IMPACT OF CLEFT LIP WITH OR WITHOUT CLEFT PALATE ON 
PARENTAL KNOWLEDGE OF RISK AND OPINIONS OF GENETIC TESTING

by

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Impact of Cleft Lip with or without Cleft Palate on Parental Knowledge of Risk and Opinions of Genetic Testing

Abstract

by

HANNAH LEIGH COLABRESE

The purpose of this study was to examine the uptake and impact of environmental and genetic information by parents of children with isolated CL/P. A 33-item questionnaire queried parents on impact of the diagnosis, beliefs regarding the origin of CL/P, recurrence risk, risk reduction, interest in genetic testing, and perceived barriers to testing. A recurrence risk of 2-5% was reported by 40.4% of the participants. No variables were identified as significant predictors of overestimating risk. The majority of participants indicated interest in testing (59.1%, 97/164). Parents interested in testing perceived greater emotional burden (p= .006). Predictors of interest included greater emotional burden (OR=1.19; p =.030) and minority status (OR=5.78; p =.030). Parents of affected females were more likely to be interested in testing, particularly as perceived burden on family activities increased. This study indicates that, if developed, genetic counselors should participate in the testing process for this population.
CHAPTER I: INTRODUCTION

Orofacial clefting (CL/P and CPA) is one of the most common congenital anomalies with a worldwide incidence of approximately 1 in 700 live births. The two phenotypes, cleft lip with or without cleft palate (CL/P) and cleft palate alone (CPA), are typically described as separate entities due to differences in the embryological events leading to their formation. Each of these malformations can be observed as part of a syndrome or as isolated events. For the purposes of this study, only isolated CL/P cases will be examined.

Nonsyndromic CL/P is a multifactorial disorder presumed to result from a combination of both genetic and environmental etiologies. Classified as a major anomaly, this defect has both medical and cosmetic consequences for the patient. These impairments frequently require both immediate and long-term interventions and therapies. Detection during the prenatal period could provide time for parents to adjust to, and cope with, their child’s diagnosis. Additionally, prenatal detection could allow parents to become educated about their child’s cleft and begin to organize steps for care after birth.

Parents of a child with isolated CL/P can be given empiric recurrence risk figures for their future pregnancies. These risk numbers may vary depending on the number of affected individual in the family, their degree of relatedness, and the severity of each affected individual’s facial cleft. Thus, a recurrence risk may vary considerably for different families, but is generally less than 5%.

There is little converging evidence to support methods for risk reduction outside of the avoidance of known teratogens, such as alcohol consumption during pregnancy, or
being treated with anticonvulsants. However, multiple studies have been conducted to examine the effects of prenatal vitamins or folic acid supplementation during pregnancy to prevent orofacial clefts. Research has shown both positive and negative association of clefting and supplementation (Bille et al., 2007; Chevrier et al., 2007; Czeizel & Dudas, 1992; Czeizel, Timár, & Sárközi, 1999; Hayes, Werler, Willett, & Mitchell, 1996; Shaw, Lammer, Wasserman, O’Malley, & Tolarova, 1995; Shaw, Carmichael, Laurent, & Rasmussen, 2006; Werler, Hayes, Louik, Shapiro, & Mitchell, 1999; Wilcox et al., 2007), and there is no indication that the dosage of folic acid should be increased for individuals with a family history of CL/P.

Many studies have attempted to identify the genes or polymorphisms responsible for nonsyndromic CL/P. To date, few loci have been conclusively identified as playing a role in the genetic etiology of isolated orofacial clefting. As additional supporting evidence is obtained from genetic and epidemiological studies, more specific risk assessments may be possible for families with these genetic changes. This study was undertaken to determine what information parents have received regarding the risk of recurrence for cleft lip and palate in future pregnancies and how this may affect their opinions of genetic testing and utilization of such technology for prenatal management.

**Purpose of Study and Specific Aims**

The purpose of this study was to examine parental knowledge, interest in genetic testing, and impact of both environmental and genetic information by parents of children with isolated CL/P. It was hypothesized that parents who perceived their child’s orofacial cleft as more burdensome (i.e. greater impact of their child’s orofacial cleft on family functioning and parental emotions) would overestimate their recurrence risk and
have more interest in susceptibility testing for CL/P. This hypothesis was examined through the following aims:

1. Elicit parental perceptions of burden regarding physical and cosmetic impairments of their child’s cleft.
2. Determine parental knowledge of recurrence risk and possible risk reduction methods.
3. Explore parental interest in a genetic test for CL/P if it were available.

**Significance for Genetic Counseling**

The goal of this research was to gain insight into how parent(s) of a child with CL/P perceive their recurrence risk based on their individual experiences with their child’s cleft and what they believe they can do to decrease this risk. This study aimed to measure interest in susceptibility testing for genotypes that may lead to CL/P. As research progresses and more genes and polymorphisms become identified as genetic components of nonsyndromic CL/P, susceptibility testing may become available. Thus, gaining insight about parental understanding and attitudes before this technology is available will help genetic counselors to prepare for the future needs of this patient population.
CHAPTER II: BACKGROUND AND LITERATURE REVIEW

Cleft Lip and Palate

General Background

Orofacial clefting (CL/P and CPA), one of the most common congenital anomalies, results from a failure in fusion of facial and/or palatal structures during early embryonic development. Clefting defects are complex traits that are heterogeneous in their embryology, etiology, and phenotypes. Medical and social issues of these defects may include: failure to thrive, language development difficulties, poor and hypernasal speech, increased frequency of otitis media, conductive hearing loss, and psychological issues of peer acceptance or social isolation (Nussbaum, McInnes, & Willard, 2007). Thus, these abnormalities have a significant impact on oral or facial function and appearance.

Epidemiology and Phenotypes

The incidence of CL/P, estimated to be 1-2 in 1,000 live births, demonstrates ethnic and gender disparities. Incidences among ethnic groups vary significantly, with Native Americans having the greatest incidence of 3.6 in 1,000 live births, followed by Japanese, Chinese, Caucasian, Hispanic, and African Americans with the lowest incidence of 0.3 in 1,000 (Curtin, 1996). Males are two times (2:1) more likely to have CL/P than females, but this gender effect is reversed for cleft palate alone.

Phenotypically, cleft lip ranges from a small notch in the upper lip to a complete cleft involving the lip, palate, and nares. Approximately 25% of all cases of orofacial clefting involve only the lip, either unilaterally or bilaterally (Bergsma, 1979). When unilateral, left-sided involvement is twice as frequent and is the most common form of
cleft lip. However, about 50% of cases of facial clefting involve both the lip and palate (Bergsma, 1979). For cleft palate alone, multiple phenotypes exist including cleft uvula, submucosal cleft, and clefts in the primary and/or secondary palate.

**Syndromic versus Isolated Clefting**

Orofacial clefting exhibits multiple etiologies with two basic subdivisions: syndromic and nonsyndromic (isolated). Syndromic forms of clefting are further classified as part of a known syndrome with either a chromosomal or single-gene etiology, or as an unrecognized syndrome with multiple congenital anomalies. More than 400 syndromes have CL/P or CP as a feature, and approximately 30% of individuals with CL/P and approximately 50% of individuals with CP are classified as syndromic (Lidral, Moreno, & Bullard, 2008). Thus, a majority of individuals with an orofacial cleft have no associated malformations or other syndromic features. Classification of a cleft as isolated or nonsyndromic is typically given to an individual after a thorough dysmorphology examination.

**Inheritance and Etiology**

CL/P is generally thought to be caused by a combination of both genetic and environmental influences, and therefore is considered a multifactorial disorder. Due to its complex etiology, the specific factors leading to the development of an orofacial cleft have not been elucidated, but multiple sources of evidence support its inheritance pattern (Lidral & Moreno, 2005).

The majority of CL/P cases occur in families with no history of CL/P or any other birth defects, but when there is a positive family history of CL/P (20% to 30%), no
predictable pattern is seen (Merritt, 2005; Young, O’Riordan, Goldstein, & Robin, 2001). Regardless of family history status, there is an observed increase in risk for first-degree relatives after the birth of an affected individual (Cohen, Gorlin, & Fraser, 2003). Twin studies have observed a concordance of 33% for CL/P in monozygotic twins and 2-5% in dizygotic twins (Curtin, 1996), bolstering the evidence for both genetic and environmental components in the inheritance of CL/P.

The first occurrence or the unpredictable recurrence of orofacial clefting in a family may be explained by shared genetic factors and shared, but variable, environmental factors. Several environmental agents have been identified as teratogenic, and may possibly contribute to the development of a cleft. Such teratogens include: maternal smoking, maternal alcohol consumption, valproic acid or other folic acid antagonists, and deficits in maternal folate metabolism or nutrition. However, not every fetus exposed to such agents develops a cleft. This suggests that moderating factors exist, including genetic background, offering additional supporting evidence for multifactorial etiology.

Detection and Evaluation

High-resolution ultrasound is the only available technology allowing prenatal detection of an orofacial cleft. Although detection rates are operator-dependent, cleft lip is relatively easy to detect if a clear and appropriate image is obtained. But it is not uncommon for cleft lip to be first noted at delivery. Most palatal defects are discovered upon examination of the neonate (Wang, Leung, & Tang, 2007).

After an orofacial cleft has been detected, further evaluation is necessary to help determine the etiology and treatment prognosis. Prenatally, comprehensive ultrasound
can be utilized to rule out the presence of additional abnormalities. In infants, a dysmorphism examination must be performed to rule out syndromic forms of clefting. Specialists should be contacted for further and complete evaluation and further follow-up of these infants, as well as for discussion of treatment options and outcomes. This can be most effectively achieved by multidisciplinary craniofacial clinics.

Genetics of CL/P

Identifying the genetic component of a multifactorial trait is difficult because the heritable factors must be separated from environmental influences and critical time periods of development. Despite this challenge, the identification of genetic changes associated with nonsyndromic CL/P has progressed since the completion of the Human Genome Project. While the role of a few genes has been confirmed, the array of contributing genes and their interactions have yet to be fully determined.

Statistical analysis of families for multigenic and monogenic inheritance patterns has identified specific chromosomal regions containing genes that may contribute to nonsyndromic CL/P; it is postulated that 2 to 14 different loci may influence development of CL/P (Schliekelman & Slatkin, 2002). Using this information, different methods have been utilized in an attempt to identify these loci including linkage and association studies across the genome. Results of these studies have identified possible loci on chromosomes 1, 2, 4, 6, 14, 17, and 19 (Marazita et al., 2004). While several candidate genes for nonsyndromic CL/P have been identified, few have been confirmed. Some research efforts have focused on syndromes that have orofacial clefting as a major feature and exhibit a Mendelian inheritance pattern, especially van der Woude syndrome. Such studies have suggested that monogenic loci also act as susceptibility genotypes for
nonsyndromic CL/P. Variants in these genes that have been positively associated with isolated CL/P are assumed to contribute to approximately 10% of nonsyndromic orofacial clefting (Stanier & Moore, 2004).

*Interferon Regulatory Factor 6 (IRF6)*

Interferon regulatory factor 6 (*IRF6*) is a transcription factor located on chromosome 1q32-q41. Mutations in this gene cause van der Woude syndrome (VWS) and popliteal pterygium syndrome (PPS). *IRF6* was selected as a candidate gene for nonsyndromic clefting because of its association with these Mendelian disorders that exhibit orofacial clefting prominently in their phenotypes (Jugessur & Murray, 2005). Studies of *IRF6* mutations in mice suggest that these mutations repress the TGF-β signaling pathway, causing increased apoptosis in the epithelium before fusion of the palatal shelves (Cox, 2004).

In 2004, Zucchero *et al.* conducted a study of 8003 individuals, including those with a positive family history (n = 6775) and those without a family history (n = 1248) of clefting. Ten different populations (Vietnam, Brazil, Denmark, United States, etc.) were represented in this sample, and the subjects with an orofacial cleft were examined to rule out additional malformations or the presence of a syndrome. Thirty-six single nucleotide polymorphisms (SNPs) were analyzed, with particular emphasis on the SNP associated with the common V247I variant of *IRF6* (Zucchero *et al.*, 2004).

Using the Family Based Association Test software, the multiple alleles found at *IRF6* were tested for their association with CL/P. The association analysis determined that homozygosity for the V/V genotype was significantly associated with clefting (P<0.001), while the V/I and I/I genotypes were negatively associated with clefting.
(P<0.005). Additionally, a significant difference in the genotype frequency among probands and unaffected individuals (P<0.001) confirmed these associations, as the V/I and I/I frequencies were underrepresented in subjects with CL/P.

This study concluded that the SNP underlying the V274I variation displayed highly significant transmission disequilibrium, along with other SNPs within or surrounding IRF6. Zucchero et al. (2004) concluded that these variants, when occurring simultaneously and in certain combinations on a single chromosome, might lead to CL/P. Additional analyses of the study population revealed that the recurrence risk for siblings of an affected child with the V/V genotype ranged from nine to twelve percent, which is greater than the current empiric risk figures (2-5%) given to families after the birth of an affected child (Lidral et al., 2008; Zucchero et al., 2004).

_Forkhead Box E1 (FOXE1)_

_Forkhead Box E1 (FOXE1), located on chromosome 9q22-q33, is a transcription factor involved in embryonic pattern formation._ A study by Moreno et al. (2009) utilized a genome-wide linkage scan of individuals with nonsyndromic orofacial clefting to identify possible loci containing variants contributing to nonsyndromic CL/P. A combined total of 388 families was obtained from seven populations (e.g. Colombia, United States, Philippines), and a multi-stage analysis, including genotyping, association analysis, sequencing, and expression analysis, was performed. Initial results from the genome-wide association scan revealed a LOD score of 5.5 at chromosome 9q22-q33 (Moreno et al., 2009).

In the last stages of their association study, Moreno et al. (2009) used 34 SNPs to finely map a critical region of 9q containing four candidate genes, including _FOXE1_.

Using family-based association methods, the association of single SNPs with clefting phenotypes was examined and showed a strong association ($p = 1.45 \times 10^{-8}$) of genotypes 5' of FOXE1. Through these association methods and analysis of protein expression, other candidate genes within 9q22-q33 were excluded. In order to more clearly define the association of FOXE1 with isolated CL/P and CPA, genotyping of a 15 SNP cluster in FOXE1 was performed on specific cohorts. Moreno et al. (2009) determined that the associations for each SNP varied within the populations included in this study and were strongest in those of Caucasian background. Association patterns for all orofacial clefting phenotypes revealed three highly significant SNPs across all populations studied for all isolated cleft phenotypes (CL, CL/P, CPA), specifically rs1867278 ($p = 7.44 \times 10^{-13}$), rs3758249 ($p = 5.01 \times 10^{-13}$), and rs4460498 ($p = 6.51 \times 10^{-12}$). Thus, Moreno et al. (2009) identified FOXE1 as a major gene for CL/P in multiple populations.

*Muscle Segement Homeobox 1, (MSX1)*

Studies of Msx protein function show high expression in epithelial and mesenchymal tissue throughout craniofacial development (van den Boogaard et al., 2008). Although certain association studies suggest that MSX1 mutations may be family-specific, this gene has been implicated in nonsyndromic clefting.

A 2003 study by Jezewski et al. recruited 917 individuals with isolated clefting ($n = 799$ CL/P; $n = 118$ CPA), and 500 control individuals. The entire MSX1 gene was sequenced in each individual in attempt to detect variants that might confer susceptibility for orofacial clefting. When a sequence variant was detected, parents ($n = 324$) were screened to validate the variant. Forty-eight variants were detected in MSX1, and these were categorized as “common” if detected in more than 1% of the study population. Of
the twenty-six variants designated as common alleles, 11 showed linkage disequilibrium. The authors suggested that more MSXI mutations exist, which may or may not be deleterious (Jezewski et al., 2003).

Fifteen variants in both coding and noncoding regions of MSXI were identified as possibly being deleterious (Jezewski et al., 2003). Of the 16 individuals who had these variants, only one was a control subject without a personal or family history of clefting. A power calculation of the case and control numbers suggested that sequencing of 600 to 12,000 control individuals would be required to determine the significance of any one variant. The authors determined that this was not practical, and instead grouped all of the variants together for statistical analysis (Jezewski et al., 2003). When the frequency of all disease-associated variants was compared between patients and controls, a p-value of .017 was obtained. However, when each variant was tested with no Bonferroni correction, no single variant was determined as significant ($\alpha = 0.003$).

Jezewski et al. (2003) concluded that if the mutations detected in this study are confirmed as causal mutations for nonsyndromic clefting, these particular MSXI variants would contribute to approximately 2% of all cases of nonsyndromic CL/P. However, the authors suggest that such mutations may be more likely to be specific to families with a positive history of clefting.

