

PARENTAL KNOWLEDGE OF PHENYLKETONURIA AND
THE EFFECTS OF PHENYLALANINE LEVELS OF
CHILDREN WITH PHENYLKETONURIA

By

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ABSTRACT

Parental knowledge of phenylketonuria (PKU) may influence metabolic control of plasma phenylalanine (Phe) concentrations in children with PKU. Parents of children with PKU aged birth to 18 years were recruited to participate in a research study after attending the 2010 and 2012 annual Tennessee PKU Foundation meetings and via PKU support groups found on Facebook. Parents completed an online questionnaire to assess overall knowledge of PKU and their children's Phe management.

Because of the small sample ($n = 7$), results are reported as case studies. In general, knowledge scores were higher for parents of the teenagers than for the younger children. Parents reported that children with lower serum Phe levels were on less restrictive diets and received less frequent Phe monitoring. The only child with elevated Phe levels was on the most restrictive diet and received more medicated foods and Phe-reducing medication.

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CHAPTER ONE

INTRODUCTION

Rationale

Phenylketonuria (PKU) is an inborn error of metabolism, or a metabolic disorder, caused by the body's inability to metabolize the amino acid phenylalanine (Phe) due to a deficiency or complete absence of a hepatic enzyme phenylalanine hydroxylase (PAH). PAH works hand-in-hand with an enzyme cofactor known as tetrahydrobiopterin (BH4) to convert Phe to tyrosine (1). Phe is an essential amino acid and small amounts are important for proper growth and development in infants and small children (2). However, too much Phe can cause unfavorable outcomes. When plasma Phe concentrations are elevated above the acceptable range, large amounts of Phe enter the bloodstream and travel to the brain. At first, individuals with PKU will experience cognitive impairments, such as trouble concentrating, behavior problems and decreased IQ scores. If left untreated, elevated Phe levels will eventually cause irreversible damage to an individual's cognitive function, leading to mental retardation (1).

PKU was first discovered in 1934 by a Norwegian doctor, Asbjorn Folling, who observed an offending odor from the urine of his mentally handicapped patients. Folling discovered that the odors were due to a chemical substance called phenylacetic acid. Further analysis concluded that the urine of Folling's patients contained elevated levels of phenylketone. Later in 1950, Pulitzer-prize winner Pearl Buck published the novel entitled *The Child Who Never Grew*, which was dedicated to her daughter who developed severe mental retardation due to undetected PKU. It was not long after Folling discovered PKU that Buck soon realized that her daughter suffered from the condition. Buck's novel

was written and published in order to benefit those other individuals who cared for loved ones with mental retardation. In 1951 Buck's publication of *The Child Who Never Grew*, a German professor by the name of Horst Bickel developed the first medicated formula for children with PKU. PKU formulas have since been enhanced; however, Bickel's initial formula was the first to provide adequate protein and nutrients while keeping Phe levels at an acceptable range for those individuals with PKU. In 1958, a blood test was developed to detect PKU. Robert Guthrie found an inexpensive method of testing elevated Phe levels with a single drop of blood. This method, later termed the Guthrie test, went into effect in acute care facilities in 1966. Doctors were now able to test infants at birth for PKU and provide means of Phe level management in order to reduce the incidence of mental retardation secondary to untreated PKU within the United States. In 2007, the FDA approved the use of KUVAN for those individuals diagnosed with PKU (3).

PKU exists in two forms: classic PKU and hyperphenylalaninemia (HPA). Classic PKU is the most common form of PKU and is generally more severe than HPA. Individuals with plasma Phe levels $>1200 \mu\text{mol/L}$ ($>20 \text{ mg/dL}$) are classified as having classic PKU (2). Classic PKU causes a significant reduction in PAH activity. Typically, these individuals have PAH enzymatic activity that is less than 5% (4). People with classic PKU typically follow a strict low protein, meaning severe restrictions are placed on dairy and protein intake. These restrictions are individualized. Dietary restrictions are directly dependent on the individual's age, gender and presence of other disease states. Classic PKU patients are also more likely to rely on special infant/toddler or adult

formulas and medicated foods that provide proteins without Phe, while providing the essential amino acids and tyrosine.

The opposite is true for individuals with HPA, which is a less severe form of PKU. Individuals with plasma Phe levels between 360–1200 $\mu\text{mol/L}$ (6–20 mg/dL) are classified as having HPA (2). PAH activity in individuals with HPA is less than 10% (4). Individuals with HPA are also on protein restricted diets but not to the extent as those with classic PKU. Although individuals with HPA may not require the formulas and medicated foods that are necessary for patients with classic PKU, registered dietitians advise supplementation of tyrosine so the amino acid will be available for protein synthesis (2).

PKU is a lifelong condition which requires strict dietary intervention to control Phe levels. Children with PKU rely on parental knowledge of PKU management and parents' cooperation to assure that their blood Phe levels remain within an acceptable range. It is, therefore, important that parents of children with PKU continue learning about various aspects of PKU to be knowledgeable of the etiology of the condition and to comprehend the dietary management of PKU.

Statement of the Problem

The purpose of this thesis was to investigate parental knowledge of PKU and management of plasma Phe levels in children diagnosed with PKU.

Statement of the Research Questions

1. Are parents of children with PKU knowledgeable about Phe management?

2. Does parents' knowledge of PKU influence the plasma Phe concentrations of children with PKU?

Assumptions

1. Participants will provide honest and accurate answers.
2. Participants will read and understand the instructions provided.
3. Participants currently have at least one child living in the home that is diagnosed with PKU.
4. Participants will provide the child's most recent blood Phe level to the best of their knowledge.

Definition of Terms

Amino acid – The building blocks of proteins. In all, there are 20 amino acids that exist. Of the 20 known amino acids, 20 are termed “essential”. Phenylalanine is an essential amino acid, meaning we must consume sources of phenylalanine from the diet since our bodies do not produce it.

Autosomal recessive – Refers to a genetic disorder that occurs in people who have received one copy of an autosomal gene from each parent. The parents do not actually have the disorder; they are only carriers of the gene since it is a recessive gene.

Classic PKU – The most severe form of PKU. Individuals diagnosed with classic PKU have a blood Phe levels > 20 mg/dL if left untreated. Treatment of classic PKU requires a protein-restricted diet in order to limit the intake of Phe.

Cofactor – A molecule that must coordinate with an enzyme in order for that enzyme to function.

Eczema – An inflammatory response on the skin that causes blistering and reddening of the skin and typically causes the affected area to burn and itch.

