

Although our small sample size does not allow us to draw any conclusions about our population, individuals provided us with enlightening responses. Li-Fraumeni syndrome is clearly a life-altering diagnosis. Parents

considering whether to test their at-risk children for this devastating condition do not appear to be taking the decision lightly. There is no straightforward answer as to whether children should undergo p53 genetic testing. This and future studies addressing this issue may improve communication between health care providers and parents about pediatric genetic testing for cancer predisposition syndromes.

Future Studies

As we limited our study to individuals who have children 27 years of age or younger, it may be beneficial to expand the study population to all individuals who have a diagnosis of or are at risk of inheriting Li-Fraumeni Syndrome. This would likely improve the sample size. Additionally, performing a telephone survey would most likely improve the survey response and sample size. A telephone survey would also allow us to ask probing questions and obtain more qualitative responses.

It would be interesting to see how the recently enacted genetic information non-discrimination act (GINA) and health care reform will change the concerns individuals have regarding insurance discrimination. Literature often cites this to be a major deterrent to genetic testing (Patenaude et al., 1996), (Veach, Bartels & LeRoy, 2001), (Hall, McEwen & Barton, 2005). Responses from this study are consistent with those reports. With changing regulations on insurance discrimination and an evolving health care model, individuals may alter their ideas about this possibility.

Finally, it might be worthwhile to perform a similar study on providers who may encounter issues such as pre-symptomatic p53 genetic testing. This could be done by identifying providers who care for patients who have a family history of Li-Fraumeni syndrome and providing them with a similar survey as the one in our study. Comparisons could then be made between responses of parents and provider. Results from this study could provide insight on differing perceptions between parent and medical specialist.

Appendix A : Letter of Invitation

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Department of Genetics-Unit 209
Phone: (713) 792-7555 Fax: (713) 794-4421

<Date>

<Name>
<Address Line 1>

<Address Line 2>

Dear Ms/Mr. <Name>:

I am writing to thank you for your continued participation in our research involving Li Fraumeni
Syndrome (LFS), and to let you know about a new research opportunity. I would like to invite you to take part in a research study entitled *Attitudes of families with Li-Fraumeni Syndrome, a rare hereditary cancer predisposition syndrome towards predictive testing in children.* We are interested in obtaining information about parental attitudes toward p53 genetic testing in their children.

We are inviting you because you have participated in our LFS research at M. D. Anderson Cancer Center (MDACC). The study will include individuals with a diagnosis or those who have family members with a diagnosis of Li-Fraumeni Syndrome. Your decision to join this research study is voluntary. You may decline to participate, or choose to discontinue participation at any time. Your decision about participation in this study or answering questions will not change the care or services that you receive from MDACC.

Participation in this research study involves completing the enclosed survey regarding your feelings toward p53 testing in your child. You or somebody in your family has been diagnosed with Li-Fraumeni Syndrome, a cancer predisposition condition. As you know, LFS is a rare hereditary condition that increases cancer risk, and is most often attributed to genetic changes in the p53 tumor suppressor gene. We have identified a mutation, or change in the p53 gene in you or a family member. As you may know, p53 testing is not routinely performed in minors for a variety of reasons. We are interested in learning how you feel about having your child tested for the p53 mutation. The questions that you will be answering will help the researchers and physicians to better understand the needs of families with children at risk for LFS and provide the appropriate services. We will ask you questions about how you feel about genetic testing in your children.

If you agree to participate in this study, please complete the questionnaire that is included in this packet and return to us in the pre-addressed envelope. By consenting to

this study, you will give us access to this questionnaire, as well as your MDACC medical records.

If you choose to participate in the study, you will be asked to give your identification number on the questionnaire. Your identification is: (Kindred number and Unique number). This number allows us to determine who has responded to the study.

This questionnaire is also available online. If you prefer to do online survey, please notify us at 713-745-3477 and we will send you the instructions. The online survey consists of the same questions as the one that is included in this packet and was created using a professional account on Survey Monkey, which is a confidential survey making tool. Your response will be maintained strictly confidential and will only be shared with study staff.

Although your participation in this project may not have direct benefit to you, it will provide useful information that may advance our understanding of genetic testing. Some of the questions on the survey may make you feel uncomfortable. You may decline to answer any questions or stop taking the survey at any time. If you decide to participate in the study, it is very important that you answer as honestly as you can to the questions that are asked. Please complete this survey alone.

If you have any questions or would like more information, please contact Leslie Newman at 713-745-3477 or Dr. Strong, MD at (713) 792-7555.