Additional studies conducted in other populations (Otero, Gutierrez, Chaves, Vargas, & Bermudez, 2007; Park et al., 2007) have also found an association between MSXI and nonsyndromic clefting. Several types of mutations (single base insertions, one to six base deletions, intronic CA repeats, substitutions) have been identified in this gene,
which have not been detected in the control subjects. Thus, *MSXI* remains a strong candidate gene for isolated CL/P.

*Other Genes*

Candidate gene studies have potentially identified polymorphisms or variants observed in up to 25% of individuals with cleft lip with or without cleft palate (Lidral *et al.*, 2008). Several other genes have been identified as being causative of nonsyndromic clefting, such as *GABRB3, SUMO1, TGFA, TGFB1, TGFB3, BCL3*, and *RARA* (Alkuraya *et al.*, 2006; Ardinger *et al.*, 1989; Chenevix-Trench, Jones, Green, Duffy, & Martin, 1992; Gaspar *et al.*, 2002; Inoue *et al.*, 2008; Lidral, *et al.*, 2008; Stein *et al.*, 1995). *GABRB3, SUMO1, and TGFA* are strongly expressed in developing craniofacial or palatal tissues. The functions of *BCL3* and *RARA* in craniofacial development have not been fully described (Alkuraya *et al.*, 2006; Carinci, Scapoli, Palmieri, Zollino, & Pezzetti, 2007; Inoue *et al.*, 2008). Linkage studies have identified variants within the region containing *TGFB3* in approximately 15% of families with CL/P. *BCL3* and *TGFB1* remain candidate genes due to linkage studies showing association of CL/P and chromosome 19q (Lidral *et al.*, 2008). However, studies of these 7 genes and their chromosomal regions typically had small sample sizes or focused on specific populations. These findings have not been confirmed. Larger studies with representative samples are needed to further evaluate the possible involvement of these candidate genes.

*Environmental Influences on CL/P*

Environmental influences have the potential to significantly modify the phenotype of a multifactorial trait. Studies of monozygotic twins have revealed concordance of
approximately 33% (Bergsma, 1979), suggesting that environmental factors play a large role in CL/P. While a number of different exposures have been studied, including alcohol, tobacco smoke, lack of proper nutrients, and chemical solvents, there is no consensus regarding a dosage effect for these exposures. It is postulated that variation across individuals may be related to mutations in genes in specific metabolic pathways, nutritional status, or teratogenic exposures which may alter the in utero environment and subsequently affect the risk for orofacial clefting (Chevrier et al., 2005).

Metabolism

Folic acid supplementation and its effectiveness in preventing birth defects has received great attention in research and clinical practice. Its efficacy in reducing the risk of neural tube defects has raised questions of whether it may be effective in decreasing the incidence other major birth defects such as cleft lip (Botto, Olney, & Erickson, 2004). Numerous studies have attempted to determine if folic acid exhibits a protective effect against orofacial clefting; however, no consensus has been reached. It has also been suggested that the effects of folic acid may be dose-dependent. However, polymorphisms in genes that regulate folate metabolism may be moderating the effects of folic acid, possibly contributing to the inconsistent effects observed.

A meta-analysis by Johnson & Little (2008) sought to evaluate the evidence for the role of folate in orofacial clefting. Twenty-two studies regarding CL/P and supplementation, totaling 5,717 subjects, were included in the meta-analysis. Eighteen of the 22 studies looked at multivitamin use, and of these, 13 included folic acid. In a majority of the studies, multivitamin supplementation generally occurred from the
periconceptional period through the first trimester of pregnancy. However, many studies did not report the amount of folic acid in the multivitamin.

The results of the meta-analysis suggested that vitamin supplementation in general initiated before or during pregnancy was associated with a decreased risk of CL/P (OR 0.75; 95% CI 0.65-0.88) (Johnson & Little, 2008). When the analysis was restricted only to studies that specifically mentioned the inclusion of folic acid (n = 13), the association of supplementation was less pronounced (OR 0.82; 95% CI 0.70-0.97) (Johnson & Little, 2008).

Methylenetetrahydrofolate reductase (MTHFR) is a well-studied folate metabolism gene with over 60 single nucleotide polymorphisms (SNPs) contributing to reduced enzymatic activity. Although the protein remains functional in the presence of these SNPs, its efficacy in the folate metabolic pathway is impaired (Prescott & Malcolm, 2002). The two most common SNPs that cause decreased activity are at positions 677(C>T) and 1298(A>C). Johnson & Little (2008) evaluated 13 studies of MTHFR genotypes and orofacial clefting. They determined that there was no association between infant or maternal MTHFR genotypes at these two common SNPs and the occurrence of CL/P or CPA. But, paternal MTHFR genotypes at the 677(C>T) allele were associated with an increased risk for CL/P if the genotype was TT rather than CC (OR 1.63; 95% CI 1.00-2.65).

Johnson & Little (2008) drew several important conclusions from their meta-analysis. First, they concluded that there was no strong evidence that folate has an important role in the etiology of orofacial clefts. They emphasized that other components of multivitamins could be involved or acting in combination with folate to produce a
protective effect, and that this possibility could not be excluded. Second, although some studies reviewed revealed a decrease in the occurrence of CL/P with widespread folic acid fortification or supplementation of food sources, a marked decrease in prevalence, similar to that for neural tube defects, was not observed. Third, the effects of folic acid might be dose-dependent and therefore the role of folate could not be properly determined. Lastly, analyses of genes involved in folate metabolism, particularly MTHFR, did not provide conclusive evidence for a role in clefting etiology and required further study.

Because of the lack of a clear association between facial clefting and folic acid, there is no consensus among health professionals regarding supplementation to prevent orofacial clefting. The American College of Obstetrics and Gynecology (ACOG, 2003) recommends folic acid supplementation to reduce the prevalence of neural tube defects, but does not specifically recommend the use of folic acid to reduce the incidence of CL/P. Other health organizations, such as the March of Dimes, support this recommendation by ACOG and comment that there is no known detrimental effect to increased folic acid intake and supplementation may act to reduce the risk.

**Teratogens**

A teratogen is any substance that interferes with normal embryonic development and induces the formation of fetal malformations. Two important considerations regarding teratogenic exposures are the dosage and timing of the teratogen during development. The most frequently studied agents include alcohol, tobacco smoke, and medications such as folic acid antagonists. Such substances have been implicated as environmental components of the multifactorial etiology of orofacial clefting.
Maternal alcohol consumption can be detrimental to fetal development, potentially causing physical defects, mental deficits, or pregnancy complications. These effects may or may not be observed after consuming alcohol. One of the most severe results of alcohol consumption during pregnancy is fetal alcohol syndrome (FAS), which is characterized by multiple craniofacial malformations, growth retardation, and defects in the central nervous system. CL/P has been observed in 9 to 18% of individuals with FAS (DeRoo, Wilcox, Drevon, & Lie, 2008) suggesting that alcohol consumption may play a role in disrupting lip and palate formation.

A recent epidemiological study (DeRoo et al., 2008) surveyed 1,366 mothers, including women who had a child with CL/P (n = 377), about environmental exposures and nutrition during the first trimester. The authors found that women who had 5 drinks on one occasion during the first trimester were twice as likely to have a child with cleft lip (OR 2.2; 95% CI 1.1-4.2), and these effects were exacerbated if this consumption pattern occurred on three or more occasions during the first trimester (DeRoo et al., 2008). These findings are consistent with several other studies regarding an association between significant alcohol consumption and CL/P (Munger et al., 1996; Romitti et al., 1999; Shaw & Lammer, 1999; Werler, Lammer, Rosenberg, & Mitchell, 1991), supporting the recommendation that women should abstain from alcohol during pregnancy.

Smoking during pregnancy has been associated with prenatal growth retardation, low birth weight, prematurity, and placental complications. It is thought that the vasoconstrictive effects of smoking impact the fetus and placenta, and are the basis for the observed consequences. A meta-analysis of 24 association studies of tobacco smoke
and orofacial clefting (Little, Cardy, & Munger, 2004) concluded that maternal smoking during pregnancy moderately increases the risk for isolated CL/P (RR 1.35; 95% CI 1.25-1.46). Additionally, a weak dose-response effect was found suggesting that a causal relationship between smoking and cleft formation exists (Little et al., 2004).

When evaluating the possibility of teratogenic effects from alcohol, tobacco smoke, or medications, the probability that these exposures may occur together must be considered. Thus, they may act as confounding variables of each other and the observed associations with clefting may be more complex. However, it is clear that each of these exposures, either alone or in combination, may have detrimental effects.

**Folic Acid Antagonists**

Studies have examined the effects of folic acid antagonists in orofacial clefting. It was suggested that if folic acid supplementation decreases the risk of CL/P, then folic acid antagonists should increase the risk of CL/P (Hernandez-Dias, Werler, Walker, & Mitchell, 2000; Little et al., 2008; Metneki, Puho, & Czeizel, 2005; Werler et al., 1999). Dihydrofolate reductase inhibitors, such as methotrexate or trimethoprim, and antiepileptic drugs (valproic acid) are two classes of folic acid antagonists, which act by displacing folate from the enzyme catalyzing its conversion to the more active metabolite, 5-methyltetrahydrofolate. This prevents synthesis of substrates for other enzymes in the folate metabolic pathway, impairing folate absorption, or increasing folate degradation (Hernandez-Dias et al., 2000).

A multicenter case-control study of women treated with a folic acid antagonist during pregnancy (n = 15,319) was completed to determine if these medications increase the risk of birth defects (Hernandez-Dias et al., 2000). Mothers were interviewed six
months after their delivery about their use of medications during pregnancy. Of those interviewed, 13% of mothers had a child with orofacial clefting. Other birth defects included cardiovascular malformations (25%) and urinary tract malformations (7%). This represented a relative risk of 2.6 for CL/P in children of women taking dihydrofolate reductase inhibitors during pregnancy.

Additionally, Hernandez-Dias et al. (2000) observed that treatment with dihydrofolate reductase inhibitors without multivitamin supplementation during pregnancy increased the relative risk of CL/P and CPA to 4.9 (95% CI 1.5-16.7). Treatment with antiepileptic drugs during pregnancy was also associated with an increased risk of having a child with an orofacial cleft (RR 2.5; 95% CI 1.5-4.2) (Hernandez-Dias et al., 2000). The authors concluded that unlike dihydrofolate reductase inhibitors, concomitant use of antiepileptic drugs and multivitamins did not reduce the risk of orofacial clefting (Hernandez-Dias et al., 2000).

Parental Perceptions, Parental Attitudes, and Family Impact of CL/P

When parents learn of a fetal or neonatal abnormality, the anticipation of a healthy baby is dramatically changed. The immediate feeling upon receipt of such news has been simply described as “shock” (Rey-Bellet & Hohlfeld, 2004). Parents are forced to put the diagnosis into perspective – what does this mean for their child and what do they do next? Of the studies that have been conducted, the authors provide essential insight for anyone involved in the care of these children and their parents. Studies focusing on prenatal diagnosis in general have found that most expectant parents want information during the prenatal period, because this information can help with access to
resources during or after the pregnancy (Berk, Marazita, & Cooper, 1999; Lippmann, 1999; Nusbaum et al., 2008; Rey-Bellet & Hohlfeld, 2004; Young et al., 2001).

Berk et al. (1999) conducted a descriptive comparison study of physicians (n = 570) and parents of children with an orofacial cleft (n = 97). A questionnaire addressing parental desire for involvement, desire for knowledge, and reaction to learning of a birth defect were administered to each group. They observed that parents have strong desires to gather information and become actively involved when making prenatal decisions (Berk et al., 1999).

Lippmann (1999) carried out a qualitative study (n = 36) examining how women in a prenatal setting used their experiences and knowledge of medical concepts during their decision-making process on whether to undergo prenatal diagnosis. This study found that women combined medical information with their own values and experiences, termed “embodied knowledge.” The author described that decision-making for prenatal diagnosis is an interactive process (Lippmann, 1999). Lippmann (1999) also concluded that genetic counselors or other health professionals should listen to and validate a woman’s experiences, while recognizing that her decisions are likely to not be a direct result of receiving distressing medical information (Lippmann, 1999).

Nusbaum et al. (2008) conducted a qualitative study of 20 parents whose infants had isolated CL/P. A semi-structured interview elicited parental attitudes on various aspects of their child’s diagnosis. Many participants were dissatisfied with the manner in which the diagnosis was presented, which included concerns about not receiving educational information or a referral to a craniofacial center (Nusbaum et al., 2008). The authors discovered that after learning their child had CL/P, women attempted to recall
their actions during pregnancy and the possible impact those actions may have had on
their baby’s development and health (Nusbaum et al., 2008). Parents reported that
prenatal diagnosis allowed them to prepare for the birth, including gathering information
about feeding, surgeries, and resources available through regional treatment clinics
(Nusbaum et al., 2008). These data suggest that providing accurate information in a
timely and supportive manner may aid in the interpretation and decision-making
processes of parents dealing with the diagnosis of CL/P.

Nusbaum et al. (2008) included a single question to ask parents if they would
utilize a genetic test for clefting if it were available. The authors found that a majority of
parents expressed interest; however, the respondents questioned the utility and
interpretation of such testing (Nusbaum et al., 2008). Participants cited the lack of in
utero treatment, the interpretation of “whatever percent chance,” and the limited impact
of the result upon the decision to have more children as reasons for not pursuing genetic
testing (Nusbaum et al., 2008). While Nusbaum et al. (2008) focused on analyzing
parental attitudes surrounding a clefting diagnosis, they only partially assessed parental
interest in genetic testing. Additionally, the authors did not address issues of recurrence
risk or characterize parental opinions of genetic testing.

Retrospective studies (Rey-Bellet & Hohlfeld, 2004; Young et al., 2001) have
determined that parents initially desire basic and essential information about their child’s
orofacial cleft and that a majority of the educational content covered in initial
appointments can be addressed during follow-up appointments. Young et al. (2001)
conducted a descriptive study of 38 parents of a newborn with CL/P. The authors
concluded that critical points to be covered in initial counseling included issues of
normalcy, physical appearance, and reassurance that the parents did not cause their baby’s cleft (Young et al., 2001). They found that topics including etiology, surgical repair, and the genetic basis of CL/P were not an immediate concern.

Rey-Bellet and Hohlfeld (2004) conducted a retrospective, descriptive study of 29 couples receiving genetic counseling for their child’s orofacial cleft. When evaluating the efficacy of genetic counseling following the diagnosis of CL/P, the authors found that parents had many misconceptions about the defect. Reported beliefs about CL/P included that the defect was an open wound and therefore painful and life threatening, and that the defect was associated with impaired intelligence. The authors concluded that it was important to provide the appropriate counseling and management, which could be provided through a multidisciplinary craniofacial clinic.

Finally, the family impact and quality of life in children with CL/P has been examined across age groups by Kramer and colleagues (Kramer, Baethge, Sinikovic, & Schliephake, 2007; Kramer, Gruber, Fialka, Sinikovic, & Schliephake, 2008; Kramer, Gruber, Fialka, Sinikovic, & Schliephake, 2009). In their series of studies, Kramer et al. (2007; 2008; 2009) used the Impact on Family Scale (IOFS) to assess the impact of a child’s isolated orofacial cleft on multiple dimensions of family life (financial impact, social relationships, personal impacts, coping/mastering strategies, concerns of siblings). In a study of parents with children between the ages of 6 to 24 months with isolated orofacial clefts (n = 130), Kramer et al. (2007) discovered that, in general, the family impact of the child’s diagnosis was relatively small. In all measured dimensions of families with young children, the greatest effect was on personal impact and difficulty with coping/mastering for the family, and the lowest effect was financial impact. Kramer
et al. (2007) observed that of all cleft phenotypes, families raising a child with cleft lip (unilateral or bilateral) experienced the most difficulty with coping, whereas families raising a child with cleft palate had the highest IOFS scores in all other dimensions, indicating the greatest negative impact.

When Kramer et al. (2008) studied families raising preschool aged children with orofacial clefts, their results were consistent with their previous study, showing that the family impact of their child’s cleft diagnosis remained relatively small. Personal impact and coping/mastering persisted as the most affected family dimensions, with families with a child with cleft lip experiencing greatest difficulty with coping/mastering. Although in this study cohort, families including children with diagnoses of CL/P also had increased personal impact scores, along with children with cleft palate.

In their most recent study, Kramer et al. (2009) examined families raising children aged 8 to 12 years with an orofacial cleft. Again, the greatest effects were observed for coping/mastering and personal impact. In this age group, a gender discrepancy was noted with respect to coping/mastering strategies, showing that families with boys with CL/P or CPA experienced more significant effects on coping/mastering than those families with girls. Reviewing all of their results over the three researched age groups, Kramer et al. (2009) concluded that IOFS scores are similar across age groups, suggesting that the family impact of a child’s orofacial cleft, specifically regarding coping mechanisms and strategies, does not change as the affected child ages and develops.
Summary

Orofacial clefting is one of the most common birth defects, causing physical and cosmetic impairment. Because the phenotype and severity of the defect is variable, each affected child and their family may experience different impacts on growth and development. Although several genes contributing isolated forms of clefting are under investigation, the complex etiology of the defect has created significant barriers to progress in this area. Additionally, literature exploring the usefulness of prenatal vitamins or folic acid supplementation in decreasing risk for orofacial clefting is inconclusive. Due to the conflicting nature of these studies and the lack of a consensus statement by professional organizations, the counseling of families for isolated CL/P may be subject to significant variation by providers. Recurrence risk estimates are based on empiric data, thus are nonspecific for families that may be at greater risk due to mutations in susceptibility genes.