Enzyme – A molecule typically comprised of a protein base that acts as a catalyst by increasing the rate of a chemical reaction in living organisms. Individuals with PKU have a deficiency of an enzyme called phenylalanine hydroxylase (PAH).

Hepatic – Occurring in the liver.

Hyperphenylalaninemia (HPA) – A less severe form of PKU. Individuals with mild HPA have a blood Phe level < 10 mg/dL when not on a low protein diet in which Phe intake is limited.

Inborn error of metabolism – A group of rare genetic disorders that affect how food is metabolized into energy needs for the body. PKU is an example of an inborn error of metabolism.

KUVAN (sapropterin dihydrochloride) – A prescription medication approved by the FDA in 2007 that is taken to decrease blood Phe levels in patients diagnosed with PKU. KUVAN typically is more responsive to individuals with HPA versus classic PKU.

Metabolism/Metabolize – Describes chemical reactions that occur in the cells a living organism. In PKU, Phe is *metabolized* to tyrosine.

Microcephaly – The visual occurrence of an abnormally small head circumference.

Newborn screening – Used to detect severe diseases that can be treated if detected within the first couple weeks of a newborn's life.

PKU is now screened for at birth in all states of the US.

Phenylalanine (Phe) – One of the 10 essential amino acids that make up a protein molecule. The inability to metabolize excess Phe to tyrosine is a distinguishing feature of PKU. Blood Phe levels that are elevated for long periods of time can cause excessive amounts of Phe to accumulate in the brain which can cause cognitive impairments or even mental retardation.

Phenylalanine Hydroxylase (PAH) – The enzyme that functions deficiently in individuals with PKU. PAH is essential when converting Phe to tyrosine in the liver. When PAH is deficient it causes an increase in blood Phe levels which gives rise to the existence of PKU.

Phenylketonuria (PKU) – An inborn error of metabolism that is characterized by a deficiency in the enzymatic function of PAH which inhibits the conversion of Phe to tyrosine. This causes a build-up of Phe in the blood which can lead to mental retardation.

Registered Dietitian (RD) – A food and nutrition expert who has completed academic requirements to advise people on diet therapy. The RD is able to provide diet and disease knowledge to help individuals with PKU control their blood Phe levels.

Tetrahydrobiopterin (BH4) – A cofactor that coordinates with the PAH enzyme to assist in the conversion of Phe to tyrosine.

Tyrosine – A nonessential amino acid, meaning it is naturally occurring in the body (5).

CHAPTER TWO

REVIEW OF LITERATURE

Introduction

The purpose of this literature review is to provide a background on the cause and treatment of PKU and describe the trends in research on parental knowledge and its effects on the Phe levels of children with PKU, when controlling for age and cost of treating PKU.

PKU Defined

Phenylketonuria (PKU) is an autosomal recessive disorder that is characterized by the body's inability to properly convert the amino acid phenylalanine to tyrosine due to a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH) (6). Elevated plasma Phe concentrations provoke detrimental effects on the developing infant's central nervous system. PKU, when untreated, is associated with delayed infant growth and development as well as impaired cognition that lasts a lifetime (2, 6). MacDonald et al. (7) report that management of plasma Phe concentration in small children is achieved through parental knowledge of PKU as well as motivation to enforce the restrictions associated with the necessary diet therapy. Treatment of PKU requires life-long compliance of a strict Phe-free dietary regimen. Since most animal products are rich in Phe, animal foods are avoided and Phe-free protein supplementation is required to achieve adequate nutrition (5, 8 – 9).

PKU is collectively defined as an inborn metabolic disorder in which a deficiency of the hepatic PAH enzyme inhibits the conversion of the essential amino acid Phe to tyrosine (10). Inadequate PAH enzymatic function, therefore, results in plasma Phe

accretion within the body. A coenzyme called tetrahydrobiopterin, or commonly identified as BH₄, coincides with the PAH enzyme to assist in the metabolism of Phe (1). In individuals without PKU, the body utilizes moderate amounts of Phe derived from dietary protein sources to manufacture proteins. Phe that is not used in protein synthesis is converted to tyrosine with help from the PAH enzyme and BH₄ coenzyme (1, 2). However, in cases of untreated PKU, excessive amounts of plasma Phe has a negative impact on cognitive function which contribute to undesirable outcomes; the most devastating is severe mental retardation in the developing infant (4).

The severity of PKU is dependent upon the plasma Phe levels. In general, experts in the field of genetic disorders, such as PKU, recommend that plasma Phe levels remain in the range of 2 – 6 mg/dL (120 – 360 μmol/L). Patients with Phe levels maintained within this range have a milder form of the PKU condition that is referred to HPA. Phe levels exceeding 20 mg/dL (1200 μmol/L) are diagnostic for classical PKU. Classic PKU may cause symptoms in small children such as mental retardation, “abnormal electroencephalography with seizures, abnormal behavior with hyperactivity, autistic or schizophrenic signs, eczema and lightly pigmented skin, and a musty odor” (2) when left untreated. Treatment of PKU is sought once Phe levels exceed 6 mg/dL (360 μmol/L) in order to relinquish such symptoms (9).

Nutrition therapy is the most common and effective form of treatment for patients with PKU (2, 6 – 8). Since plasma Phe concentrations are elevated above normal ranges, the primary purpose of nutrition therapy in combating PKU is to restrict dietary intake of Phe. Phe is found in protein sources such as meat, dairy, legumes, nuts and eggs. Acceptable food groups for individuals with PKU include fruits, vegetables, fats, sugars

and medicated food that provide limited amounts of protein such as breads, pasta, and baked goods. These foods, although incomplete in protein requirements, can provide adequate calories while increasing the selection of foods allowed (1). Eliminating all protein from the diet can lead to protein malnutrition, therefore inhibiting growth and development in infants and small children (6). During infancy, initiation of Phe-free amino acid formula is typically recommended to supply infants with adequate nutrition while maintaining low and stabilized plasma Phe concentrations (2). Throughout childhood, adolescence, and adulthood, people with PKU should continue drinking low-Phe formula designed to meet the body's needs as it matures. Successful management of PKU requires life-long adherence to a low Phe diet (10). Due to the complexities that exist with monitoring plasma Phe and dietary intake, it is necessary for parents of children with PKU to possess some knowledge of PKU (7).

Age of Diagnosis and Treatment

Age is a determining factor for diet therapy in patients with PKU. The age at which patients are diagnosed plays a role in whether or not nutrition intervention will have any effect on cognitive outcome. All states in the United States screen for PKU at birth (11). Wappner and colleagues (9) state that identifying PKU early allows for vast improvements in the cognitive and behavioral outcomes of PKU patients by providing early treatment before symptoms are detected. The recommended therapeutic range for plasma Phe is generally more flexible as children age. Adolescents and adults are still advised to comply with lifelong dietary intervention.