Thank you very much for considering this invitation to participate in our study.

Sincerely,

Leslie Newman, BS

Graduate School of Biomedical Sciences
Chair
Email: leslie.a.newman@uth.tmc.edu

Louise C. Strong, M.D

Sue and Radcliffe Killam
Professor of Cancer
Genetics

APPENDIX B: Questionnaire

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Instructions: We are interested in learning about your attitudes toward p53 testing for healthy children under the age of 21. As you may know, p53 genetic testing for cancer susceptibility has not been routine in healthy minor age children due to several medical, social, and psychological reasons, however p53 alterations do affect cancer risk in children, and we wish to learn about your experience and attitudes toward such testing. **The following questions are directed toward your personal feelings about genetic testing in healthy minors.**

Please indicate your agreement with each of the following statements using the scale below.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
1. Children under age 18 should be given the opportunity to be tested for the p53 mutation	1	2	3	4	5
2. Parents should decide if their children are allowed to have a p53 test or not, even if a doctor disagrees	1	2	3	4	5
3. Even though some of the cancers associated with p53 mutations do not affect children until they reach adulthood, children should still be offered p53 testing	1	2	3	4	5
4. Children should be involved in making the decision about whether or not they participate in p53 testing	1	2	3	4	5
5. If children are tested and they carry a p53 mutation (that is, they test positive), they should be told about their test result immediately	1	2	3	4	5
6. Even if there is no known prevention, treatment, or cure for the cancers associated with p53 mutations, children should be offered p53 testing	1	2	3	4	5
7. If children are tested and they turn out to carry a p53 mutation (that is, they test positive), then this information should be shared with the child's pediatrician	1	2	3	4	5
8. I want my child to be tested for a p53 mutation before age 18	1	2	3	4	5
9. If children are tested and they do not carry a p53 mutation (that is, they test negative), they should be told about their test result immediately	1	2	3	4	5
10. The benefits of children participating in p53 genetic testing outweigh the risks	1	2	3	4	5
11. I am in favor of p53 gene testing for children	1	2	3	4	5

CONTINUED ON NEXT PAGE…

	I am in favor of p53 gene testing for my child if: (Circle One)			
		Yes	No	Unsure
12	My child has developed cancer	1	2	3
11	One of my other children has developed cancer	1	2	3
12	He/She agrees to have testing	1	2	3
13	He/She requests testing	1	2	3
14	He/She is older than ten	1	2	3
15	If the results would help manage my child's health	1	2	3
16	If results would help other family members	1	2	3

17	At what age do you feel it is appropriate to test an individual for a p53 mutation?

Please complete the following for each of your biological children.

1 Child's year of birth	2 Is this child living?	3 If No, at what age did the child pass away?
	Yes ☐ No ☐	**Age:** **Cause of death:**

4 Gender	5 Have you shared your family's genetic testing results with this child?
Male ☐ Female ☐	Yes ☐ No ☐ Not Applicable ☐

The following questions pertain to conversations you may or may not have had with your child about their risk of inheriting an alteration in the cancer susceptibility gene, p53, and genetic counseling and testing.

	How often have you:						How comfortable were you with this?			
		Not at all	Rarely	Some-times	Often		Not at all	A little bit	Mostly	Very
6	Talked with this child about genetic counseling and testing for p53?	1	2	3	4		1	2	3	4
7	Asked this child how he/she felt about genetic testing?	1	2	3	4		1	2	3	4
8	Tried to reassure this child that <u>you</u> would be OK?	1	2	3	4		1	2	3	4
9	Tried to reassure this child that <u>he/she</u> would be OK?	1	2	3	4		1	2	3	4

CONTINUED ON NEXT PAGE…

Please indicate the steps you have (or have not) taken regarding seeking genetic testing for your child.						
		I have no interest in this	I haven't thought about it	I have thought about it	I am committed to it	I've already done it
10	Discussed genetic testing with this child	1	2	3	4	5
11	Sought information regarding testing for a p53 mutation in this child	1	2	3	4	5
12	Made an appointment with a doctor/genetic counselor	1	2	3	4	5
13	Met with a doctor/genetic counselor	1	2	3	4	5
14	Had this child tested for a p53 mutation	1	2	3	4	5
15	Shared this child's genetic testing results with him or her	1	2	3	4	5

CONTINUED ON NEXT PAGE…

THE FOLLOWING QUESTIONS (15-19) ARE FOR INDIVIDUALS WHOSE CHILD HAS HAD GENETIC TESTING.