This study was designed to determine the impact of a child’s diagnosis of isolated CL/P on the family, and evaluate parental perceptions and knowledge regarding various aspects of their child’s orofacial cleft, with particular attention to the concepts of recurrence risk, risk reduction methods, and future genetic testing. It is anticipated that this information will help genetic counselors identify deficits or misconceptions in knowledge that could be addressed during counseling, as well as help to gauge parental interest in genetic testing if it were to become available in the future.
CHAPTER III: METHODS

Study Design

This exploratory, descriptive study sampled parents who enrolled their child with a diagnosis of CL/P in services provided by the Bureau for Children with Medical Handicaps (BCMH), a state registry maintained by the Ohio Department of Health (ODH). A 33-item mailed questionnaire was sent to the parent(s) of each child to assess the parental perceptions of burden associated with a child’s cleft, determine the information parents have received regarding recurrence risk and risk reduction, and describe their opinions about genetic testing for isolated CL/P.

Participants

Parents were invited to join the study by a mailed questionnaire. The following inclusion criteria were used:

1. The child must have an isolated CL/P as determined by the absence of additional physical abnormalities or mental deficiencies, per parent report

2. The affected child must be 18 years or younger.

3. The parent(s) must be at least 18 years old.

Data from participants who did not meet the inclusion criteria were excluded from the study.
Recruitment and Mailing Process

Potential participants included parent(s) of a child actively enrolled in the BCMH registry for an orofacial cleft. These participants were recruited by sending a mailed questionnaire to the child’s home address listed in the registry as of April 2010.

The process for mailing the surveys to participants is as follows. Envelopes with a BCMH logo/designation were sent to the researcher(s) at Case Western Reserve University and a cover letter from BCMH (Appendix D) was included with the survey. The materials within the BCMH envelopes were included in the following order: BCMH cover letter, invitation to participate from Case Western Reserve University (Appendix E), 33-item questionnaire (Appendix F), and a postage-paid, business reply envelope addressed to the researcher(s) at Case Western Reserve University. The sealed envelopes were delivered to BCMH. At BCMH, printed labels with the addresses for the participants (those actively enrolled in BCMH under the condition orofacial cleft) were applied to each envelope by designated staff members of BCMH. Neither the envelopes nor the surveys were coded before they were mailed. The envelopes were mailed once the labels were affixed.

The cover letter from BCMH informed parents that BCMH had mailed out the surveys directly, and that the researchers at Case Western Reserve University did not have access to any names or addresses. The invitation to participate instructed the participant not to include any identifying information (name, child’s name, etc.) on the survey or prepaid envelope (name or address). This invitation emphasized the confidential nature of the study data. As of April 2010, there were 1,331 individuals with CL/P aged 0 to 18 actively enrolled in BCMH. The invitation to participate was
addressed specifically to the parent(s) of the enrolled child. Only designated staff members of BCMH were involved with the labeling process, thus the researcher(s) at Case Western Reserve University had no access to patient names or addresses.

Participation was voluntary and responses to the questionnaires were anonymous. By completing the survey, consent was implied. If the parent wished to participate, he or she completed the questionnaire and returned it using a provided, postage-paid, business reply envelope. If the parent(s) did not wish to participate, they were instructed to discard the contents of the mailed envelope.

**Questionnaire Design**

The questionnaire was designed by the researcher, and was further developed by input from the Director of the Genetic Counseling Training Program at Case Western Reserve University (ALM), a board certified genetic counselor (DC), and two clinical geneticists (LK and AM). Two members of a survey development team at Case Western Reserve University reviewed the final draft of the questionnaire.

The questionnaire was divided into three sections, totaling 33 questions (Appendix F). All of the questions were forced-choice; however, ten questions provided parent(s) with the opportunity to provide additional information and a free response field was included at the end of the questionnaire.

The first section of the questionnaire focused on demographics, family history, and clinical information about the child’s cleft diagnosis. The multiple choice questions covered topics such as age, gender, severity of the child’s orofacial cleft, presence of individuals in the family with an orofacial cleft and their degree of relatedness to the affected child, and current stage of management for the child’s orofacial cleft. In order to
determine whether or not the child’s orofacial cleft could be assumed to be isolated, a checklist of physical and mental features that may be associated with syndromic forms of CL/P was included. When the data from the completed surveys were reviewed, all questionnaires that indicated a child with any of the features listed that are suggestive of syndromic CL/P were excluded from the analyses.

**Aim 1: Elicit parental perceptions of burden regarding physical and cosmetic impairments of their child’s cleft.** In order to assess parental perceptions of burden (i.e. impact of their child’s orofacial cleft on family functioning and parental emotions), the Family Impact Scale (FIS) (Locker et al., 2002) was adapted for use in this study.

The FIS was developed as a component of the Child Oral Health Quality of Life Instrument (COHQOL©) and validated for orofacial conditions by Locker et al. (2002). Within the larger instrument, the FIS was administered to parents or caregivers of children with an orofacial condition, including clefting. The FIS consisted of 14 questions divided into four sections, defined as parental/family activity, parental emotions, family conflict, and financial burden. Cronbach’s alpha for the entire 14-item scale was 0.83. The alphas for the multi-item subscales included in this study were -0.72 for parental and family activity and -0.70 for parental emotions. The financial burden subscale consisted of a single item, thus alpha could not be calculated.

The FIS was shortened to a 10-item scale for this study. For the purposes of this study, the family conflict section was eliminated to reduce respondent burden and because the child’s argumentative behaviors were not a focus for this study. The FIS contained questions used a four-point ordered scale, with answers describing frequencies including never, once or twice, sometimes, and often/everyday. In order to emphasize
that the questions were to be answered about the participant’s child with a cleft, phrases including “because of your child’s cleft” or “his or her cleft” were added to each item.

**Aim 2: Determine parental knowledge of recurrence risk and factors associated with possible recurrence risk reduction, and Aim 3: explore parental interest in a genetic test for CL/P, if it were available.** The third section of the questionnaire was designed to assess parental knowledge of recurrence risk and possible recurrence risk reduction options, as well as parental interest in a genetic test for CL/P if it were available. The third section of the questionnaire contained multiple-choice items with opportunities for the participants to elaborate. Only biological parents of a child with an orofacial cleft were asked to complete this section.

Three questions were designed to gather information about recurrence risk and sources of risk information. The first question asked whether a specific family member or members were perceived as the cause - genetically, environmentally, or otherwise - of the child’s cleft. The second question asked participants to identify their recurrence risk, which included extreme (0% and 100%), multifactorial (2 to 5%), and Mendelian (25% and 50%) risk figures. The third question asked parent(s) to identify all health care professionals with whom they had discussed risk information.

A single item was designed to determine what information or beliefs the parent(s) had about methods for risk reduction during pregnancy. Common teratogenic exposures (tobacco and alcohol), prenatal vitamins, and folic acid were included as options for risk reduction. Additionally, alternative reproduction methods of donor eggs and donor sperm, as well as the option of having no more children, were included. When designing this question, an Internet search of discussion boards and support websites for parents of
a child with a orofacial condition were searched and commonly reported beliefs of proper nutrition and exercise were incorporated into this question. In order to elicit any beliefs not included in the question, an option of “Other (Please describe)” was included.

Finally, interest in genetic testing, individuals to be tested, and barriers to testing were presented as contingency questions. Parent(s) who indicated interest in genetic testing were asked about on who they would be interested in having tested and what, if any, barriers they perceived to proceeding with testing. Parent(s) who indicated no interest in genetic testing were asked to skip to the end of the questionnaire where they were queried on perceived barriers to testing. Possible barriers to testing were generated from common reasons or beliefs that prevent individuals from proceeding with a genetic test, such as cost or anxiety.

After the questionnaire was designed, three individuals without a clinical or scientific background were asked to complete the questionnaire. Additional instructions prior to each part of the questionnaire were clarified, based on their suggestions or questions while completing the survey. Based on these individuals, it was determined that the time required to complete the questionnaire ranged from 5 to 15 minutes.

Statistical Analysis

Data were entered into Predictive Analytics SoftWare (PASW), or SPSS, version 18.0, for analysis. Descriptive statistics were used to describe the study population and analyze the discrete responses to the questionnaire. Statistical comparison of frequency data was performed using Chi-square analyses and means were analyzed using Student’s t-test. When comparing subpopulations within the study sample, Levene’s Test for Equal
Variances was performed prior to further statistical analyses. For all t-tests, the level of significance was set at $p \leq 0.05$.

The hypothesis that parents perceiving greater burden from their child’s diagnosis would be more likely to overestimate their recurrence risk was evaluated by a multivariate regression analysis. Possible association between parental perception of burden and interest in genetic testing was determined by a bivariate logistic regression. Interactions of study variables were tested for association by logistic regression.

Qualitative Data Analysis

Qualitative data were obtained from the questionnaires either by answer choices allowing elaboration (e.g. “Please describe.”) or from a free response question at the end of the questionnaire. Data from the free response question were analyzed for dominant themes and categorized accordingly by the researcher (Appendix G). A second researcher (ALM) independently reviewed the classification of free responses and their classifications for agreement and accuracy.

Data Safety and Monitoring

This study was approved by the Institutional Review Boards of University Hospitals Case Medical Center (Appendix A) and the Ohio Department of Health (Appendix B).

Questionnaires were numbered sequentially as they were received and the dates of arrival and dates of data entry were recorded. After data was entered, all questionnaires were stored sequentially and only the researchers had access to the questionnaires for further review and analysis. To ensure appropriate progress and execution of the study
and its methods, the researcher reviewed the study’s progress monthly with various committee members.
CHAPTER IV: RESULTS

Response Rate

At the time of mailing, there were 1,331 children actively enrolled in BCMH under the condition of orofacial cleft. Of the 1,331 mailings, 27 were returned to BCMH because they were undeliverable. Of the 1,304 questionnaires that were successfully mailed, 391 questionnaires were returned to the researcher(s) at Case Western Reserve University (Table 1). Two questionnaires were blank and one was damaged during handling and unusable. The overall response rate for the study was 30.0%.

<table>
<thead>
<tr>
<th>Number of children (ages 0-18) actively enrolled in BCMH for CL or CL/P</th>
<th>1,331</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires returned to BCMH as “undeliverable”</td>
<td>27</td>
</tr>
<tr>
<td>Questionnaires received by the researcher(s) at Case Western Reserve University</td>
<td>391</td>
</tr>
<tr>
<td>Questionnaires damaged during mailing</td>
<td>1</td>
</tr>
<tr>
<td>Blank questionnaires, declined participation</td>
<td>2</td>
</tr>
<tr>
<td>Response rate ( = \frac{391}{(1,331 - 27)} \times 100 )</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

Table 1 – Response Rate

Included Population

A combination of data obtained about the parent’s age, the child’s age, and the clinical information about the child’s cleft was utilized to determine which participants met the inclusion criteria. Of the 388 questionnaires that were completed and returned intact, 176 (n = 45.4%) individuals met the above stated inclusion criteria. One questionnaire was incomplete and could not be used for statistical analysis. The final number of questionnaires included in this study is 175. The number of responses
analyzed for each question may vary because of missing responses. Additionally, parents not biologically related to their child with an isolated cleft (n = 11) were asked not to complete Part C of the questionnaire, which queried parents about recurrence risk, risk reduction, and genetic testing. Therefore, the responses analyzed for Part C are no greater than 164.

Demographic Information

Demographic information of the respondents is summarized in Table 2. Respondents excluded from the study did not differ demographically from the included population, although statistical comparison of categorical data between included and excluded populations was limited by small sample sizes for some criteria. Of the 175 respondents included in this study, a majority of the questionnaires was completed by the biological mother (88.6%). The mean age of respondents was 35.6 years (SD = 7.9; range = 20-62 years) and a majority of the respondents described their race as White (90.9%, 159/175). Approximately two-thirds of participants (62.6%, 109/174) had some college education or higher.
<table>
<thead>
<tr>
<th>Relationship to child with a cleft (n = 175)</th>
<th>n</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological mother</td>
<td>155</td>
<td>88.6</td>
</tr>
<tr>
<td>Biological father</td>
<td>7</td>
<td>4.0</td>
</tr>
<tr>
<td>Biological mother and father</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Adoptive mother</td>
<td>7</td>
<td>4.0</td>
</tr>
<tr>
<td>Adoptive mother and father</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respondent age (n = 171)</th>
<th>Mean = 35.6 years; SD = 7.86; range = 20-62 years</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Respondent race (n = 175)</th>
<th>American Indian</th>
<th>1</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asian</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Hispanic or Latino</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>159</td>
<td>90.9</td>
</tr>
<tr>
<td></td>
<td>Two or more races</td>
<td>6</td>
<td>3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education (n = 174)</th>
<th>8th grade or less</th>
<th>2</th>
<th>1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some high school, no GED</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>GED</td>
<td>7</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>High school diploma</td>
<td>52</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td>Some college</td>
<td>41</td>
<td>23.6</td>
</tr>
<tr>
<td></td>
<td>College</td>
<td>53</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td>Graduate or Professional school</td>
<td>15</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Table 2 – Demographics of Respondents

Respondents were asked about personal and family histories (biological partner and extended family members) of orofacial clefting (Table 3). Six non-biological parents reported information about the child’s biological parents and family’s history of orofacial clefting as well.
Six biological mothers and 7 biological fathers were identified as having an orofacial cleft. Of these, two respondents reported that both biological parents had an orofacial cleft. There was a positive family history of orofacial clefting in extended relatives in 26.0% (44/169) of this population.

Of the 175 children with isolated clefts, the mean age was 8.0 years (SD = 5.1; range: 5 months-18 years) and the male-to-female ratio observed was 1.46:1 (104 males:71 females) (Table 4).

All four phenotypes (unilateral cleft lip, bilateral cleft lip, unilateral CL/P, bilateral CL/P) were reported in this population, with approximately half of the population reporting a phenotype of unilateral cleft lip and cleft palate (50.6%, 88/174). Most diagnoses were made in the delivery room (64.3%,110/171). At the time of this survey, a majority of the children were either between primary repair procedures (49.7%, 85/171) or did not require further surgery (42.7%, 73/171).

<table>
<thead>
<tr>
<th>Biological mother (n = 169)</th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cleft</td>
<td>163</td>
<td>96.4</td>
</tr>
<tr>
<td>Bilateral cleft lip</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Unilateral CL/P</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Bilateral CL/P</td>
<td>3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological father (n = 169)</th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cleft</td>
<td>162</td>
<td>95.9</td>
</tr>
<tr>
<td>Unilateral cleft lip</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Unilateral CL/P</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Bilateral CL/P</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Cleft palate alone</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extended family members (n = 169)</th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative family history</td>
<td>125</td>
<td>74.0</td>
</tr>
<tr>
<td>Positive family history</td>
<td>44</td>
<td>26.0</td>
</tr>
</tbody>
</table>

Table 3 – Personal and Family History of Orofacial Clefting
Demographics of Affected Children

Table 4 – Demographics of Affected Children

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child gender</strong> (n = 175)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104</td>
<td>59.4</td>
</tr>
<tr>
<td>Female</td>
<td>71</td>
<td>40.6</td>
</tr>
<tr>
<td><strong>Child age</strong> (n = 175)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean = 8.0 years; SD = 5.1; range = 5 months-18 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Orofacial cleft phenotype</strong> (n = 174)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral cleft lip</td>
<td>36</td>
<td>20.7</td>
</tr>
<tr>
<td>Bilateral cleft lip</td>
<td>12</td>
<td>6.9</td>
</tr>
<tr>
<td>Unilateral cleft lip and palate</td>
<td>88</td>
<td>50.6</td>
</tr>
<tr>
<td>Bilateral cleft lip and palate</td>
<td>38</td>
<td>21.8</td>
</tr>
<tr>
<td><strong>Time of diagnosis</strong> (n = 171)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During pregnancy</td>
<td>56</td>
<td>32.7</td>
</tr>
<tr>
<td>In the delivery room</td>
<td>110</td>
<td>64.3</td>
</tr>
<tr>
<td>Within 2 or 3 days of birth</td>
<td>5</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Treatment stage</strong> (n = 171)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not had first surgery</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Between cleft surgeries</td>
<td>85</td>
<td>49.7</td>
</tr>
<tr>
<td>Repaired, requiring no further surgery</td>
<td>73</td>
<td>42.7</td>
</tr>
<tr>
<td>Repaired, requiring secondary surgery</td>
<td>12</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Demographics of Excluded Children

Questionnaires representing 216 children were excluded from the study because they had an isolated cleft palate alone or were syndromic (Table 5), defined as the presence of an orofacial cleft and additional findings by parent report. Approximately 80% of the excluded population was reportedly syndromic.