As children age they become independent of parental influence and compliance despite parents' level of knowledge. A 1991 study published in the *European Journal of*

Pediatrics (12) observed mean IQ scores and Phe intake of participants between ages 11 and 18 ($n = 34$) with classical PKU. The findings were consistent with results from previous studies. As children progress into adolescence, there seems to exist an indirect relationship between plasma Phe concentrations and IQ scores. High blood Phe levels result from untreated PKU. Elevated blood Phe levels cause detrimental but reversible impairments of cognition such as trouble concentrating, restlessness, reduced reaction times and the inability to process given information which is connected to low IQ scores in children and young adults with PKU. Low IQ scores and problems in school are a direct cause of elevated Phe levels in children with PKU. Weglage and colleagues observed mean IQ scores of participants with PKU (93.6 ± 12.6) and found they are significantly lower than IQ scores of their peers (100 ± 15), mothers (98.2 ± 11.3) and fathers (105.4 ± 11.9). Results showed that even though the children met with doctors on a regular basis, PKU knowledge of the children and their mothers was low and 59% of PKU children from this study could not maintain a Phe-free diet without help from their mothers (12). Dietary intervention for PKU is severely restrictive (14). The age of children with PKU can inhibit knowledge of PKU and prevent continuation of a Phe-controlled diet.

Cost to Treat PKU

When taking into consideration means for monitoring and controlling Phe levels in children, the most appropriate methods for PKU management may not be achievable. Children with PKU must frequently monitor blood Phe levels (11). Taking into consideration the age of the child and the severity of the child's PKU status, most states require blood Phe level testing as often as one time each month (9). Children with PKU

may also require medical foods in order to sustain low Phe concentrations (6). PKU formulas and medicated foods are the largest cost factors in dietary treatment of PKU. In one calendar year during 1999, families spent \$3,000 to \$5,000 on low Phe formula alone (10). In 2012, the reported annual spending for PKU formula averaged \$7,100. Insurance does not always cover medical expenses associated with PKU treatment. According to the National PKU Alliance, insurance coverage is different in each state. Some states provide coverage only towards the cost associated with medical foods, while other states require health departments to provide PKU formula and limited sources of low protein foods at no cost to the public. Presently, “38 states have passed legislation that requires at least some coverage” toward PKU expenses (5). Currently in Tennessee, legislation has been passed to provide coverage towards licensed professional medical services under the supervision of a physician and those special dietary formulas which are medically necessary for the therapeutic treatment of PKU (5). The amount of coverage depends upon the insurance plan’s contract. Medicated foods still remain a non-covered item in Tennessee

Wappner et al, (9) surveyed parents ($n = 1,064$) of children with PKU and found that insurance did not provide coverage for all costs related to PKU. Although the majority of parents claimed their insurance provider paid for PKU formula, only 49% of blood tests were covered. Clinic directors stated that the cost of blood screenings ranged from \$10 to \$20 to more than \$80 after insurance coverage. Some parents are unaware of what insurance covers or does not cover. A study from 2004 (10) found that 40% of families were oblivious as to which expenses were covered by their health care provider. Therefore, lack of parental knowledge along with, lack of health insurance or denial of

health care coverage towards certain medical expenses associated with PKU can provide a barrier to effective treatment. It is important for parents to research various health insurance plans, understand the plan's benefits and determine which category of medical foods are covered, assess the amount of contributions that will be made to the monthly premiums, make sure favored hospitals and PKU clinics are in-network with the chosen provider, and ask questions concerning coverage (5). If the insurance company issues a denial towards PKU coverage, a letter of medical necessity may need to be obtained from the PKU child's doctor in order to file an appeal (Appendix F).

Dietary Compliance

Since dietary compliance poses perhaps the largest threat to the prognosis of patients with PKU, parental influence established in the early years is critical for the child to understand the importance of managing the child's disorder. Researchers discovered that once PKU is under control during infancy, Phe levels of infants were a direct reflection of the parent's level of knowledge and compliance. As children get older they are less likely to be influenced by their parents and are more susceptible to temptation from peers. Singh et al. (13) aimed to analyze the success of an educational camping experience for adolescent girls ($n = 13$). While away at camp, the participants received education on the PKU diet and were tested on their level of compliance via pre/post survey questionnaires. At the start of the week, only one out of the 13 girls had Phe levels within therapeutic range of 2-6 mg/dL. All other participants had Phe levels greater than 6 mg/dL. The girls were given a post survey at the end of their camp experience which found that 6 of the 13 girls exhibited the desired therapeutic range. Overall, the participants were able to maintain control of Phe levels throughout the course of camp.

The results were short lived; levels increased once the participants returned home. Conclusions of this study suggest that perhaps adolescents are still too young to have good metabolic control single handedly. Therefore, because “dietary treatment of PKU is multifaceted, challenging, and lifelong” (8), it is essential for the parent to contribute their knowledge of PKU for the benefit of the child. Durham-Shearer et al. (11) commended the camp intervention on providing knowledge and short-term improvement in the camper’s PKU management.

Physical Development

Bilginsoy et al. (10) proposed that favorable outcomes of PKU in children are heavily weighted on the patient and family members. It is essential for parents to be active participants in helping their children monitor and control their Phe levels by having knowledge of the PKU diet and providing means to observe both plasma levels and dietary intake. A 2004 study considered responses from PKU patients ($n = 32$) in Utah. The goal of this study was to determine how PKU was controlled by patients between the ages of two and 18 years and their caretakers by studying intake and prospective Phe concentrations. The results from the survey determined that 91% of caretakers were knowledgeable on the dietary constraints involved with PKU. However, only 63% kept track of their child’s physical development to determine if they were perhaps too protein restricted which could hinder the child’s ability to grow properly.

Gokmen-Ozel et al. (14) studied the association between maternal knowledge and Phe levels in children with PKU. It is importance for parents to have knowledge of PKU and the Phe restricted diet in order for children with PKU to exhibit normal growth and development as well as maintain blood Phe levels. This study provides results from a

questionnaire in which mothers of children with PKU (n = 144) were asked to complete a questionnaire to assess overall knowledge of PKU. The mean maternal knowledge score was determined as 61.5%. Overall, mothers had more knowledge on the basic understanding of PKU. Mothers were more successful in answering questions on the causes and outcomes of PKU. Mothers had less knowledge about specific issues concerning diet therapy. Maternal knowledge of Phe exchanges in the diet was scored at 22.9%. An upward trend in maternal knowledge scores and education level was determined at the conclusion of this study.