*If this child has **not** had genetic testing, please SKIP TO # 20.*

Please indicate how important you feel each of the following was in your decision to pursue genetic testing in this child using the 1-5 point scale. The following list includes reasons some people give for wanting to have genetic testing.						
		Not Important	Slightly Important	Somewhat Important	Important	Very Important
16	I would have been relieved to know that my child did not have a p53 mutation	1	2	3	4	5
17	My family's experience with cancer made me more concerned about my child's own risk for the disease	1	2	3	4	5
18	My child could do something to lower his/her cancer risk	1	2	3	4	5
19	I / My child could plan for the future	1	2	3	4	5
20	Other (please write)					

THE FOLLOWING QUESTIONS (20-24) ARE FOR INDIVIDUALS WHOSE CHILD HAS NOT HAD GENETIC TESTING.

*If your child has **had** genetic testing, this portion of the survey is complete. If you have other children whom you have not completed the survey for, please do so in the provided forms. If you have completed the questionnaire for all of your children, please turn to the last page.*

Please indicate how important you feel each of the following would be to you using the 1-5 point scale. The following list includes reasons some people give for wanting to have genetic testing.						
		Not Important	Slightly Important	Somewhat Important	Important	Very Important
21	I would be relieved to know that my child did not have a p53 mutation	1	2	3	4	5
22	My family's experience with cancer makes me more concerned about my child's own risk for the disease	1	2	3	4	5
23	My child can do something to lower his/her cancer risk	1	2	3	4	5

24	I / My child can plan for the future	1	2	3	4	5
25	Other (please write)					

The following list includes reasons some people give for NOT wanting to have genetic testing. Please indicate how important you feel each of the following would be for you using the same 1-5 point scale.						
		Not Important	Slightly Important	Somewhat Important	Important	Very Important
26	I'm afraid I would get too upset	1	2	3	4	5
27	I'm afraid my child would get too upset	1	2	3	4	5
28	I am concerned that having the test might cause problems with my child's insurance	1	2	3	4	5
29	There is nothing my child can do about getting cancer	1	2	3	4	5
30	I am concerned about my family's reaction	1	2	3	4	5
31	I am worried about how it would affect my child's future	1	2	3	4	5
32	Other (please write)					

Thank you for completing this section of the survey. If you have other children whom you have not completed the survey for, please do so in the provided forms. If you have completed the questionnaire for all of your children, please turn to the last page.

The following are questions about YOU. Please complete the following sections.

1 Gender	2 What is your marital status?	3 What is the highest grade or level of schooling you completed?
Male ☐ Female ☐	☐ Single ☐ Married ☐ Separated ☐ Divorced ☐ Widowed	☐ Some high school ☐ High school graduate ☐ Some college ☐ College graduate (4 Year Degree) ☐ Associate's degree ☐ Upper-level degree (Masters, PhD, MD)

4 What is your current occupational status?	5 What is your (combined) annual household income?
☐ Employed (Full Time) ☐ Employed (Part Time) ☐ Unemployed (Not seeking a job) ☐ Unemployed (Seeking a job) ☐ Homemaker ☐ Student ☐ Retired	☐ Less than $25,000 ☐ $25,000 - $50,000 ☐ $50,000 - $75,000 ☐ More than $75,000

Thank you very much for completing this questionnaire. The information you have provided has been very helpful and we appreciate your thoughtful answers.

Appendix C - Reminder Letter to Non-Responders

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Date

Name

Address

Dear

Over the last several weeks we have tried to contact you at the above address about our study *Attitudes of families with Li-Fraumeni Syndrome, a rare hereditary cancer predisposition syndrome towards predictive testing in children.* As of <*the date shown at the top of this letter*>, we have we have not received the questionnaire back from you nor have we received a refusal to take part in this study.

We are interested in obtaining information about parental attitudes toward p53 genetic testing in their children. The questions that you will be answering will help the researchers and physicians to better understand the needs of families with children at risk for LFS and provide the appropriate services. Participation in the study involves signing an informed consent and completing a questionnaire.

If you are interested in taking part in this study and have lost the informed consent and questionnaire, we have enclosed another copy for your convenience. If you do not wish to take part in this part of the study, please indicate this and also return the blank questionnaire to us in the pre-addressed envelope.

We appreciate your participation in the study. If you have any questions, please contact me at your earliest convenience at 713-745-3477 or Dr. Louise Strong at (713) 792-7555.

Sincerely,

Leslie Newman, BS
U.T. M.D. Anderson Cancer Center
1515 Holcombe Blvd., Box 209
Houston, Texas 77030-4009

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Vita

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