Table 5 – Demographics of Excluded Children

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child gender</strong> (n = 211)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
<td>50.7</td>
</tr>
<tr>
<td>Female</td>
<td>104</td>
<td>49.3</td>
</tr>
<tr>
<td><strong>Orofacial cleft phenotype</strong> (n = 211)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syndromic with CL/P</td>
<td>100</td>
<td>46.3</td>
</tr>
<tr>
<td>Syndromic with cleft palate alone</td>
<td>70</td>
<td>32.4</td>
</tr>
<tr>
<td>Syndromic with unspecified phenotype</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Isolated cleft palate alone</td>
<td>37</td>
<td>17.6</td>
</tr>
</tbody>
</table>
Among the 107 children with cleft palate, 37 (34.6%) were determined to be isolated. This is less than the expected frequency reported from epidemiological data suggesting that 50% of children with a cleft palate have additional anomalies (Murray, 2010). Additionally, a female-to-male ratio of 1.31:1 was observed (21 females:16 males), which is slightly lower than epidemiological data suggests of a 1.5:1 female-to-male ratio for individuals with an isolated cleft palate alone.

Interest in Genetic Testing

A majority of respondents indicated interest in genetic testing (59.1%, 97/164). In order to test the proposed hypotheses regarding burden, recurrence risks, and interest in genetic testing, the study population of biological parents (n = 164) was then dichotomized into parents interested in genetic testing and parents not interested in genetic testing. The demographics between these two groups were compared and found not to be statistically different.

Family Impact Scale (FIS)

Two subscales were created from the data collected from the FIS to provide more detail about the burden of the child’s diagnosis. The rating scale used the following responses for statistical analysis: values: 0 = never, 1 = once or twice, 2 = sometimes, and 3 = often/everyday. A family activity subscale was created using the first five questions (Appendix F, questions 15-19) of the FIS, which addressed on daily activities and family life. A parental emotion subscale was created from the questions of FIS targeting multiple emotional dimensions (e.g. guilt, anxiety) (Appendix F, questions 20-23).
Financial burden was assessed by a single item. The responses were summed, resulting in potential maximum scores of 15 for the family activity and 12 for the parental emotion subscales. Higher scores indicate a greater burden perceived by the parent(s).

The subscale scores were averaged for parents interested in genetic testing and parents not interested in genetic testing (Table 6). Parents interested in genetic testing had higher mean scores on the family impact and parental emotion subscales.

<table>
<thead>
<tr>
<th>FIS Subscale</th>
<th>Interest in Genetic Testing</th>
<th>N</th>
<th>Mean Range</th>
<th>Standard Deviation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family activity</td>
<td>No</td>
<td>64</td>
<td>4.66</td>
<td>3.14</td>
<td>.141</td>
</tr>
<tr>
<td>(n = 160)</td>
<td>Yes</td>
<td>96</td>
<td>5.49</td>
<td>3.70</td>
<td></td>
</tr>
<tr>
<td>Parental emotion</td>
<td>No</td>
<td>63</td>
<td>3.05</td>
<td>2.45</td>
<td>.006*</td>
</tr>
<tr>
<td>(n = 157)</td>
<td>Yes</td>
<td>94</td>
<td>4.29</td>
<td>2.87</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 – FIS Subscale Scores with Respect to Interest in Genetic Testing

Levene’s test was performed to test the assumption of equal variance for both subscales. For both the family activity subscale and the parental emotion subscale, Levene’s test was not found to be significant (.064 and .208 respectively), indicating that equal variances can be assumed when performing the t-test for the hypotheses.

A two-tailed t-test was performed to compare the mean scores of each subscale for the parent(s) interested in genetic testing to parents not interested in genetic testing. Parents interested in genetic testing had higher scores on the emotion subscale of the FIS (p = .006) compared to parents not interested in genetic testing. When comparing the family activity scale, there was no significant difference (p = .141).
The single-item assessing financial burden was analyzed separately from the subscales. Levene’s test was not significant (p = .071). The financial impact on interest in genetic testing is not significant between the two populations (p = .099) (Table 7).

<table>
<thead>
<tr>
<th>FIS Item</th>
<th>Interest in Genetic Testing</th>
<th>N</th>
<th>Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial burden (n = 156)</td>
<td>No</td>
<td>65</td>
<td>0.69</td>
<td>.099</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>96</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Table 7 – Financial Burden with Respect to Genetic Testing

Beliefs of Cleft Origin

In both parents interested in testing and those not interested in testing, a majority of respondents (51.6% and 56.3%, respectively) reported that neither parent was the cause of their child’s CL/P (Tables 8 and 9). However, 20.9% (19/91) of parents interested in testing reported they believed they were the origin of the child’s cleft; 2 parents had a personal history of clefting, 7 parents had a family history of clefting, and 2 parents had both a family and personal history of clefting. Of parents not interested in testing, 17.2% (11/64) believed they caused their child’s cleft; 3 parents reported a family history of clefting and none had a personal history. None of the responses were found to be statistically different ($\chi^2 = 8.990; \text{df} = 4; p = .061$).
<table>
<thead>
<tr>
<th>Origin of the Child’s CL/P</th>
<th>N = 91</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>19</td>
<td>20.9</td>
</tr>
<tr>
<td>My partner</td>
<td>10</td>
<td>11.0</td>
</tr>
<tr>
<td>Neither of us</td>
<td>47</td>
<td>51.6</td>
</tr>
<tr>
<td>Both of us</td>
<td>11</td>
<td>12.1</td>
</tr>
<tr>
<td>Another family member</td>
<td>4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Table 8 – Parental Beliefs in Origin of the Child’s Cleft (Interested in Testing Population)

<table>
<thead>
<tr>
<th>Origin of the Child’s CL/P</th>
<th>N = 64</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>11</td>
<td>17.2</td>
</tr>
<tr>
<td>My partner</td>
<td>6</td>
<td>9.4</td>
</tr>
<tr>
<td>Neither of us</td>
<td>36</td>
<td>56.2</td>
</tr>
<tr>
<td>Both of us</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Another family member</td>
<td>9</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Table 9 – Parental Beliefs in Origin of the Child’s Cleft (Not Interested in Testing Population)

Recurrence Risk

Parents were asked to estimate their recurrence risks (Table 10). While the most frequently reported risk category was the multifactorial range of 2-5% (39.4%, 37/94 for parents interested in genetic testing; 41.8%, 28/67 for parents not interested in genetic testing), a majority of the study population either estimated their risk to be zero or overestimated their risk (25-100%). All four respondents indicating a recurrence of 100% also indicated interest in genetic testing. For statistical purposes, the response of 100% was excluded due to a sample size less than 5. Subsequent Chi-square analyses
showed that for the remaining four responses, the beliefs of recurrence risk between these two populations were significantly different ($\chi^2 = 9.213; \text{df} = 3; p = .027$). Those interested in genetic testing were more likely to indicate a recurrence risk higher than a multifactorial range (2-5%).

<table>
<thead>
<tr>
<th>Recurrence Risk</th>
<th>Interested in Genetic Testing, n = 94 (%)</th>
<th>Not Interested in Genetic Testing n = 67 (%)</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>9 (9.6)</td>
<td>18 (26.9)</td>
<td></td>
</tr>
<tr>
<td>2 to 5%</td>
<td>37 (39.4)</td>
<td>28 (41.8)</td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>23 (24.5)</td>
<td>11 (16.4)</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>21 (22.3)</td>
<td>10 (14.9)</td>
<td>9.213*</td>
</tr>
<tr>
<td>100%</td>
<td>4 (4.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 10 – Parental Estimation of Recurrence Risk

Sources of Risk Information

Parents were queried about which health care professional(s), if any, had talked with them about their recurrence risk. Multiple responses were permitted, and both populations reported a range from 0 to 4 health care professionals discussing this information. At least one health provider had discussed recurrence risk with 118 respondents, and geneticists and genetic counselors were the most frequently reported health care professionals discussing this information (61.1% with parents interested in testing and 60.9% with parents not interested in testing) (Table 11). Chi-square analyses revealed no statistical difference between the responses of these populations.
<table>
<thead>
<tr>
<th>Health Care Professional</th>
<th>Interested in Genetic Testing, n = 97 (%)</th>
<th>Not Interested in Genetic Testing n = 67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrician or Family Physician</td>
<td>26 (36.1)</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td>Obstetrician</td>
<td>17 (23.6)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Geneticist or Genetic Counselor</td>
<td>44 (61.1)</td>
<td>28 (60.9)</td>
</tr>
<tr>
<td>Nurse</td>
<td>4 (5.8)</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (23.6)</td>
<td>6 (13.0)</td>
</tr>
</tbody>
</table>

Table 11 – Individuals Who Have Discussed Recurrence Risk Information with Parents

Of parents interested in genetic testing, 25.8% (25/97) reported that risk information was never discussed by a health care professional, while only one parent reported having discussed his or her risk with four providers. Seventy-two parents interested in genetic testing indicated that at least one health care professional had discussed this information, with a mean of 1.50 (SD = 0.72, range = 1-4). Only one parent reported having discussed their risk with four providers.

Of parents not interested in genetic testing, 31.3% (21/67) reported that risk information was never discussed with a professional, however 46 reported that at least one health care provider had discussed their risks, with a mean of 1.48 (SD = 0.84, range = 1-4).

Risk Reduction Options

Participants were asked about what actions they believed could be taken during a pregnancy to reduce the risk of having a child with isolated CL/P (Table 12). Multiple responses were permitted, and 116 parents cited at least one action for risk reduction.
The option selected most often by parents was taking a prenatal vitamin (76.7%, 89/116), and most believed that taking folic acid daily (75.9%), avoiding tobacco exposure during pregnancy (71.6%), and not consuming alcohol during pregnancy (66.4%) would reduce their risk. Fourteen respondents indicated that other methods for risk reduction exist, with 10 participants providing further details (Appendix H). There were no statistical differences in the beliefs about risk reduction with respect to interest in genetic testing.

<table>
<thead>
<tr>
<th>Method</th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take a prenatal vitamin</td>
<td>89</td>
<td>76.7</td>
</tr>
<tr>
<td>Take folic acid</td>
<td>88</td>
<td>75.9</td>
</tr>
<tr>
<td>No smoking</td>
<td>83</td>
<td>71.6</td>
</tr>
<tr>
<td>No consuming alcohol</td>
<td>77</td>
<td>66.4</td>
</tr>
<tr>
<td>Eat plenty of vegetables</td>
<td>67</td>
<td>57.8</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>14.7</td>
</tr>
<tr>
<td>Not having any more children</td>
<td>13</td>
<td>11.2</td>
</tr>
<tr>
<td>Using donor eggs or donor sperm</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>No exercise during pregnancy</td>
<td>2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 12 – Beliefs for Methods of Risk Reduction

In addition to the 116 respondents in Table 12, 26 reported that nothing could be done to reduce the risk of having a child with CL/P (Appendix H); six respondents attributed their child’s cleft to God and explained that nothing could decrease their risk.

One parent (questionnaire 111) referred to a cluster of clefts in New Jersey that was reported to be related to pesticides in drinking water. This parent later indicated in their free response that since having a child with a cleft and hearing about a possible link with food and water contamination, their family had switched to all organic products.

One parent (questionnaire 166) attributed the cleft to fate, because “sometimes it just
happens,” and another parent (questionnaire 380) referred to family history and to “hope you don’t have family with cleft lips or palate.” Two parents (questionnaires 167 and 198) attributed either prescription or illicit drug use to their child’s cleft, and four parents (questionnaires 214, 276, 308, and 381) stated that proper nutrition and pregnancy well-being were very important, such as “not to get stressed out, arguing, or be depressed” (questionnaire 276). One parent believed that “protective intercourse” would reduce their risk (questionnaire 231), which may be indicative of this parent’s belief in reducing risk by not having more children.

**Barriers to Genetic Testing**

Parents interested in genetic testing (n = 97) were asked who they think should be tested in their family and what barriers they perceived to proceeding with testing (Table 13). The most frequently reported individual for whom testing would be desired was the participant’s child with a cleft (79.2%, 76/96). A majority of respondents was also interested in testing themselves (68.8%, 66/96). Participants expressed the least interest in prenatal testing (20.8%, 20/91).

<table>
<thead>
<tr>
<th></th>
<th>N  = 96</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child with a cleft</td>
<td>76</td>
<td>79.2</td>
</tr>
<tr>
<td>Yourself</td>
<td>66</td>
<td>68.8</td>
</tr>
<tr>
<td>Your partner</td>
<td>45</td>
<td>46.9</td>
</tr>
<tr>
<td>Your other children</td>
<td>41</td>
<td>42.7</td>
</tr>
<tr>
<td>Prenatal</td>
<td>20</td>
<td>20.8</td>
</tr>
</tbody>
</table>

**Table 13 – Individuals to be Tested**
(Interested in Testing Population)
Parents interested in testing perceived a variety of barriers to testing (Table 14). Of the 97 parents interested in testing, the most frequently reported barrier was cost (78.4%, 76/97). In contrast, 12.4% of the population (12/97) reported that nothing would stop them from proceeding with genetic testing for isolated CL/P. Almost one-third of interested parents (29.9%, 29/97) indicated that they were not having more children and testing was therefore unnecessary. Three respondents perceived other barriers not presented on the questionnaire, including “what is involved in the testing, how complicated or invasive the testing may be” (Appendix I, questionnaire 354), compensation, and access to testing before reproductive age.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>76</td>
<td>78.4</td>
</tr>
<tr>
<td>Not having more children</td>
<td>29</td>
<td>29.9</td>
</tr>
<tr>
<td>Fear of discrimination by insurance companies</td>
<td>21</td>
<td>21.6</td>
</tr>
<tr>
<td>Informing children of risk</td>
<td>12</td>
<td>12.4</td>
</tr>
<tr>
<td>No barriers</td>
<td>12</td>
<td>12.4</td>
</tr>
<tr>
<td>Anxiety of positive result</td>
<td>8</td>
<td>8.2</td>
</tr>
<tr>
<td>Informing family members of risk</td>
<td>5</td>
<td>5.2</td>
</tr>
<tr>
<td>Fear of discrimination by employers</td>
<td>4</td>
<td>4.1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 14 – Perceived Barriers to Genetic Testing (Interested in Testing Population)

Participants who indicated no interest in genetic testing (n = 67) were only asked about their perceived barriers to testing (Table 15). The most frequently reported barrier was that the parents were not planning on having more children (47.8%, 32/67). Also,
parents not interested in testing frequently selected “Other” (46.3%, 31/67), and provided several different reasons for not electing to test. The reasons cited were frequently questions of utility such as the results having no impact on prenatal decision-making and that fact that there was no treatment until after birth, along with faith- or spiritually-based reasons for not proceeding with genetic testing (Appendix I).

<table>
<thead>
<tr>
<th>障礙</th>
<th>N</th>
<th>百分比 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>不打算再生小孩</td>
<td>32</td>
<td>47.8</td>
</tr>
<tr>
<td>其他</td>
<td>31</td>
<td>46.3</td>
</tr>
<tr>
<td>成本</td>
<td>11</td>
<td>16.4</td>
</tr>
<tr>
<td>告知兒童風險</td>
<td>6</td>
<td>9.0</td>
</tr>
<tr>
<td>恐懼保險公司歧視</td>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>對結果進行恐懼</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>告知家人風險</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>懼怕雇主歧視</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Table 15 – Perceived Barriers to Genetic Testing (Not Interested in Testing Population)**

** Regression Analysis**

A multiple regression analysis was performed to determine which variables were associated with parental estimation of recurrence risk. Covariates included in analyses were the affected child’s gender, race (Caucasian vs. minority), parent education, and the subscales of the FIS (parental activity, parental emotional, and financial burden). No covariates were found to be statistically significant predictors of parental beliefs in recurrence risk. However, respondent education level and the parental emotion subscale of the FIS both approached significance with p-values of .062 and .069, respectively.
A binary logistic regression was performed to determine whether parents perceiving greater burden from their child’s diagnosis were more likely to be interested in genetic testing. Higher scores on the parental emotion subscale of the FIS were found to be predictive of interest in genetic testing (OR = 1.19, p = .030). Additional analyses performed to test the association between interest in testing and variables included affected child’s gender, race (Caucasian vs. minority), severity of the child’s cleft, and the subscales of the FIS (parental activity, parental emotion, and financial burden). Only minority status to be a significant predictor of interest in genetic testing (OR = 5.78, p = .030).