These findings are supportive of the proposal made by MacDonald et al. (8). They provided examples of barriers that inhibit compliance of the PKU diet. Barriers included: 1) Illiteracy or cognitive impairment of patients or parents, 2) Poor knowledge/insight into dietary treatment, and 3) Low educational status. In order to improve patient dietary compliance, it is important for PKU patients and parents to not only appreciate the benefits of adhering to a low phenylalanine diet, but more importantly to understand the consequences associated with noncompliance. Bekhof et al. (4) surveyed the parents of PKU patients (n = 161). The relationship between parental knowledge of PKU and the plasma Phe levels of children was observed to determine compliance of low Phe diets. As hypothesized, Phe levels are lower in children whose parents have more knowledge of PKU.

KUVAN

KUVAN, approved by the FDA in 2007, is the only approved medication that helps regulate Phe levels in children with PKU. In individuals without PKU, the PAH enzyme coincides with the coenzyme BH₄ to break down Phe that enters the body from

the diet to smaller chemical components such as tyrosine. KUVAN is the pharmaceutical form of BH4. Therefore, when individuals with PKU take KUVAN, the BH4 helps to speed up the PAH activity leading to faster and more effective break down of Phe and reducing Phe levels in the body. KUVAN, combined with diet therapy, can help manage Phe levels in individuals with PKU (5). KUVAN comes in the form of a dissolvable tablet that should be taken once a day, at the same time each day and can be mixed with 4-8 ounces of juice or water. Not everyone with PKU will experience a successful decrease in Phe levels while taking KUVAN; the drug tends to work more effectively on those individuals with HPA versus classic PKU. However, research has shown a response rate in individuals with PKU from infancy through adulthood. People of all ages can take KUVAN.

Support Groups

There exist eight national PKU support groups. One of these PKU groups, National PKU Alliance, created an online page that is accessible via Facebook. Individuals can view various postings such as PKU recipes, PKU charity walks, or upcoming PKU meeting. Currently, Tennessee has one PKU support group called the Tennessee PKU Foundation. The group members meets regularly to participate in activities that provide support to parents and children with PKU, promote community awareness of PKU and offer educational classes and information to parents with children who have PKU. Their mission statement is as follows:

The mission of the Tennessee PKU Foundation is to provide support and education to individuals and families affected by PKU and similar metabolic disorders, raise community awareness, support PKU research, and promote the overall health and

well-being of Tennesseans living with PKU and similar metabolic disorders (15). Since PKU is such a rare disease, PKU support groups provide access to current and accurate research and information for parents who have children with PKU. These groups grant parents a method of communication amongst one another and allow children with PKU a way in which to interact with other individuals with PKU. Support groups act as a coping mechanism for families dealing with PKU. Interacting with other families of PKU can provide parents and children with PKU a sense of normality.

Summary

Dietary compliance is important to insure that patients with PKU maintain low Phe levels. However, compliance cannot be achieved without parental knowledge and support. Since diet therapy is the preferred treatment option for PKU, it is essential that patients and caregivers continue educating themselves on the PKU diet and new treatment options.

The purpose of this study is to determine what effect parental knowledge has on the Phe levels of children with PKU. It is hypothesized that when controlling for age of the child, the amount of knowledge parents have on PKU will be indirectly related to the Phe levels in children with PKU.

CHAPTER THREE

METHODS

Introduction

Metabolic control of plasma Phe in children with PKU is possibly dependent on parental knowledge since managing PKU is multidimensional. The goal of this study was to assess parental understanding of PKU and the PKU diet and determine how parental knowledge influences plasma Phe management in children with PKU. Therefore, the specific research question was “what effect does parental knowledge have on the Phe levels of children with PKU?”

Subjects and Sample

Participants for this research study included parents of children with PKU, aged between birth and 18 years. Participants attended the annual Tennessee PKU Foundation meeting on December 11, 2010 and 2012 in Nashville, Tennessee. Some participants attended both meetings in 2010 and 2012, while others attended only one meeting. It was not determined in the survey whether the participants attended one or both meetings. Upon entering the meetings, parents were asked to sign an attendance sheet to document attendance and participation. Parents were asked to provide their name, address and email address. The participants for this study were recruited from the attendance list. All subjects participated voluntarily and subject qualification was dependent on attendance at the annual Tennessee PKU Foundation meeting either in December of 2010 or 2012. Names of all subjects were kept confidential and were not documented or reported in any area of this study. Participants for this study were contacted through email via Survey Monkey. Parents were also recruited via support groups on Facebook. Two support

groups on Facebook were notified about the research study: Tennessee PKU Foundation and National PKU Alliance. A link was uploaded onto the Facebook group pages allowing participants access to the survey via Survey Monkey (Appendix A).

The survey was released to participants from the Nashville meeting and those participants from the Facebook support groups at the same time. Participants were given approximately three weeks to complete and submit their survey responses. Exactly two weeks from the date that the survey was initially released, the survey was resent as a reminder to participants who had not yet responded. At the end of the study period, only seven individuals completed the study requirements in full by submitting demographic information along with answers for the knowledge portion of the survey and could be included in the study population.

In some instances, families had more than one child with PKU. All children were diagnosed by neonatal screening. In all children with PKU, the diagnosis of PKU was supported by the detection of serum Phe levels greater than 1 mg/dL. The sample included children with both classic PKU and HPA. Otherwise, there were no selection criteria for the subjects.

Consent Forms

Upon accessing the survey, participants were required to review a debriefing section which provided information on why the survey was created and the purpose for the research (Appendix B). Because the study was conducted online, informed consent was collected prior to parental participation. Consent to this study allowed the investigator to collect data on each participant and their child with PKU from the provided demographic information, medical intervention, Phe screen, dietary restrictions

and supplements, and PKU knowledge assessment. Permission to contact parents from the list was granted by the Tennessee PKU Foundation (Appendix C). This study was approved by the Middle Tennessee State University's Institutional Review Board (IRB) to protect the rights and welfare of the research participants (Appendix D).

Instrumentation

Using a survey questionnaire has many strengths such as affordability, ease of distribution, objectivity of responses, the option to use closed questions (versus open-ended) which provide quantitative data and the quick collection of responses. The disadvantages in using a survey instrument include trusting the participants to respond honestly, participants may misinterpret questions, open-ended questions can generate large amounts of data that can take a long time to process and analyze, and respondents may answer superficially especially if the questionnaire takes a long time to complete.

The study was first piloted to a group of three participants for clarity and length of time required for completion of the. Minor modifications were made to the instrument's design to improve comprehension of the questionnaire.