Logistic regression of interest in genetic testing and its interaction with the affected child’s gender and perceived burden on family activity by the respondent showed that there was a gender discrepancy regarding interest in testing for different levels of burden (Figure 1). The interaction between gender and differing levels of burden on the family activity FIS subscale was found to be highly significant (p = .008). As perceived burden on family activities increased, parents of affected males were less likely to be interested in genetic testing and parents of affected females were more likely to be interested in genetic testing.
Figure 1 – Odds of Interest in Genetic Testing by Affected Child Gender and FIS Family Activity Subscale Scores

Qualitative Data

Qualitative data from item 33 of the questionnaire, an open response item soliciting any other information the respondent wished to provide, were analyzed for common concepts and themes. Sixty-three respondents provided data in the box designated for free response. Comments that qualified previous answers, only included personal information not applicable to the study, referred specifically to the construction or content of the questionnaire, or that were solely encouraging words and wishes to the researcher(s) were not analyzed. When categorizing the remaining 59 comments, inter-rater reliability between the researcher and ALM was 89.7%. The comments were sorted into 11 categories (Appendix G): acceptance (n = 10), adaptation (n = 4), belief in environmental causes (n = 12), belief in genetic causes (n = 3), desire for education or
intervention (n = 4), difficulty with acceptance/coping (n = 3), faith/spirituality (n = 5), frustration/lack of information and support (n = 9), interest in future risks (n = 3), support and appreciation of medical services (n = 4), and uncertainty of origin (n = 6). Some participants identified more than one theme. Three overarching themes (Appendix G) were generated from the 11 categories, including: (1) navigating the "whys and will it happen again" – what caused it and risk of recurrence?, (2) navigating the “outside world” – working with the health care system and resources, and (3) navigating the “inside world” – psychological and spiritual aspects.
CHAPTER V: DISCUSSION

As susceptibility loci continue to be identified and a larger proportion of the genetic component of isolated CL/P is understood, genetic testing for these alleles may become available. This study is the first to attempt to characterize parental opinions in genetic testing for isolated CL/P, by defining who might be interested in testing and what barriers may prevent them from proceeding with testing. Additionally, this study described parental perceptions of recurrence risk and their beliefs about options for risk reduction. The specific aims of this study were to (1) elicit parental perceptions of burden regarding physical and cosmetic impairments of their child’s cleft, (2) determine parental knowledge of recurrence risk and possible risk reduction methods, and (3) explore parental interest in a genetic test for CL/P, if it were available.

Study Population and Demographics

Demographically, the respondents in this study population are similar to those found in previous studies of parents of children with isolated CL/P (Kramer et al., 2007; Kramer et al., 2008; Nusbaum et al., 2008; Young et al., 2001). However, the demographics of affected children included in the current study did differ somewhat from most previous studies (Kramer et al., 2007; Kramer et al., 2008; Kramer et al., 2009; Nusbaum et al., 2008; Young et al., 2001). This study included children ages 0 to 18 years, whereas previous studies have focused only on specific age groups. The proportion of male to female children with orofacial clefting is very similar that described by Kramer et al. (2007; 2008; 2009), with the sample consisting of approximately 60% males and 40% females. The the percentage of children reported to have only a cleft lip
(27.6%) versus cleft lip and palate (72.4%), differs from previous studies where cleft lip alone represented a greater percentage of orofacial clefts (ranging from 38.7-52.9%) (Kramer et al., 2007; Kramer et al., 2008; Kramer et al., 2009; Nusbaum et al., 2008). Evidence from most studies supports the finding that 70% of CL/P is isolated, which was supported in this study as 175 children had an isolated form of CL/P (63.6%, 175/275), per parental report. Therefore, when compared to epidemiological data, the results of this study are a fair representation of CL/P phenotypes.

**Interest in Genetic Testing**

One aim of this study was to explore parental interest in a genetic test for CL/P, if it were available. The results of this study show that a majority of the respondents (59.1%, 97/164) were interested in genetic testing for isolated CL/P. This is consistent with Nusbaum et al. (2008), who also found that a majority of their population was interested in predictive testing. Thus, it would appear that a majority of parents support the use of genetic testing for isolated CL/P and would consider testing, if it were available.

Parents were most interested in testing their affected child (79.2%, 76/96), presumably to detect the mutation causing the cleft in the child and, as some parents indicated, to determine the risk for future generations to be affected. A majority of respondents were also interested in testing themselves (68.8%, 66/96), which could help define their recurrence risk. Interestingly, respondents were less interested in testing their partners as well (46.9%, 45/96). As questions about the testing process (i.e. sequential versus couple testing) were not asked on the survey, it is not known if respondents, upon
receiving a negative result, would have been interested in testing their partner. Decision-making processes within the context of parental genetic test results were not characterized.

As only 20.8% (20/96) of participants indicated interest in prenatal testing for isolated CL/P, it would appear that at the current time, most parents do not find much utility in prenatal genetic diagnosis for isolated CL/P and, perhaps view it as more useful for pediatric and preconceptional purposes. Of the 56 parents receiving the diagnosis prenatally, only 7 (12.5%) indicated interest in prenatal testing, and of the 110 parents receiving the diagnosis at delivery, only 12 (10.9%) expressed interest in prenatal testing. Based on the usual time of CL/P diagnosis and low interest in prenatal diagnosis, one could surmise that parents do not believe that genetic testing may influence decisions regarding pregnancy outcome and that genetic testing for isolated CL/P would have low uptake in a prenatal setting.

In this study population, few parents who previously learned of their child’s diagnosis by ultrasonography would pursue genetic testing for the same diagnosis in future pregnancies. Of 110 parents learning of their child’s diagnosis postnatally, only 12 respondents (10.9%) expressed interest in prenatal genetic testing for isolated CL/P. Parents not interested in genetic testing indicate that they would not alter pregnancy outcome because of genetic test results (Appendix I). These results suggest that a small percentage of parents who received their child’s diagnosis in the delivery room would opt for an earlier time of diagnosis by prenatal testing. The level of interest in prenatal diagnosis among parents receiving a postnatal diagnosis of CL/P in a previous pregnancy
is consistent with previous studies (Sagi et al., 1992; Berk et al., 1999; Wyszynski et al., 2003).

The current study showed that a majority of parents were interested in predictive testing for CL/P, but have varied opinions regarding the timing and utility of such testing. Given the results of this study regarding testing preferences, and depending on parental intent for use of the information, it may not be helpful to order testing on an affected child. If parents do not wish to have more children, there is no indication to perform a genetic test, as the child’s genotype would not impact future family planning or treatment course (Kodish, 1999). However, parents who intend to determine their recurrence risk for family planning purposes should have access to genetic testing to determine the at-risk alleles in their family. It seems that overall, only a small proportion of parents were interested in using genetic testing results for family planning purposes.

Barriers to Genetic Testing

This study characterized what parents perceived as barriers to testing. Not surprisingly, most parents interested in testing perceived the cost of the test as a barrier (78.4%). In contrast, only 16.4% of parents not interested in testing perceived cost as a barrier to testing. This may be because these participants did not anticipate having to pay for testing, since close to 50% stated they were not having additional children.

For parents interested in testing who were not planning to have any more children (29.9%), perhaps their interest in testing was driven by a desire to define their personal risk or obtain an explanation for their child’s cleft.
Interestingly, one-fifth of parents interested in testing (21.6%, 21/97) feared discrimination by insurance companies. This may be due to a lack of knowledge about the recent enactment of the Genetic Information Nondiscrimination Act (GINA). If testing becomes available for this population, it would be appropriate for genetic counselors to address these concerns (as well as the fear of employer discrimination) by educating parents about GINA.

Lastly, approximately half (46.3%, 31/67) of parents not interested in testing chose “other” reasons for not proceeding with a genetic test questioned the utility of the test or gave faith- or spiritual-based reasons (Appendix G) for their child’s cleft, and their reasoning for not pursuing testing.

Family Impact

Another aim of this study was to elicit parental perceptions of burden with respect to their child’s orofacial cleft. It was hypothesized that parents perceiving a greater burden from their child’s diagnosis would display more interest in genetic testing for isolated CL/P.

The difference between parental emotion scores was highly significant (p = .006) with respect to parental interest in genetic testing. Parents interested in testing reported greater negative impact, suggesting a greater burden on parental emotions. Thus, the hypothesis that parents who feel a greater impact from their child’s diagnosis would be more interested in genetic testing for isolated CL/P was partially supported. Parents interested in genetic testing had a higher mean score for financial burden (.95) compared to parents not interested in testing (.69), but this was not found to be significant.
(p = .099). The average family activity subscale scores between participants who were interested in genetic testing and those who were not were not found to be significant (p = .141).

Overall, based on the results of this study, it appears that greater perceived emotional burden predicted greater interest in genetic testing. These results are significant for genetic counselors participating in the management for these families. If testing for isolated CL/P becomes available, genetic counselors should be cognizant of the potential emotional impact from the diagnosis on parents who seek testing, as they may require more supportive counseling before and during the testing process.

**Recurrence Risk**

Approximately 40% of participants identified a recurrence risk consistent with a multifactorial etiology (2-5%), but a majority of parents substantially overestimated the recurrence risk. These results support the need for parental education by genetic counselors and geneticists.

Although not statistically significant, the recurrence risk data revealed two trends. First, eighteen respondents who were not interested in genetic testing viewed their future risk to be 0%. It is unknown whether these participants truly believed their recurrence to be 0%, or if they perceived no risk because they were not planning on having more children. The second trend noted was that parents who reported a higher recurrence risk (25%, 50%, or 100%) were more likely to want genetic testing. Interestingly, of the 4 participants reporting a recurrence risk of 100%, all indicated interest in genetic testing.
A multiple linear regression analysis found a trend toward an inverse relationship between parental education level and risk estimation, showing that parents with a lower educational level were more likely to overestimate their recurrence risk (OR = 1.88; p = .062). A linear relationship was observed for emotional burden and risk estimation; as perceived emotional burden increased parents were more likely to overestimate their recurrence risk (OR = 1.83; p = .069).

Although these effects were not statistically significant, the current study showed that parents with a lower level of education or greater emotional burden, including guilt and anxiety, endorse high recurrence risks. Different levels of education could impact the respondent’s ability to understand recurrence risks, which can be given in multiple numerical formats (e.g. fractions, percentages). As for emotional burden, perhaps participants who experienced emotional symptoms at an increased frequency (as much as often/everyday), had more difficulty accepting that they were at an increased risk over the general population. Alternatively, the possibility of having another child with the same condition might increase emotional distress, which might affect these participants’ ability to perceive low odds of recurrence.

**Beliefs of Risk Reduction Options**

In general, the results of this study suggest that a majority of participants with children with isolated CL/P believed that specific actions and avoidance of specific exposures during pregnancy could reduce the risk of having a child with an orofacial cleft. Approximately three-quarters of participants believed that taking a prenatal vitamin and/or folic acid would contribute to risk reduction. And although the positive effects of
folic acid are controversial in the literature, the daily use of a prenatal or multivitamin is recommended for all women of childbearing age (ACOG, 2003). Interestingly, while a majority of respondents agreed that avoidance of tobacco and alcohol during pregnancy contributed to a decreased risk for orofacial clefting, more than half of respondents citing at least one method for risk reduction believed that eating vegetables during pregnancy could decrease their risk. However, while this behavior supports pregnancy well-being, the scientific literature has not found this to be a direct method for reducing the risk of orofacial clefts.

Lastly, the question of risk reduction was not designed to assess what respondents did or did not do during pregnancy, but what they believed could be done to reduce risk. Given that this study is retrospective, it is unknown what environmental or genetic information about risk reduction parents may have heard after the birth of their child with CL/P. Although ongoing research is attempting to determine methods to reduce the risk of orofacial clefting, there are few actions that have been substantiated that decrease recurrence. However, it is clear from the results of this study that more participants believed that there were methods for risk reduction than parents who believed that nothing could be done.

Predictors of Interest in Genetic Testing

Using the data collected from this study, a binary logistic regression was used in attempt to identify predictors of interest in genetic testing for isolated CL/P. Using all available data (n = 153), race, gender of the affected child, parental education, and scores
from the FIS subscales were analyzed for association. Within this study population, three predictors were identified.

When race was collapsed into two categories – whites and minorities, logistic regression revealed that minority status was a strong predictor of interest in genetic testing, with an odds ratio of 5.78 ($p = .030$). This result is surprising, based on past literature associating uptake of genetic testing and race/ethnicity. When access to genetic testing is excluded as a barrier to receiving genetic testing, multiple studies in different clinical areas (e.g. prenatal genetic diagnosis, predictive testing for hereditary cancer syndromes) have shown that uptake of genetic testing differs among individuals of different racial and ethnic backgrounds.

In prenatal diagnosis situations, Kuppermann, Gates, & Washington (1996) reported that African-American and Hispanic women were less likely to pursue prenatal diagnosis than Caucasian and Asian females. In contrast, a study of 157 females referred for amniocentesis revealed almost equivalent rates (approximately 82%) of uptake for Caucasian, African-American, and Asian women, but 30% less (uptake of 51.5%) in Hispanic women (Saucier et al., 2005). A recent study of $BRCA1/2$ genetic testing by Olaya et al. (2009) revealed no influence of race on individuals choosing to have predictive testing, compared to those who declined. Additional literature exists that supports both equal and unequal rates of uptake among individuals of different backgrounds, however, these studies frequently considered other sociodemographic factors in their analyses.

Even though the association between race/ethnicity and uptake of genetic testing is controversial, the results of the current study are in contrast to a majority of such
literature. The results of this study, that minorities (American Indian, Black, Hispanic/Latino, two or more races) are significantly more likely to be interested in genetic testing (OR = 5.78) for isolated CL/P, are difficult to interpret, particularly because isolated CL/P does not occur at an equal frequency across racial or ethnic backgrounds. As the number of minority individuals included in the study was small (n = 16) compared to the Caucasian population (n = 159), a more diverse population is required to determine whether the association calculated is accurate.

Emotional burden was also identified as a predictor of genetic testing. As discussed previously, this supports the hypothesis that parents who perceived a greater emotional burden were more likely to be interested in genetic testing (OR = 1.191; p = .030).

Lastly, respondent interest in genetic testing was found to be different for affected males and females at different levels of perceived impact on family activities (p = .008). As perceived burden on family impact increased, parents of an affected male were less likely to be interested in testing and parent(s) of an affected female were more likely to be interested in testing. This result is a novel finding; however, it is unclear whether parents consciously would accept or decline genetic testing based on their child’s gender.

Most parents in this study believed that both genetic and environmental influences contributed to the formation of an orofacial cleft. Perhaps, the fact that female children would be “childbearing” may explain the increased likelihood for parents to pursue genetic testing for affected females. Further research is needed in order to explain these interactions, as motivations for genetic testing were not a focus of this study.
Qualitative Data

Parents were given the opportunity to provide more information, prompting sixty-two parents to elaborate on previous answers or describe different aspects of their family life and child’s experiences (Appendix G). The qualitative data from these free responses were analyzed for themes and were sorted into the following 11 categories: acceptance, adaptation, belief in environmental causes, believe in genetic causes, desire for education or intervention, difficulty with acceptance/coping, faith/spirituality, frustration/lack of information and support, interest in future risks, support and appreciation of medical services, and uncertainty of origin.

Although some respondents included comments that had elements of frustration or anxiety, the overall tone of most comments was positive and encouraging. Also, this study identified similar themes as to those described by Nusbaum et al. (2008). Categorized by Nusbaum et al. (2008) as dissatisfaction in how parents received the diagnosis, the following two comments were categorized within the theme of frustration/lack of information support in the present study:

When our son was born with cleft lip/palate [palate], we didn’t know what it was. No one at Hospital would help/explain anything to us. They did however re-iterate over and over that the defect had nothing to do with error on their part?! They also insisted for 2 days that I breast feed while my son lost weight. We were sad, terrified, and confused. No one at gave us any information on cleft babies (Questionnaire 162).

I think when genetics are involved certain things are predetermined and unavoidable. Didn’t appreciate having a geneticist tell me not taking prenataals may have caused it. I am a healthy, intelligent adult who vomited for 8 weeks of my pregnancy including the vitamins. I AM NOT at fault. He is a beautiful and rambunctious boy who barely understands his defect (Questionnaire 310).
Here, classified as faith/spirituality, is a respondent comment representative of the category “Religion as an Aid in Coping” described by Nusbaum et al. (2008):

Genetic testing for cleft lip and palate may inadvertently [sic] scare a new mom or dad into avoiding future pregnancies or terminating pregnancy. We were blessed to receive immediate assurance and education about our son’s birth defect after his birth. Faith and trust in the Creator God provides all the stability one needs in the face of any adversity. Please consider your work and research in light of the reverence [sic] due to the One who holds the power of life and death in His capable hands (Questionnaire 264).

The questions included in this study before the free response question focused on recurrence risk, risk reduction, and genetic testing. Themes describing these topics were identified, such as the desire for education/intervention:

This genetic test would be great to have available for new parents. But, there must be additional and strong treatments offered with the test results to help parents be educated about ways to reduce the risks (i.e. folic acid) (Questionnaire 153).

Also, a few respondents displayed interest in defining future risks, providing insight to their motivation for testing. The following response illustrates the information that this respondent wished to gain from genetic testing:

Only would want info regarding my children’s possibilities on having children with clefts. Know percentage if different from other children with chance of having clefts. One with the cleft and others without cleft. Cleft children – privilege of being a cleft mom. Would change nothing, but only to fix if possible for him, due to pain in surgery (Questionnaire 331).

In summary, a majority of the themes generated from the qualitative analysis are consistent with previously described themes or categories (Berk et al., 1999; Lippmann, 1999; Nusbaum et al., 2008), however novel themes were identified from parental comments concerning genetic testing and beliefs in causes of the child’s cleft.
Limitations

The sample for this study was obtained from BCMH, a statewide program composed of children with birth defects. Although this resource provided a large regional sample, it may be composed of a self-selecting group of parents, since they have chosen to enroll their child in BCMH and complete yearly checkups and paperwork to ensure renewal of membership. Thus, the study sample may be composed of an increased number of parents who actively seek information and treatment for their child’s condition, which may lead to falsely increased interest in genetic testing or knowledge of risk in a sample of parents of children not enrolled in this program. This study was also subject to ascertainment bias, since only parents of children with CL/P were included. No control population composed of parents of children without health problems or birth defects was used, and the interest in genetic testing may not be as high in a control group.

An additional limitation introduced to the study due to obtaining the population from BCMH was the lack of a fair representation of financial burden. Families enrolled in BCMH receive financial assistance for appointment fees, testing costs, and surgeries. Thus, the impact of financial burden, with respect to being interested in genetic testing, may not be representative of parents who do not receive financial assistance.

The demographics of this population were not highly diverse, as the vast majority of respondents were Caucasian and had at least some college education. This study revealed significant results regarding minority status and interest in genetic testing; however, this statistic was calculated from a limited sample size and cannot be generalized to a more diverse population or specific minority populations when represented by greater numbers. An inverse relationship was also observed between the
respondent’s education level and risk estimation, but was not statistically significant. Potentially, this relationship might reach statistical significance in a study population that includes a greater number of individuals without some level of college education.

Parents of children at all stages of treatment were included in this study. Most children were between cleft surgeries or had completed treatment at the time of this investigation. Because of the retrospective nature of this study, parents were asked to reflect upon their perceived physical and emotional burdens over the course of their child’s lifetime. This may have tempered responses, as opposed to parents were completing the FIS before or near surgery or other difficult times in their child’s life. Alternatively, parents may not have consciously considered the physical or emotional aspects assessed by the FIS, and their answers might be inflated when considering how much impact the child’s diagnosis had over an extended period of time.

When assessing parental interest in genetic testing, particularly when determining who parents would be interested in testing in their family, the mode of prenatal genetic testing was not specified. It is not known how parents think prenatal genetic testing is performed, whether the test is a screening tool or an invasive procedure, such as amniocentesis. This lack of clarification may have contributed to a misrepresentation of parental interest in prenatal diagnosis of CL/P.

Lastly, the sample size of this study was not large enough to detect a small effect size by statistical tests. Overall, this study had significant power to detect a small to medium effect size. If a larger population were to be surveyed, results with marginal or slight statistical significance may be found to have statistical significance or be chance occurrences within this population.
Future Studies

A few findings of this study were determined as marginally significant or revealed trends that did not reach statistical significance, requiring further study. The novel finding that a child’s gender may be a predictor for interest in genetic testing for CL/P remains to be confirmed. This finding could be studied in more detail along with examining parental preferences for the process of testing and motivations for pursuing genetic testing. Additionally, such information could be combined with parental estimations of recurrence risk to determine if differences exist between different levels of risk perception. This study did not attempt to characterize how recurrence risks are estimated, and further studies would be appropriate in order to describe such a process.

The results of this study, in contrast to previous studies, revealed that minorities were significantly more likely to be interested in genetic testing. This association, although statistically significant, was calculated from a small minority population. A more diverse population should be studied in an attempt to determine whether the association calculated in this study is an accurate representation of minority group interest in genetic testing for isolated CL/P.
CHAPTER VI: CONCLUSIONS

Although susceptibility testing for genotypes associated with isolated CL/P or predictive genetic testing for CL/P is not yet available, the identification of genetic variants associated with these phenotypes are the first steps to developing such clinical testing. The results of this study showed that a majority of parents with a child affected with isolated CL/P were interested in genetic testing. It appears that the uptake or demand for this testing would be greatest in pediatric or preconceptional counseling settings. Thus, it would be appropriate for genetic counselors to be familiar with the testing process and result interpretation in order to properly meet the needs of these families.

In order to help identify parents more likely to pursue genetic testing, parent and child demographics and specific responses were analyzed for specific predictors for interest in testing. The results from this study population showed that minorities were significantly more interested in testing than Caucasians, although this conclusion was based on a small minority population and may not be true in clinical practice. Additionally, parents experiencing greater emotional impact from their child’s diagnosis were more interested in testing, and parents experiencing greater impact on family activities differed in their interest in genetic testing based on their child’s gender. For genetic counselors, this may mean that these parents require more psychosocial support. Counselors should be prepared to address the unique emotional issues and social changes experienced by this population, and take on a supportive role in addition to an educational role.
Finally, some deficits in parental knowledge were identified in this study. A majority of parents incorrectly estimated their recurrence risk as being less than or greater than the multifactorial range. Additionally, parents had some misconceptions about methods for risk reduction. These findings indicate the need to educate parents about their recurrence risk and explain it within the context of multifactorial inheritance.

It is clear from the results of this study that the role of genetic counselors and geneticists is needed in the care of families and children with isolated CL/P. Genetic professionals can offer support and direct parents to appropriate resources (both medical and psychosocial), as well as take an active role in educating parents about recurrence risk and risk reduction. Finally, the need for genetic counselors and geneticists will likely increase if genetic testing becomes available for this population, given the level of interest measured in this study.
Appendix A – Notification of IRB Approval
University Hospitals Case Medical Center (UHCMC)

UNIVERSITY HOSPITALS CASE MEDICAL CENTER
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

The University Hospitals Institutional Review Board has reviewed the proposal and informed consent
Submitted by: Matthews, Anne
Entitled: Cleft Lip with or without Cleft Palate on Parental Knowledge of Risk and Opinions of Genetic Testing
UH IRB Number: 11-09-35

Please be advised that with respect to: (1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure informed consent
(3) The risks and potential medical benefits of the investigation

The Board Considers This Project:
☑ FULLY ACCEPTABLE, without reservation; approved through 1/6/2011
☐ NOT ACCEPTABLE for reasons noted:

REMARKS: The continuing review is due by the date noted above.
IRB requires prompt reporting of the completion of a study.
Please reference the IRB number on future reviews and correspondence

Expedited Approval per 45 CFR 46.110(b)(1)
Questionnaire Study
HIPAA Exempt (Privacy Board)
Waiver of Signed Informed Consent Approved under 45 CFR
46.117(c)(2)

Date of Committee Review:
Date of Approval: 1/7/2010

TYPE PROJECT ☑ New ☐ Renewal ☐ Addendum/Amendment
HUMAN RISK ☐ Yes ☑ No
SOURCE OF SUPPORT ☐ None ☑ Departmental ☐ Outside Funding
Agency: Agency Study Number:

ARE ANY OF THE FOLLOWING INVOLVED? ☑ No ☐ Yes
☐ Minors ☐ Neonates ☐ Fetuses/Abortuses ☐ Prisoners ☐ Pregnant ☐ Mentally ☐ Mentally
Women ☐ Retarded ☐ Disabled

Protocols involving children approved under
☐ 45 CFR 46.404 ☐ 45 CFR 46.405 ☐ 45 CFR 46.406*

*Both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one has legal responsibility for the care and custody of the child.

The UHCMC IRB operates under the HHS Federal Wide Assurance of Compliance number 00003937 and IRB registration numbers 00000684 and 00001691

Joey Gibbons, MD, Chairman;
Baldara Daly, PhD, RN, Vice Chair; or Claudia Hoyen, MD, Vice Chair, or Paul Smith, DO, Vice Chair, or Anthony Post, MD, Vice Chair
LG

Revised 03/01/2004
Appendix B – Notification of IRB Approval
Ohio Department of Health (ODH)

THE OHIO DEPARTMENT OF HEALTH
HUMAN SUBJECTS INSTITUTIONAL REVIEW BOARD
FWA00001963
IRB00002180

ACTION OF THE REVIEW BOARD
(CERTIFICATION)

With regard to the employment of human subjects in the proposed research entitled:

"Impact of Cleft Lip with or without Cleft Palate on Parental Knowledge of Risk and Opinions of Genetic Testing"

CDC of HHS Federal Project Number (if any):

Principal Investigator: Anne Matthews, PhD

Agency: Case Western Reserve University

Division: Bureau: Children with Medical Handicaps

The Institutional Review Board has taken the following action:

X Approved □ Expedited Review □ Waiver of Written Consent
□ Disapproved X Full Board Review □ Exempt

Requirements:
- None

It is the responsibility of the principal investigator to retain a copy of each signed consent form for at least three (3) years beyond the termination of the subject’s participation in the proposed activity. Should the principal investigator leave the ODH, signed consent forms are to be retained by the Division Chief for the required retention period. This application has been approved for the period of one (1) year. No procedural changes may be made without prior review and approval. You are reminded that the identity of the research participants must be kept confidential.

Date: 2/24/2010

Signed: [Signature]

CC: James Bryant, MD
Appendix C – Notification of IRB Amendment Approval
University Hospitals Case Medical Center (UHCMC)

UNIVERSITY HOSPITALS CASE MEDICAL CENTER
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

The University Hospitals Institutional Review Board has reviewed the proposal and informed consent
Submitted by: Matthews, Anne
Entitled: Cleft Lip with or without Cleft Palate on Parental Knowledge of Risk and Opinions of
Genetic Testing
UH IRB Number: 11-09-35

Please be advised that with respect to: (1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure
informed consent
(3) The risks and potential medical benefits of the investigation

The Board Considers This Project:
☐ FULLY ACCEPTABLE, without reservation; approved through 1/8/2011
☐ NOT ACCEPTABLE for reasons noted:

REMARKS: The continuing review is due by the date noted above.
IRB requires prompt reporting of the completion of a study.
Please reference the IRB number on future reviews and correspondence

Expedited Approval per 45 CFR 46.110(b)(2)
Questionnaire Study
Waiver of Signed Informed Consent Approved under 45 CFR 46.117(c)(2)

Date of Committee Review: 3/18/2010
Date of Approval: 3/18/2010

TYPE PROJECT ☐ New ☐ Renewal ☑ Addendum/Amendment
HUMAN RISK ☐ Yes ☑ No
SOURCE OF SUPPORT ☐ None ☑ Departmental ☐ Outside Funding
Agency: Agency Study Number:

ARE ANY OF THE FOLLOWING INVOLVED? ☐ No ☐ Yes
☐ Minors ☐ Neonates ☐ Fetuses/Abortuses ☐ Prisoners ☐ Pregnant ☐ Mentally Retarded ☐ Mentally Disabled

Protocols involving children approved under:
☐ 45 CFR 46.404 ☐ 45 CFR 46.405 ☐ 45 CFR 46.406*

*Both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably
available, or when only one has legal responsibility for the care and custody of the child.

The UHCMC IRB operates under the HHS Federal Wide Assurance of Compliance number 00003837 and IRB registration numbers 00000684 and 00001691

Joseph Giacomini, MD, Chairman;
Barbara Daily, PhD, RN, Vice Chair; or Claudia Hoyen, MD, Vice Chair, or Paul Smith, DO, Vice Chair, or Anthony Post, MD, Vice Chair

LW

Revised 02/01/2004
Appendix D – ODH/BCMH Letter Addressed to Parents

Dear Parents:

The Bureau for Children with Medical Handicaps, in partnership with the Department of Genetics at Case Western Reserve, is conducting a survey to gather information about parents/caregiver knowledge of genetics and cleft lip and palate. BCMH is sending you this confidential survey on behalf of Hannah Colabrese, graduate student. Participation in this survey is strictly voluntary and will not affect any services to which your child may be eligible. Information obtained will be used to tailor future educational opportunities for public health nurses and used for program planning. The researcher will receive only anonymous information and none of that information can be connected back to you. The survey should be completed by either the biologic or adoptive parent. If you choose to participate, please complete the survey and return it in the enclosed stamped envelope. The survey is strictly anonymous – please DO NOT include your name or address on the survey or return envelope.

If you should have questions please contact Sam Chapman, RN, MPH, Chief Nurse Administrator at Sam.Chapman@odh.ohio.gov or 614-466-0394. Thank you in advance.

Sincerely,

D.J. Sam Chapman, RN, MPH
Chief Nurse Administrator
Bureau for Children with Medical Handicaps

SC/lb
Appendix E – Invitation to Participate

Dear Parents,

We are writing to ask for your help in a study about your child’s cleft lip or cleft lip and palate. We wish to know more about parents’ knowledge of the genetics and inheritance of cleft lip. We also hope to find out if parents would be interested in genetic testing for cleft lip and palate, if it were available. This study will be carried out in the Department of Genetics at Case Western Reserve University as part of a graduate student’s thesis. We are contacting parents of children with a cleft lip or cleft lip and palate in Ohio who are registered with the Bureau for Children with Medical Handicaps (BCMH), a department of the Ohio Department of Health (ODH). BCMH is mailing the survey to you. Your information has been kept private by BCMH and was not given to the researchers or Case Western Reserve University. The Institutional Review Boards of the University Hospitals Case Medical Center and ODH have approved this study.

This anonymous survey should take about 15 minutes to complete. We have included an addressed, stamped envelope for you to use to return the survey. So that the survey answers will be anonymous, please do not write your name on the survey and please do not put your return address on the enclosed envelope.

Answering this survey is completely voluntary. If you have a child who has a cleft who is 18 years or younger, we would greatly appreciate your participation. Your anonymous answers will help us to know more about parents’ knowledge of the inheritance of cleft lip or cleft lip and palate. Also, if genetic testing for clefts becomes available in the future, we hope that this information will help genetic counselors and other health professionals to be better prepared to help families who have children with clefts.

There are no wrong answers to this survey. There are no known risks or benefits to you for participating in the study. There is no cost to you for participating in the study, but you will not be paid to participate. You may choose to answer all, some, or none of the questions in the survey. Some questions may make you feel uncomfortable. Please feel free to skip any question you do not wish to answer. If you do not wish to participate, please throw this survey away.

Your answers to the survey are anonymous and the surveys will be kept confidential. Your answers will not be shared with anyone and will be reported only as summary statistics. If you want to write additional comments on the survey, they will be anonymous because your name is not connected with your survey. Your name and address was not given to the researchers. BCMH sent out the survey and did not give any identifying information to the researchers. There will be no way to identify you with your survey. When you return the survey, your consent to participate in this study is implied. If you have lost the return envelope, you may send the survey to: Genetic Counseling Program, Department of Genetics, Case Western Reserve University, 10900 Euclid Ave, Cleveland OH 44106-4955.

If you have any questions or comments about this study, please email Hannah Colabrese at hlc34@case.edu or call her at (216) 368-1891. You may also contact Dr. Matthews at alm14@case.edu or at (216) 368-1821. If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about concerns regarding the study; research participant’s rights; research-related injury; or other human subject issues, please contact University Hospitals Case Medical Center’s Chief Medical Officer at (216) 844-3695 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakewood 1400, Cleveland, Ohio, 44106-7051.

Thank you for your time,

Hannah Colabrese, BS
Graduate Student
Genetic Counseling Training Program
Case Western Reserve University

Anne Matthews, RN, Ph.D.
Associate Professor of Genetics
Director, Genetic Counseling Program
Case Western Reserve University
Appendix F – Cleft Lip or Cleft Lip and Palate: Parent Questionnaire

If you have more than one child with a cleft lip or cleft lip and palate, please respond to the questions with regard to your youngest child with a cleft.

PART A - BACKGROUND INFORMATION

The following eight (8) questions are about yourself or about your family members. Please circle the letter to indicate your answer.

1. What is your relationship to your child?
   a. Biological mother
   b. Biological father
   c. Adoptive mother
   d. Adoptive father
   e. Other (Please describe.)

2. As the parent, what is your age? ________________

3. Do either of the biological parents have a cleft lip or cleft lip and palate?
   a. No
   b. Yes – please circle the appropriate answer below.