Data Collection

The survey was released at the beginning of February 2013 to 22 parents of PKU children between birth and age 18 who attended the Tennessee PKU Foundation meeting in December of 2010 and/or 2012 in Nashville, Tennessee. The survey was uploaded online through Survey Monkey and sent via email to the participant. The email included an explanation of the purpose for the research study, the length of the survey, confidentiality and voluntary participation. After reading the explanation of consent, parents confirmed consent by completing and submitting the questionnaire. Parents of

PKU patients completed the questionnaire to assess their knowledge of PKU. Parental knowledge, the continuous independent variable, was measured by a series of multiple-choice questions relating to PKU physiology and management.

The survey instrument was developed from three previously published PKU questionnaires (4, 7, 14). Questions in the survey consisted of background information from the parent (11 questions), basic knowledge about the disease (6 questions), and general dietary knowledge (5 questions). Participants did not receive help from the researcher. Survey forms were printed and separated upon return. All returned survey responses were put into a folder and locked inside office 105 in the Ellington Human Science building on Middle Tennessee State University's campus to assure confidentiality.

Plasma phenylalanine concentrations, the continuous dependent variable, from the previous month were used as an indicator of metabolic control in this study. Plasma phenylalanine concentrations were collected through the survey and were based on the child's most current lab value.

Qualitative Analysis

Due to the small number of individuals who responded to the study and great diversity among them, there was an insufficient sample size to allow for meaningful statistical analysis. The insufficient sample size has a low probability of detecting statistical significance. Therefore, a case study approach was used to evaluate the frequency of the results of the demographics and knowledge of PKU in participants. Participants were asked four general demographic questions pertaining to the gender, age, relationship, and geographic location of the child with PKU. The next set of demographic

items assessed where parents receive information on PKU, dietary treatment of the child, and how the child's Phe level is monitored based on three factors: 1) Whether or not the child is currently seeking medical intervention, 2) The frequency at which the child's Phe level is monitored, and 3) The child's most recent Phe level. The remaining 11 items assessed overall knowledge of PKU which required parents to provide answers to questions about the cause, pathophysiology, complications and treatment for PKU.

CHAPTER FOUR

RESULTS AND DISCUSSION

Participants

The study was initially designed to assess quantitative data to answer the research question. It was assumed that releasing the survey to support groups created on-line via Facebook would draw in a large sample. However, due to the small number of individuals who responded there was an insufficient number of participants who completed the survey for meaningful statistical analysis. Therefore, each participant will be discussed individually in the format of a case study.

By the beginning of March 2013, 12 parents had responded to the survey. Initially, it seemed as though there would be 12 participants; however, two participants were instructors at Middle Tennessee State University and one participant was the registered dietitian at Reeves-Sain in Murfreesboro, Tennessee, who volunteered to review the survey for clarity, readability and to determine the length of time required to complete the survey. These three individuals were all parents but none of them have a child with PKU. For these reasons, they were removed from the study. A requirement for all individuals participating in this study was to complete the entire survey. There were two portions of the survey. The first portion was determined basic demographic information of the child with PKU, while the second portion assessed the parent's knowledge of PKU. Both portions required completion in order for the parent to be eligible to participate in the study. Two more survey respondents were eliminated due to inadequate completion of the survey; these participants completed the demographic portion of the survey but left all knowledge responses blank. Seven participants who

reported their children ranging in age from birth – 18 years completed the study. All seven participants reported as being either the mother or father of the child with PKU.

There were vast differences in the ages of the children. The mean age was 6.85 years with a range of birth (< 1-year-old) to 18 years, ($SD = 7.40$). The final sample varied with regard to dietary status and monitoring and management of Phe levels. At the time of the evaluation, five of the seven children were on a Phe- restricted diet while the other two were not. It is not known why these two children had never followed a restricted diet, perhaps because their PKU was not severe enough. It is interesting to note that the blood Phe levels were < 2mg/dL for these two. Selected demographic data and serum Phe monitoring and management for the study population are in Table 1 and the dietary restrictions and medications are in Table 2.

Table 3 provides knowledge questions and frequency of correct responses. The mean knowledge score was 7.86 with a range of 4 to 11 ($SD = 2.48$). All parents knew that PKU screening should be done at birth (question 6), Only two parents knew the acceptable range of serum Phe for people with PKU (question 7) and that serum Phe levels increase if a person does not eat for two days (question 9). The two parents who reported they had never received PKU counseling scored the lowest (4 and 5 out of 11) on the knowledge test and reported that their children never have their blood Phe level monitored. One had a blood Phe <2 mg/dL and the other one's child had a blood Phe 2-6 mg/dL.

A description of each parent's response is described in the following section in a case study format.

Table 1
Selected demographic data and blood Phe monitoring and management

Age (Years)	Gender	Parent	Receive Counseling	Blood Phe level	Frequency of Phe monitoring	Parent's knowledge score
0	Female	Mother	No	< 2 mg/dL	Never	5 of 11
2	Female	Mother	Yes	2 - 6 mg/dL	Once a month	11 of 11
3	Male	Mother	Yes	2 - 6 mg/dL	Biweekly	8 of 11
4	Male	Mother	Yes	2 - 6 mg/dL	Once every three months	8 of 11
4	Male	Mother	No	2 - 6 mg/dL	Never	4 of 11
17	Female	Father	Yes	11 - 15 mg/dL	Once every three months	9 of 11
18	Male	Father	No	< 2 mg/dL	Twice a year	9 of 11

Table 2
Dietary restrictions and use of Phe-free formula, medicated foods, tyrosine and KUVAN

Age (Years)	Gender	Blood Phe level	Dietary restriction	Formula	Medicated foods	Tyrosine	KUVAN
0	Female	< 2 mg/dL	No	No	No	No	No
2	Female	2 - 6 mg/dL	M, D, N, B, P	Yes	No	No	No
3	Male	2 - 6 mg/dL	M, D, N, B	Yes	Yes	No	No
4	Male	2 - 6 mg/dL	M, D, N, B, P	Yes	No	No	Yes
4	Male	2 - 6 mg/dL	No	No	No	No	No
17	Female	11 - 15 mg/dL	M, D, N, B, P	Yes	Yes	No	Yes
18	Male	< 2 mg/dL	M, D, N	Yes	No	Yes	No

Table 3
PKU knowledge questions and frequency of correct responses (n = 7)