<table>
<thead>
<tr>
<th>Type of Cleft</th>
<th>Biological Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-sided cleft lip</td>
<td>Mother</td>
</tr>
<tr>
<td>Two-sided cleft lip</td>
<td>Mother</td>
</tr>
<tr>
<td>One-sided cleft lip and palate</td>
<td>Mother</td>
</tr>
<tr>
<td>Two-sided cleft lip and palate</td>
<td>Mother</td>
</tr>
<tr>
<td>Cleft palate only</td>
<td>Mother</td>
</tr>
</tbody>
</table>

4. How many children do you have? Include your child who has a cleft lip or cleft lip and palate.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Cleft?</th>
<th>Child’s Relationship to you?</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>Y, N</td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td>Biological, Adoptive, Foster</td>
</tr>
<tr>
<td>b.</td>
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<td></td>
<td>Biological, Adoptive, Foster</td>
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<td>c.</td>
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<td>Biological, Adoptive, Foster</td>
</tr>
<tr>
<td>e.</td>
<td></td>
<td></td>
<td>Biological, Adoptive, Foster</td>
</tr>
</tbody>
</table>

5. Do other family members have a cleft lip or cleft lip and palate?
   a. Yes. Please identify the family member (e.g., uncle, cousin) and the type of cleft (e.g., one-sided cleft lip). ________________________________

   b. No
(6) Do any of your children (other than your child with a cleft) have birth defects, major medical problems, or a genetic condition?
   a. Yes (Please describe) __________________________________________________

   b. No

(7) What is your race?
   a. American Indian and Alaska Native
   b. Asian
   c. Black
   d. Hispanic or Latino origin
   e. Native Hawaiian and Other Pacific Islander
   f. White
   g. White, not Hispanic
   h. Two or more races

(8) What is the highest level of school you have completed?
   a. 8th grade or less
   b. Some high school, without a GED
   c. GED
   d. High school diploma
   e. Some college
   f. College
   g. Graduate or Professional school

   What is your degree? ____________________________________________________

The following six (6) questions are about your child with a cleft. Please circle the letter to indicate your answer.

(9) What is the gender of your child with a cleft lip or cleft lip and palate?
   a. Male
   b. Female

(10) What is your child’s age? _______________________

(11) What type of cleft does your child have?
   a. Unilateral (one side) cleft lip
   b. Bilateral (both sides) cleft lip
   c. Unilateral (one side) cleft lip and palate
   d. Bilateral (both sides) cleft lip and palate

(12) When was your child’s cleft diagnosed?
   a. During pregnancy
   b. In the delivery room
   c. Within 2 or 3 days of birth (in the nursery after birth)
   d. After 2 or 3 days of age

   Please specify the age when your child was diagnosed: ______________________
(13) Currently, at what stage of surgical treatment for facial clefting is your child?
   a. My child has not had his/her first cleft surgery.
   b. My child is between cleft surgeries.
   c. My child’s cleft is repaired and requires no further surgery.
   d. My child will not be receiving any surgeries.

(14) In addition to a cleft, does your child have any of the following health conditions? Circle all that apply.
   a. Developmental delay
   b. Mental retardation
   c. Severe nearsightedness
   d. Hearing loss
   e. Heart defect or disease
   f. Other birth defect (Please describe.)

PART B - FAMILY IMPACT

The following ten (10) questions are about how your child’s cleft lip or cleft lip and palate has affected your or your partner’s day to day life. Please circle the word to indicate your answer.

(15) Have you or the other parent taken time off work to care for your child related to his or her cleft?

   Never    Once or Twice    Sometimes    Often/Everyday

(16) Has your child required more attention from you or the other parent, compared to the attention provided to your other children?

   Never    Once or Twice    Sometimes    Often/Everyday

(17) Have you or the other parent had less time for yourselves or other family members because of your child’s cleft?

   Never    Once or Twice    Sometimes    Often/Everyday

(18) Has your sleep, or your partner’s sleep, been disrupted because of your child’s cleft?

   Never    Once or Twice    Sometimes    Often/Everyday

(19) Have your typical family activities been interrupted because of your child’s cleft?

   Never    Once or Twice    Sometimes    Often/Everyday

(20) Have you or the other parent been emotionally upset by your child’s cleft?

   Never    Once or Twice    Sometimes    Often/Everyday
(21) Have you or the other parent felt guilty about your child's cleft?
   Never   Once or Twice   Sometimes   Often/Everyday

(22) Have you or the other parent worried that your child will have fewer life opportunities because of his or her cleft?
   Never   Once or Twice   Sometimes   Often/Everyday

(23) Have you felt uncomfortable in public places because of your child's cleft?
   Never   Once or Twice   Sometimes   Often/Everyday

(24) Has your child's cleft caused financial difficulties for your family?
   Never   Once or Twice   Sometimes   Often/Everyday

PART C - INHERITANCE AND GENETIC TESTING

The following nine (9) questions ask about the inheritance of cleft lip or cleft lip and palate and genetic testing. Please circle the letter to indicate your answer.

If you are not the biological parent of your child with a cleft, please do not fill out this section and skip to question 33.

(25) Please complete this sentence: "I believe my child has a cleft because of . . ."
   a. Me
   b. My partner
   c. Neither of us
   d. Both of us
   e. Another family member (Please specify.) ............................................................................

(26) In your opinion (even if you are not planning on having any more children), what do you believe is (or would be) your chance of having another child with a cleft lip or cleft lip and palate?
   a. 0%
   b. 2 to 5%
   c. 25%
   d. 50%
   e. 100%

(27) Who has talked with you about your chance of having a future child with a cleft? Circle all that apply.
   a. Family physician or pediatrician
   b. Obstetrician
   c. Geneticist or genetic counselor
   d. Nurse
   e. Other (Please specify.) ...........................................................................................................
   f. No one has discussed this information.
(28) What, if anything, can someone do during pregnancy to reduce the chance of having a child with a cleft? Circle all that apply.
   a. Not smoke during pregnancy
   b. Not drink alcohol during pregnancy
   c. Take a prenatal vitamin daily
   d. Take folic acid daily
   e. Eat plenty of vegetables during pregnancy
   f. Not exercise during pregnancy
   g. Use donor eggs or donor sperm
   h. Not have any more children
   i. Other (Please describe) ____________________________________________

(29) Genetic testing for causes of isolated cleft lip or cleft lip and palate is not currently available. However, if it were to become available, would you be interested in testing?
   a. Yes
   b. No – if no, please skip to question 32.

(30) If genetic testing were to become available, who would you have tested?
   Circle all that apply.
   a. Your child with a cleft lip or cleft lip and palate
   b. Your other children
   c. Future children during pregnancy (prenatal testing)
   d. Yourself
   e. Your partner

(31) If genetic testing were available and you wanted testing, is there anything that would stop you from going ahead with testing? Circle all that apply.
   a. Cost of the test
   b. Anxiety of having a positive test result
   c. Anxious or concerned about informing family members that they may be at risk
   d. Anxious or concerned about informing my children that they may be at risk
   e. Worried about discrimination by insurance companies
   f. Worried about discrimination by employers
   g. I’m not having any more children
   h. Other (Please describe) ____________________________________________
   i. Nothing would stop me with going ahead with testing

If you answered question 31, please skip question 32.
(32) If you are not interested in genetic testing, why not? Circle all that apply.
   a. Cost of the test
   b. Anxious or concerned about having a positive test result
   c. Anxious or concerned about informing family members that they may be at risk
   d. Anxious or concerned about informing my children that they may be at risk
   e. Worried about discrimination by insurance companies
   f. Worried about discrimination by employers
   g. I'm not having any more children
   h. Other (Please describe)

(33) If you have any additional information that you would like to share, please write in the box below.

Thank you for participating in this study. Please place the completed questionnaire into the provided, postage-paid envelope. Do not write your name or address on the survey or on the provided envelope.

Hannah Colabrese  
10900 Euclid Avenue  
Genetic Counseling Program  LOC 4955  
Department of Genetics  
Case Western Reserve University  
Cleveland, OH 44106-4955
Appendix G – Qualitative Data: Categorization of Free Responses from Participants

Navigating the “whys and will it happen again” – what caused it and risk of recurrence?

**Belief in Environmental Causes**

**Questionnaire 17**  My wife and myself do not have any family members with any birth defects. We believe there were environmental causes for his defect. My son only has speech delay but is a normal little boy.

**Questionnaire 92**  When I had my son they stated that I was missing a vitamin or that he grew fast in the first 3 months. The genetic didn’t come in to play until he was 9 years old. By then he was on his fifth surgery. We are now down with surgeries but he is going to lose all his teeth due to the cleft and palate [sic] and he is only 18 years old. As he was growing up I worked with him.

**Questionnaire 111**  This is the first time I have been asked about my son’s cleft. Ohio just started tracking birth defects about 5-6 years ago. [I]’s defect is more severe than his Dad’s (lip only). I have met too many parents with kids where they have no idea where the cleft came from. The cluster in NJ makes me believe that there are factors outside of genetics that cause clefts. We have since severely changed the food that we eat – grass-fed beef, organic fruits and veggies. However, we have not changed the H2O we drink much.

**Questionnaire 183**  I took pre-natal vitamins (per Dr.) plus extra 400 mg of folic acid once we decided to start trying. I did smoke during my pregnancy about 5 cigarettes/day. Tried quitting several times and it always increased my blood pressure. I did quit after delivery being in hospital 5 days. Wish I would’ve quit even before getting pregnant.

**Questionnaire 208**  In addition he was taken the medication Lyrica while she was conceived [sic]. That medication states if you are a father or thinking about planning a family the medication is known to cause abnormalities in fetal laboratory mice. Not sure if this has anything to due [sic] w/ her cleft lip and palate. We could not get anywhere w/ the company of Lyrica due to the fact we have no proof to support this.
Questionnaire 218  I’m proud to be my daughters mom.  I [sic] was a challenge, but its been wanterful [sic]. Only reason I feel its my problem is I was 35 years of age. Also diabetic. But the nurses told me it was not my fault.

Questionnaire 245  My son’s father is an autobody painter and he was worried that the fumes he breathed in may have been a contributing factor since neither [sic] of us can find any clefts in our family trees. My son has been tested as cognitively gifted.

Questionnaire 270  No previous history of clefts in either side of the family, my doctors believe it was caused by a pill used to quit smoking taking early in pregnancy.

Questionnaire 326  Cleft child was a twin – lost the twin @ 10 wks of pregnancy. I was told by OB/GYN this is why my child developed cleft lip and palate.

Questionnaire 341  I was taking Adipex for wt loss when I became pregnant. I didn’t know I was pregnant and took it about 6 weeks until I found out. I believe that didn’t help. I went to Miami Valley Hospital and had a level 3 ultrasound done and they didn’t detect my son having the cleft. We didn’t know until he was born. (it wouldn’t of mattered, we would have been worried the whole pregnancy if we would of known) so it’s probably best that we didn’t know. I blame myself because I was taking Adipex and I didn’t eat, sometimes I didn’t eat at all in a day. (that’s what the Adipex does is curb your appetite)

Questionnaire 364  I feel my child’s cleft lip/palate was just a medical deformity that happened. I feel prior folic acid may be the cause or the work place that we were in. There were chemicals around that I never touched but may have been in the air and breathed in unknowingly. No one in either side of our families has a birth defect of any kind. We were told our chances our [are] low because of that. She is doing beautiful and loved very much and has taught us simplicity.

Questionnaire 389  I do wonder what if anything could have prevented this. I was unaware of my pregnancy until I was already 6 weeks along and I drank about 2 drinks on one occasion. I also had taken an antibiotic and did not take prenatal vitamins until 6 weeks. I would like to know how much of this was genetic vs. environment.
Belief in Genetic Causes

**Questionnaire 105** I took prenatal vitamin with folic acid during my pregnancy. So I feel my son’s cleft lip and palate are 100% genetic related. Our daughter does not have a diagnosed cleft lip and palate, however the roof of her mouth suspiciously looks like our sons.

**Questionnaire 192** There are 4 children in my family I’m 3rd in line. My niece that was born with a cleft palate was my brother’s daughter. She was his 2nd child and he was the first born in my family. My daughter is my only child.

**Questionnaire 323** This form was filled out by grandparent/guardian so many questions are not very applicable. Father has 3 children by 3 mothers. Two had bilateral cleft lip and palate. Our grandson was told he has 50/50 chance for each child he has someday to have some defect.

Don’t Know the Cause

**Questionnaire 69** I am currently pregnant again. There has been no indication that this child has a cleft of any kind. Neither her father or I have any family history that we are aware of, of clefts.

**Questionnaire 110** I have no idea why my son has a cleft. Neither I or his father know of anyone in either of our families that have had one. We both have other children by our spouses and neither of our other children have a cleft or cleft palate.

**Questionnaire 176** Even though on question 25, I circled “Neither of us,” I am not 100% sure. I know as far back as my elderly family members can remember, that there were no cleft lip and/or palate children. However my husband comes from a much larger family that many of them live out of our state, I’ve never met them. He’s [sic] thinks there may be a distant cousin in another state, that he remembers having a scar which he thought was from a cleft. However his elders say it is not from a cleft but I have not been told exactly how she got her scar. I just don’t know if they are being honest. Sad, huh?

**Questionnaire 207** I am a fraternal twin – she does not have a cleft. I have always been interested in knowing why I was the first in my family known to have a cleft lip and palate. My son was the second and my cousin was the third – my youngest has no sign of anything at all. But both of my boys have different fathers, I don’t think that matters much.
Questionnaire 208  Our daughter is ½ white ½ black. Her dad is 55 yrs old. We do not know where the cleft came from – he has 2 kids from his first marriage and no problems there

Questionnaire 303  Its not the parents fault. I did everything right – ate right exercised – no drinking – no smoking. It just happens – I don’t think they know why.

Interest in Future Risks

Questionnaire 12  If I were to have genetic testing done it would be for my child with cleft so he would understand his chances +/-or risk of having a child with the same problem.

Questionnaire 293  Although I think it was important for my children to prepare when they are ready to start a family. I do not feel they should in anyway not have children because of the risk. My daughter had fantastic surgeons and I was so blessed to have her.

Questionnaire 331  Only would want info regarding my children’s possibilities on having children with clefts. Know percentage if different from other children with chance of having clefts. One with the cleft and others without cleft. Cleft children – privilege of being a cleft mom. Would change nothing, but only to fix if possible for him, due to pain in surgery.

Navigating the “inside world” – psychological and spiritual aspects

Acceptance

Questionnaire 1  Because of my mother’s cleft, we always knew there was a chance of having a child with a cleft. We were never concerned. When my second daughter was born with the cleft, we were never upset. We accepted the defect and would deal with the necessary medical treatment. There are much worse issues that affect other kids, we are fortunate that this is only a physical defect. We were never embarrassed. People – mostly kids – would ask “what happened to your baby’s lip?” We would say “she was born special.”

Questionnaire 46  When the twins were in the NICU, the 2nd day my husband noticed that the cleft lip/palate baby had her finger over her lip all the time. We asked the doctors and the [sic] told us that maybe when she was forming, a babies [sic] head grows from
the back to the front during the 1st-12 weeks and her hand might have been in the way during this time!

Questionnaire 96  I no longer worry about my son’s cleft. His repair was so good you don’t even notice his scar. Answers were given as prior to surgery.

Questionnaire 100  I have had 2 pregnancy [sic], did the same with both. One has a cleft lip and one does not. In our eyes they are both perfect.

Questionnaire 201  My son’s lip was not as bad as it could have been. We waited until he was 1 to have his surgery. Everything went great. And we got to come home the same day. Which worked out for the better because I had just had another son and he was only 2 weeks old when [redacted] went through surgery. It has now been 2 years since his surgery. Doing good, has problems with speech and dental problems. But other then [sic] that you wouldn’t even know he had a cleft lip.

Questionnaire 227  I love my daughter and I think that because of her cleft we are and will be closer. Looking back I wouldn’t change anything what doesn’t kill us makes us stronger.

Questionnaire 298  We have never looked at our daughter has having a handicap and were never ashamed of her of her looks. We educated her older brothers before she was born and her cleft was never an issue. She never had any issues with feeding and has been amazing! When she had surgery to repair her lip we actually missed her cleft because her looks changed. When we looked at her we never even noticed it. We were very proud to take her out in public and show everyone how beautiful she was with a cleft. She is just as beautiful now after her lip surgery as she was with her cleft showing!

Questionnaire 308  Thinking about the genetic testing, would someone choose not to have children due to a cleft lip/palate? I don’t think I would have the testing done now after really thinking about it. A cleft lip/palate is so much easier to overcome than downs syndrome, or a congenital heart defect. Life was difficult at times, but you overcome it.

Questionnaire 358  In section B, those were answers from when the child was under 2. After that, surgeries were done and he wasn’t any different than any other child.
Questionnaire 360  My daughter was diagnosed at birth. It was never picked up during an ultrasound. Hers was a mild form. She has had the lip and palate repaired but does require more procedures due to an overbite. She recently (Dec. 09) had a nasopharyngeal surgery. She is receiving speech therapy and is doing well.

Adaptation

Questionnaire 26  When my son was born, I was never shown that I needed to squeeze in on the bottle to feed my son. I went home and after a few days – my son was very upset. It took up stumbling on what to do – to know he wasn’t getting from the bottle on his own. Since I have a cleft lip and palate [sic], I am not sure if the nurses assumed I knew what to do. My mom had already passed and therefore I could not have her knowledge of what to do.

Questionnaire 46  It was very hard at 1st to take in just because we had never heard about it before. But looking at her now, she is absolutely beautiful! If you didn’t know her, you wouldn’t be able to tell. We are currently in the “braces” process!

Questionnaire 69  The first year is tough will [sic] all the extra doctor’s appointments and surgeries, in addition to the extra care needed. Now things are not much different from any other child.

Questionnaire 125  My son had a very wide cleft. We had to tape his lip the first 5 weeks of life, so the lip surgery could be done. We had to use special order bottles that were expensive and had to be ordered online. $20 for 6, and we had to buy them every other month because they went bad.

Difficulty with Acceptance/Coping

Questionnaire 167  For the “Family Impact” questions I think we were more affected pre-surgery. Emotionally, we had a hard time with feeling uncomfortable out in public. We tried not to change our lives and to continue to do regular activities, but we found ourselves staying in more than we should. It’s important to forget what others maybe [sic] thinking and to remain positive for your child.

Questionnaire 209  It was a shock to see that he was born with a cleft lip, but I think it was almost just as hard right after the surgery because he looked so different. I wasn’t prepared and had to keep
looking in his eyes and listening to his cry and tell myself yes it is still your baby. But I am very grateful for the surgery!

**Questionnaire 253**
This has been a very involved process for my child. He has had 8 surgeries and has 2 more to go at age 17. He has become very self-conoious [sic] of his nose the older he gets and still waiting for that to be corrected. He never used to say anything about it but has lately been dwelling on this terribly. He is a very sensitive boy.

**Faith/Spirituality**

**Questionnaire 131**
My daughter had a cleft lip and alveolar cleft, which will be surgically fixed at 7 to 8 years. I loved her from the moment I met her, I also believe she was and is the most beautiful child in the world. Parents who have bonding issues or feel negative towards their children with clefts need to get over the issue. These children were created from their parents and God. They are equally as precious as any other child. Everyone needs to become educated and more compassionate in regards to the many differences we all have. I hope you are able to do something positive with your results. Thank you.

**Questionnaire 177**
We didn’t find out she had a cleft lip and soft pallele [sic] until she was born. The Doctor was wonderful about it, and very positive. We used the soft bottle and she did fine. The only time my husband was off work and we lost sleep was over her 2 surgeries. Otherwise, everything was normal. She has excellent speech, and a brilliant mind, the specialists tell us. We are Christians, and God has carried us through! We are Blessed!

**Questionnaire 226**
If anything we were even more in love for him. The cleft is very fixable thanks to good doctors and God.

**Questionnaire 236**
Our children are incredible, joyful and feisty individuals. I believe their clefts will have some impact on their lives whether social or self-image, but I also believe their growing faith in the One who designed them and loves them will sustain and strenghten them through the difficulties that lie or may lie a head [sic].

**Questionnaire 286**
Genetic testing for cleft lip and palate may inadvertantly [sic] scare a new mom or dad into avoiding future pregnancies or terminating pregnancy. We were blessed to receive immediate assurance and education about our son’s birth defect after his birth. Faith and trust in the Creator God provides all the
stability one needs in the face of any adversity. Please consider your work and research in light of the reverence [sic] due to the One who holds the power of life and death in His capable hands.

“The fear of the LORD is the beginning of wisdom” Proverbs 9:10a
“He who fears the LORD has a secure fortress, and for his children it will be a refuge.” Proverbs 14:26

Navigating the “outside world” – working with the health care system and resources

Desire for Education or Intervention

**Questionnaire 55**  My son has had a rough life always sick with ear infections or sinus infections. He feels that he is ugly and in my eyes he is beautiful. He has a good outlook on life except for his face. I know people make fun of the unknown and I hope for my son’s sake that you can pinpoint the genes that are missing so they can be added when he goes to have children so they don’t have the mental and heartaches.

**Questionnaire 153**  This genetic test would be great to have available for new parents. But, there must be additional and strong treatments offered with the test results to help parents be educated about ways to reduce the risks (i.e. folic acid).

**Questionnaire 167**  I strongly agree with genetic testing and hope others don’t have the mind-set that not knowing is OK. We had the benefit of finding out about our son’s cleft lip/palate on our 20 week ultrasound. It took a lot of time for us to research his condition and to accept it. Many couples don’t find out until after birth, and it is much harder on everyone involved. The more we know, the more we can prepare.

**Questionnaire 330**  My family has no history of any clefts. My son’s father’s family has only 2 (3 including our child).
1. My son
2. My son’s half brother
3. My son’s great-great uncle
I would love to further understand who and what it comes from. I was blamed for it for absolutely no reason and I would love to know the truth. I’ve always blamed the father.
Frustration/Lack of Information and Support

Questionnaire 26  When my son was born, I was never shown that I needed to squeeze in on the bottle to feed my son. I went home and after a few days – my son was very upset. It took up stumbling on what to do – to know he wasn’t getting from the bottle on his own. Since I have a cleft lip and palate [sic], I am not sure if the nurses assumed I knew what to do. My mom had already passed and therefore I could not have her knowledge of what to do.

Questionnaire 162  When our son was born with cleft lip/palate [palate], we didn’t know what it was. No one at Trumbull Memorial Hospital would help/explain anything to us. They did however re-iterate over and over that the defect had nothing to do with error on their part?! They also insisted for 2 days that I breast feed while my son lost weight. We were sad, terrified, and confused. No one at TMH gave us any information on cleft babies. My mother-in-law contacted a friend who came to the hospital to educate us and referred us to Akron Children’s Hospital. Akron was FANTASTIC in the way the helped us and provided information!! Our son is a 16-year-old, kind, fun, loving, smart, selfless and successful teenager! He has just completed 6 ½ years of orthodontic care and is a Varsity Football player! He is a volunteer with the Ohio Special Olympics and volunteers at a local MRDD school!

Questionnaire 195  Hello. I wish I knew of cleft’s [sic]. I would have been mentaly [sic] and emotionaly [sic] prepared. Plus all the surgery’s [sic] and ear infections that cleft kids have to go through even the parents! My goodness the kids and all the surgery’s [sic] it’s awful!

Questionnaire 226  …If there is anything I would like to get out (for the sake of other parents as well as the child) it is. “Put tubes in ears”! Right when doing the cleft surgery. Palate involved or not. Please! Our dear son suffered a lot of ear ache till we finally got the consent to put tubes put in and he was different as black and white in sleeping. We love our [blank] so very much. The cleft did not lesson [sic] our love for him.

Questionnaire 271  Would love to have someone tell government that no matter what children with disability should never be considered pre existing! And we should have garenteed [sic]! Medical assistance for all familys [sic] with children w/ disabilities no matter income middle class familys [sic] really struggle
financialy [sic] because we don’t quite make the poverty level needed to get help for our children. I’m all for helping children in other countries however we are not supporting the families in our own country that need a little help! Should be state to state!

**Questionnaire 272** Cleft when 1st discovered (at birth) the 2nd time was stressful and depressing. The 1st child wasn’t discovered for 12 hrs or more when she wouldn’t eat.

**Questionnaire 310** I think when genetics are involved certain things are predetermined and unavoidable. Didn’t appreciate having a geneticist tell me not taking prenataals may have caused it. I am a healthy, intelligent adult who vomited for 8 weeks of my pregnancy including the vitamins. I AM NOT at fault. It is a beautiful and rambunctious boy who barely understands his defect.

**Questionnaire 354** From birth until his first surgery was the most difficult time period. We had many feeding problems and our selected pediatrician was not very knowledgable of this condition. Once his repair surgeries were completed it has been smooth sailing ever since.

**Questionnaire 356** I personally think it would have been founded [sic] during my pregnancy if it were not do [sic] to people not listening when I was pregnant. And the fact that it was the first time I was pregnant and didn’t know anything. I was on a state medical card insurance and the [sic] treat you different.

**Support and Appreciation of Medical Services**

**Questionnaire 1** We are extremely grateful for [redacted], doctors, and BCMH. They have all been wonderful. Nurses too!

**Questionnaire 47** More than happy to help! My son is cared for at [redacted] at the cleft palate clinic. I would recommend EVERYONE there. They saved my sanity and gave my son a future with their skills and compassion. 😊

**Questionnaire 328** My child is from China and has developed well because of BCMH.

**Questionnaire 389** We found out about our daughter’s cleft lip/palate when I was about 7 mos. along in pregnancy. We had a wonderful group of people genetic counselor, nurse practitioner, geneticist, that helped us understand and prepare us for this experience. They
are with [REDACTED]. … her surgeon Dr. [REDACTED] did an excellent job.
Appendix H – Qualitative Data: Parental Beliefs for Methods of Risk Reduction

**Questionnaire 2**  Nothing – what will be, will be.

**Questionnaire 11**  I don’t think a woman can do anything to reduce that chance.

**Questionnaire 24**  I do not know of how to reduce the chance for I have done nothing to cause it. I am hearing impaired and have been since birth.

**Questionnaire 28**  Grandfather (paternal)

**Questionnaire 32**  I don’t know.

**Questionnaire 49**  Take general care, no drug use, but ultimately it’s in God’s Hands.

**Questionnaire 55**  During my pregnancy in the ultrasound it was not detected but after birth, I watched the tape again and I could see the void.

**Questionnaire 73**  [Re: folic acid] I was severely defficent [deficient]! I had a gastric bypass.

**Questionnaire 74**  Nothing.

**Questionnaire 92**  I follow most of answer and still had a child with clelf [cleft] lip and palet [palate].

**Questionnaire 100**  I did all these and still did not know.

**Questionnaire 102**  Nothing. I am very healthy, would swim until gave birth to children, did not smoke, drink, eats [ate] very healthy, nothing! God doesn’t send you anything you can’t handle.

**Questionnaire 103**  Nothing can reduce the chances – in my opinion.

**Questionnaire 106**  We would not want to prevent it. It is in God’s hands. I did not smoke or drink during pregnancies. I took all vitamins and prescribed meds.

**Questionnaire 111**  Eat organic foods and drink spring water (bottled). In 1980s in NJ [New Jersey] they found a cluster due to pesticides in the water.

**Questionnaire 125**  According to research clefts aren’t preventable.

**Questionnaire 128**  NONE

**Questionnaire 129**  Nothing. It is solely genetic.
Questionnaire 152  Nothing, it runs in familys [families].

Questionnaire 153  Folic acid is to my knowledge a primary need.

Questionnaire 156  I don’t think you can prevent it.

Questionnaire 162  Don’t panic. Seek informational counseling on what to expect/do when you have a child with a cleft. Remember, it is now correctable and there is a lot of help available to families TODAY.

Questionnaire 166  Sometimes it just happens.

Questionnaire 167  Not using prescription drugs during or close to pregnancy.

Questionnaire 176  I took very good care of myself during pregnancy. No clue why I had a cleft baby.

Questionnaire 198  Make sure partner has not been a drug user (cocaine [cocaine]), marijuana [marijuana], god knows what he used. Mothers can lie to doctors about illegal drug use exposure and smoking. I see pregnant moms smoking all the time.

Questionnaire 205  [Re: folic acid] only to decrease chances, minimally

Questionnaire 207  I don’t think anything can be done. It’s hereditary.

Questionnaire 214  Increase potassium intake.

Questionnaire 217  Are you serious? Didn’t do this w/ my first son who does not have a cleft.

Questionnaire 218  I don’t know because, I did all the test possible. Also had 2 ameо’s [amnios].

Questionnaire 226  I blame it on folic acid. But God’s will too.

Questionnaire 228  I did everything I was suppose [supposed] too [to]. God gave this condition for whatever reason. The cleft doesn’t define who he is.

Questionnaire 231  Protective intercourse

Questionnaire 240  Nothing.

Questionnaire 243  No one knows what causes them.
Questionnaire 249  I wish I knew, I would have done it!!

Questionnaire 260  Don’t believe its controllable.

Questionnaire 261  Not exactly sure.

Questionnaire 276  Not to get stressed out, arguing, or to be depressed.

Questionnaire 280  Nothing, it is genetics.

Questionnaire 281  Nothing

Questionnaire 286  Pray and trust God – he knows what we need.

Questionnaire 293  It was told to me that it is hereditary.

Questionnaire 308  There really is nothing you can do to reduce the chance. My only thought is don’t stress out while you’re pregnant.

Questionnaire 310  Our OB told us it was predetermined my 4 weeks gestation before we even knew we were pregnant.

Questionnaire 315  I did none of these and still had a child with this condition.

Questionnaire 319  N/A – Nothing.

Questionnaire 331  Not preventable that I know.

Questionnaire 346  Not sure of what causes clefts so may all or none of the above.

Questionnaire 356  I don’t know.

Questionnaire 360  No one knows what causes cleft lip – I did everything right and still had a child with a cleft lip/palate.

Questionnaire 380  Hope you don’t have family with cleft lips or palate.

Questionnaire 381  Receive help w/ pregnancy in the beginning instead of waiting.

Questionnaire 383  It’s a common development problem. You can do everything right and still have the cleft problems.
Appendix I – Qualitative Data: Perceived Barriers to Genetic Testing

Interested in Genetic Testing

**Questionnaire 214** I would like to be compensated [compensated] for my time and travel if possible.

**Questionnaire 293** I think my children should know before they have kids.

**Questionnaire 354** What is involved in the testing, how complicated or invasive the testing may be.

Not Interested in Genetic Testing

**Questionnaire 1** If I were having more children – I would accept whatever I get and test results would not alter my decision to continue the pregnancy.

**Questionnaire 12** Doesn’t really matter to me.

**Questionnaire 20** There is no history in either side of the family; therefore, we feel it was just something God allowed to happen and don’t feel the need for genetic testing.

**Questionnaire 46** If baby would test positive, it would not matter to us. We would still keep the baby and repair everything possible.

**Questionnaire 73** Geneticist at Metro has already determined that my vitamin deficiency [deficiency] was most likely the case. My son has only a 1% chance to pass on.

**Questionnaire 74** Not interested

**Questionnaire 91** The mother of child with cleft lip and palate [palate] was doing things she should not have been doing while pregnant – drugs and alcohol. The woman I have 2 children with and am married to did not and our children are fine.

**Questionnaire 95** It wouldn’t matter if she or we had another child with a cleft.

**Questionnaire 106** Would not put the burden (blame) on my husband or I for causing the cleft.

**Questionnaire 115** It is what it is. My daughter is perfect w/ or w/o a cleft. If it happened again, we’d deal with it.
Questionnaire 116  I’m not worried if it happens, it happens. I will deal with it.

Questionnaire 122  My child is healthy and beatiful [beautiful], we can handle this issue and if we have more children, we will handle their issue if they have one.

Questionnaire 131  It does not matter, if it happens, then we deal with it. Testing would not prevent the outcome.

Questionnaire 154  I didn’t/wouldn’t have testing done. I would find out when I delivered [delivered]. How my child turns out is in God’s hands. I don’t want any1 proding [prodding] where they don’t belong.

Questionnaire 156  Don’t feel its necessary.

Questionnaire 179  Because we wanted more children and knew it wasn’t genetic. And we dealt with one, we knew we could do it again. We hope and pray not.

Questionnaire 180  Risk of false results.

Questionnaire 192  Have already had testing done (bloodwork).

Questionnaire 202  No matter what the outcome we would do what is best for our child.

Questionnaire 205  Even if I did, there’s not much you can do to prepare while the baby is in utero.

Questionnaire 209  It wouldn’t matter because it is what it is and you just love your child no matter what.

Questionnaire 217  I wouldn’t have any use for the information. We had genetic counseling after the fact that we found out at 16 weeks gestation. The geneticist couldn’t give us any clear answers or probabilities.

Questionnaire 226  Because what would it benefit to know? Why worry, we wouldn’t abort [abort] or change it.

Questionnaire 260  The results wouldn’t affect me or my decisions after.

Questionnaire 263  We had testing done when she was and she put my fears at ease.

Questionnaire 276  God gives you what he believes you can deal with and there is help out there, as a parent you have to make the choices!
Questionnaire 286  We accept with gratitude all of the children God gives us regardless of health condition.

Questionnaire 306  I already had genetic testing when I was pregnant with my son who had the cleft.

Questionnaire 319  God give [gave] me a child as a blessing not as a curse and what He gives is fine no matter what birth defect [defect] the child may have.

Questionnaire 346  My child is this way because this was God’s choice. She is perfect.
REFERENCES