Question	Correct Answer	Frequency of Correct Responses
1. What is the cause of Phenketonuria (PKU)?	PKU is inherited	6 of 7
2. If a PKU child is not treated, what happens?	The child will be mentally handicapped	6 of 7
3. What is phenylalanine (phe)?	An amino acid	6 of 7
4. What is missing in PKU?	A liver enzyme called phenylalanine hydroxylase	6 of 7
5. What is the most important rule in the dietary treatment of PKU?	Increase intake of protein substitute and limit Phe	5 of 7
6. When should dietary treatment in PKU begin?	Within the first couple weeks of the child's life	7 of 7
7. What is considered an acceptable Phe level (mg/dL) in children with PKU?	Between 2 and 6 mg/dL	2 of 7
8. If your child's blood Phe concentration gets too high, what happens?	The child's IQ score decreases	3 of 7
9. If your child does not eat for 2 days, what will happen to their blood Phe concentration?	Blood Phe level increases	2 of 7
10. Which food group should be completely avoided according to the PKU diet?	Meat	6 of 7
11. If Phe levels are too high, what should he child do?	Eat less Phe and more protein substitute	6 of 7

CASE STUDY – Subject #1

Subject #1 is the mother of a female infant under the age of one who resides in the southern region of the United States. Subject #1 reported that she received the majority of her information on PKU from her child's primary care physician. Currently, the child does not receive medical counseling/treatment from a physician or RD and does not have her Phe level monitored. Subject#1 reported that the most current blood Phe level is less than 2 mg/dL, with no restrictions in the child's diet and no dietary supplements consumed. For this reason, it is believed that the child is breastfed since she is not supplemented with medicated infant formula and her Phe level is below the normal range of 2 – 6 mg/dL. According to the National PKU Alliance (5), women can utilize breast milk as the infant's significant source of Phe while maintaining the child's plasma Phe concentration within an acceptable range. Breast milk contains less Phe than standard infant formula. Typically, patients with classic PKU are supplemented with medicated infant/toddler formula since exclusively breastfeeding any infant can provide them with too much Phe. Infants with HPA, however, can consume breast milk exclusively since they have a higher percentage of PAH hepatic enzyme function allowing them to metabolize the Phe in their mother's milk more efficiently than those with classic PKU.

Between birth and two years of age, plasma Phe concentrations are monitored via blood samples that can be taken either from the heel or big toe. The child's health care provider can instruct the caregiver on how to collect blood samples. In the early stages of treatment, blood samples should be taken for testing to take place one to two times per week. Frequent testing is advised during the first 12 months of the child's life since

growth and dietary changes occur so rapidly during this time. The desirable Phe range is between 2 – 6 mg/dL. It is an assumption that the child is a newborn and perhaps the mother has only been notified by the child's pediatrician concerning the child's PKU diagnosis. Perhaps the mother has not yet met with an RD to discuss the child's condition which would explain why the child has not yet received any medical intervention for her PKU. Perhaps the reported Phe level came from the child's newborn screen at the time of birth.

Of the seven parents, this mother scored second lowest out of all parents; she answered 5 of the 11 knowledge questions correctly. She seemed to understand that PKU is an inherited condition which if left untreated can lead to mental retardation. However, the mother was unaware of the dietary treatment for managing PKU. The investigator speculated that the mother lacks knowledge of dietary treatment for PKU because the child does not receive medical counseling for her PKU.

CASE STUDY – Subject #2

Subject #2 is the mother of a two-year-old female from the Midwest region of the United States. Subject #2 reported that she has received information regarding her child's PKU from a specialist at a hospital or clinic, research that she has done on her own, and PKU support groups. The child does receive medical counseling and treatment from either a physician or RD and her Phe levels are monitored once a month. The current Phe level is reported between 2 – 6 mg/dL which is the accepted range for children with PKU. The child has dietary restrictions placed on meat, dairy, nuts, beans and pasta intake. She is supplemented with PKU infant/toddler formula.

Out of the 11 survey questions which assessed parental knowledge on general PKU topics, subject #2 answered all questions correctly. This is perhaps because she receives her PKU information from several different sources. She has increased her knowledge of PKU through research she has done on her own and support groups.

CASE STUDY – Subject #3

Subject #3 is the mother of a three year old male from the west region of the United States. Subject #3 receives the majority of her information on PKU from a specialist at a hospital or clinic and also through research done on her own. Subject #3 reported that the child's current Phe level is within the range of 2 – 6 mg/dL and is monitored biweekly. The child is restricted on meat, dairy, nuts and beans and is supplemented with infant/toddler formula and medicated foods. Since the child is not reported as being restricted on pasta intake and he is receiving dietary supplementation via medicated foods, the child is most likely consuming a source of low protein pasta, although this was not specified by the child's mother in the survey.

Out of the 11 questions that assessed subject #3's knowledge of PKU, three questions were answered incorrectly. Question #15 inquired about the missing component in PKU. While the answer is "A liver enzyme called phenylalanine hydroxylase," subject #3 answered with "Nothing is missing." Too much tyrosine is produced in PKU." Due to the insufficient functioning of the hepatic PAH enzyme, individuals with PKU fail to adequately metabolize phenylalanine. The breakdown of phenylalanine to tyrosine is therefore inhibited, causing too much phenylalanine to be produced in the blood. When a PKU child's blood Phe concentration becomes elevated, the child's IQ score decreases, if left untreated, due to the lack of dietary intervention.

Subject #3 also answered question #20 incorrectly. When the child does not eat for several days at a time due to illness, the blood Phe concentration increases. This is due to in part to three different factors: 1) The rate at which a child grows and develops has slowed significantly by age three which can cause Phe levels to increase since less Phe is being used to create new protein, 2) When dietary intake decreases, the body automatically begins to breakdown and utilize the muscles for a means of nutrition. This releases Phe into the bloodstream, and 3) A child's diet is negatively impacted from illness. Without intake of food and medicated formulas/foods, the body will again use the muscle tissue for nutrients which increases Phe levels in the blood.

CASE STUDY – Subject #4

Subject #4 is the mother of a four-year-old male who resides in the southern region of the United States. Subject #4 stated in the survey that she received the majority of her information on PKU from a specialist at a hospital or clinic. Subject #4 confirmed that the child does receive medical counseling/treatment from a physician or RD pertaining to his PKU. The child's Phe level is currently within the ideal range of 2 – 6 mg/dL and levels are monitored once every three months. The child is restricted on meat, dairy, nuts, bean and pasta intake. Dietary supplements consumed by the child include adult formula and KUVAN.

Subject #4 answered eight of the 11 questions correctly. Subject #4 answered question #18 incorrectly. She reported that the acceptable Phe level in children with PKU is between 6 – 10 mg/dL, when in fact, the acceptable range is between 2 – 6 mg/dL. Due to this, the investigator believes that perhaps the child has classic PKU versus HPA. Although the child's Phe level is within acceptable range, the child is on

KUVAN but still restricted on all food groups containing Phe. The idea behind KUVAN is to slowly reinitiate food groups such as meat, dairy, nut, beans and pasta back into the child's diet a little at a time while monitoring Phe levels frequently to assess whether KUVAN is working and also to assess which food groups the child is more sensitive to even with the use of KUVAN. The child is supplemented with adult formula at the age of four years. The previous case study reports on a three-year-old child who was supplementing with infant/toddler formula. Therefore, the transition from infant/toddler formula to adult formula must occur at or around the time of the child's fourth birthday.

CASE STUDY – Subject #5

Subject #5 is the mother of a four-year-old male who lives in the western region of the United States. Subject #5 reported that she has not received any information regarding the child's PKU. She also confirmed that the child is currently not receiving medical intervention from a physician or registered dietitian. The child's Phe level is currently not monitored; however, the mother reported that current Phe levels fall between 2 – 6 md/dL. The child has no dietary restrictions nor does he consume any form of dietary supplementation related to his PKU.

Subject #5 answered only four of the 11 knowledge questions correctly. It is probable that either subject #5 lacks a strong understanding on the general concepts of PKU or she did not take time to read the questions in full and selected answers randomly. There is no clear pattern to indicate that subject #5 has more knowledge in one aspect of PKU over another. She was correct in that Phe is an amino acid and that PAH is the missing component that causes PKU. However, when asked specifically,

“What is the cause of PKU?” subject #5 was unable to provide an answer. She also lacks dietary knowledge pertaining to PKU.

CASE STUDY – Subject #6

Subject #6 is the father of a 17-year-old female from the southern region of the United States. Subject #6 reported that he received the majority of PKU information from research that he has done on his own and from PKU support groups. Subject #6 reported that the child does currently receive medical counseling/treatment from a physician or RD. The child’s Phe level is monitored once every three months. Currently, the child’s Phe level is between 11 – 15 mg/dL and is the only child reported from the study that has a Phe level outside of the ideal range for PKU. Subject #6 reported that meat, dairy, nuts, beans and pasta are all restricted in the child’s diet. The child is supplemented with adult formula, medicated food and KUVAN.

Overall, subject #6 has a strong understanding of the various concepts related to PKU. However, he answered question #18 incorrectly. He stated that an acceptable Phe level is 6 – 10 mg/dL in children with PKU. The child’s Phe level is between 11 – 15mg/dL. It is therefore believed that the child has classic PKU. Phe levels are higher in individuals with classic PKU versus HPA. Also, KUVAN has a higher success rate in controlling Phe levels in those individuals with HPA versus class PKU. KUVAN’s main purpose is to increase residual hepatic PAH enzyme activity to decrease blood Phe levels in individuals with PKU. It is rare that an individual with HPA who is protein restricted, supplemented with medicated formula and foods, and taking KUVAN would have a Phe level within the range of 11 – 15 mg/dL. The Phe level would remain within acceptable range. Therefore, perhaps it is necessary to believe that

the child's Phe levels are commonly elevated due to a present diagnosis of classic PKU and that a goal range for this child is between 6 – 10 mg/dL. This would explain why subject #6 chose 6 – 10 mg/dL as an acceptable Phe level in children with PKU.

CASE STUDY – Subject #7

Subject #7 is the father of an 18-year-old male who lives in the southern region of the United States. Subject #7 reported that he received most of his information regarding PKU from a specialist at a hospital or clinic. The child currently does not receive medical counseling/treatment for his PKU. His Phe level is monitored twice each year and the most recent Phe level is less than 2 mg/dL. The child is restricted on meat, dairy and nut intake. He consumes adult formula and tyrosine supplements as part of his PKU diet.

Subject #7 exhibited an overall proficient understanding of PKU. Subject #7 answered nine of the 11 questions correctly. Subject #7 did not answer correctly question #20 which asked “If your child does not eat for 2 days, what will happen to their blood Phe concentration?” Only two participants from this study answered question #20 correctly. The answer to question #20 is, “Blood Phe level increases.”

CHAPTER FIVE

CONCLUSIONS

The purpose of this study was to assess the knowledge of PKU for parents of children who have the condition. Seven parents completed the online survey that was designed to describe how parental knowledge affects the Phe levels of children with PKU. Blood Phe control is achieved by knowledge of PKU, regular blood testing, routine visits to PKU clinics, and dietary treatment.

The blood Phe levels were lower in the infant and 18-year-old than the toddler and preschool-age children, while the PKU knowledge score was second lowest for the infant's mother and slightly above the mean for the father of the 18-year-old. The PKU knowledge of parents of the infant and preschool children varied significantly with some parents having a strong understanding of PKU and other parents lacking knowledge pertaining to PKU. The PKU knowledge of parents with adolescents was proficient. The blood Phe level of the majority of the subjects was within the acceptable range of 2 – 6mg/dL for children with PKU. Overall, the blood Phe levels were lower in children whose parents had strong knowledge about dietary intervention. However, it cannot be compared to the Phe levels of children whose parents lacked strong knowledge about dietary treatment of PKU because these parents reported their child having low Phe levels of 2 – 6 mg/dL or less.

A case study approach provided documentation of the diversity that exists among children with PKU. Although PKU is treated via diet therapy, PKU is a multidimensional condition and dietary treatment is often structured around the individual's needs.

Limitations

1. The primary limitation of the present study is its small sample size. Due to the study's limited sample size, it is doubtful that true random sampling occurred.
2. Since the questionnaires were distributed through email, the researcher was forced to believe the participants completed the surveys independently and without any assistance from outside sources.
3. Some participants had more than one child with PKU. However, the survey asked for information only on the eldest child with PKU.
4. Parents were asked to provide an accurate Phe level from their child's most recent laboratory results. It is trusted that parents provided precise information of the child's Phe level to the best of their knowledge.

Recommendations for Future Research

1. To provide insight as to why some parents' knowledge scores are higher than other parents, future research should expand to include the parent's occupation, level of education, and socioeconomic status; these items could be added to the demographics portion of the survey.
2. Participants had trouble correctly answering question #18 which asked about the "acceptable Phe level in children with PKU." Subsequent research on this topic should include a revised survey that contains a revision of several questions so that they are more comprehensible to the participants.
3. Future research should concentrate on the relationship between counseling that the parent receives on PKU and the parent's knowledge score to determine if there is a direct relationship between parental counseling and knowledge score.

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APPENDICES

APPENDIX A

Parental Knowledge of PKU

In this survey, we are interested in learning more about your knowledge of and experiences with PKU.

When answering these questions, please consider your child or children who have the condition. If you have more than one child with PKU, please answer with reference to your oldest child.

This survey is to help us understand parental knowledge of PKU. Your identity as well as the answers you provide will remain confidential. Also, we are not evaluating individual responses, so answer to the best of your ability.

1. What is your child's gender?

- Female
- Male

2. How old is your child?

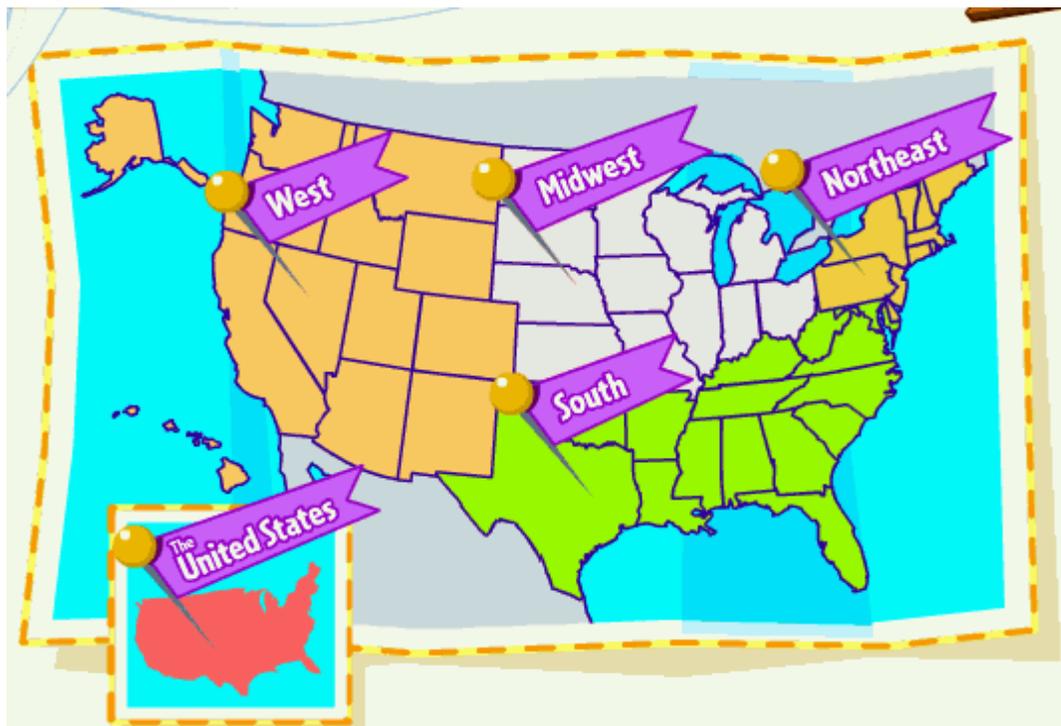
How old is your child?

3. What is your relationship to your child?

- Mother
- Father
- Step-mother
- Step-father
- Grandmother
- Grandfather
- Aunt
- Uncle
- Guardian

Other (please specify)

Regions of the United States



4. From what region of the United States do you and your child live?

- West
- Midwest
- Northeast
- South

Other (please specify if you live outside the US)

5. From where do you receive the majority of your information regarding PKU?

- My child's pediatrician or primary care physician (PCP)
- A hospital or clinic where my child is followed by a specialist (RD, CNPA, MD, etc.)
- Research that I have done on my own (articles, books, on-line resources, etc.)
- PKU support groups

I have not received any information regarding my child's PKU.

Other (please specify)

6. Currently, does your child seek medical counseling/treatment from either a physician or registered dietician for their PKU?

- Yes
 No

7. Currently, is your child's blood Phe level monitored?

- Yes
 No

8. How often is your child's blood Phe level checked?

- Never
 Weekly
 Biweekly
 Once a month
 Once every two months
 Once every three months
 Twice a year
 Once a year

Other (please specify)

9. What is your child's MOST current Phe level?

- < 2 mg/dL
 2 - 6 mg/dL
 7 - 11 mg/dL
 11 - 15 mg/dL
 15 - 20 mg/dL
 > 20 mg/dL

10. Which of the following are restricted in your child's diet?

- | | | |
|--------------|------------------------------------|-----------------------------------|
| Meat | <input type="checkbox"/> Meat Yes | <input type="checkbox"/> Meat No |
| Dairy | <input type="checkbox"/> Dairy Yes | <input type="checkbox"/> Dairy No |
| Nut | <input type="checkbox"/> Nut Yes | <input type="checkbox"/> Nut No |
| Bean | <input type="checkbox"/> Bean Yes | <input type="checkbox"/> Bean No |
| Pasta | <input type="checkbox"/> Pasta Yes | <input type="checkbox"/> Pasta No |

Other (please specify)

11. Which of the following supplements does your child consume?

- | | Yes | No |
|-------------------------------|---|--|
| Infant/Toddler Formula | <input type="checkbox"/> Infant/Toddler Formula Yes | <input type="checkbox"/> Infant/Toddler Formula No |
| Adult Formula | <input type="checkbox"/> Adult Formula Yes | <input type="checkbox"/> Adult Formula No |
| Medicated Food | <input type="checkbox"/> Medicated Food Yes | <input type="checkbox"/> Medicated Food No |
| Tyrosine Supplement | <input type="checkbox"/> Tyrosine Supplement Yes | <input type="checkbox"/> Tyrosine Supplement No |
| Kuvan | <input type="checkbox"/> Kuvan Yes | <input type="checkbox"/> Kuvan No |

Other (please specify)

Parental Knowledge of PKU

12. What is the cause of phenylketonuria (PKU)?

- PKU is inherited
- PKU is caused by a disease
- PKU is caused by eating too much sugar
- PKU is contagious
- Don't know

13. If a PKU child is not treated, what happens?

- The child will be physically handicapped
- The child will have muscle pain
- The child will have a stomach ache
- The child will be mentally handicapped
- Don't Know

14. What is phenylalanine (Phe)?

- A medicine
- An amino acid
- A carbohydrate
- A fat
- Don't know

15. What is missing in PKU?

- Phenylalanine that is needed for proper brain development
- Nothing is missing. Too much tyrosine is produced in PKU
- A liver enzyme called phenylalanine hydroxylase
- Don't know

16. What is the most important rule in the dietary treatment of PKU?

- Limit intake of protein substitute and sugar
- Increase intake of Phe and sugar
- Increase intake of protein substitute and limit Phe

- Consume large amounts of Phe
- Don't know

17. When should dietary treatment in PKU begin?

- Within the first couple weeks of the child's life
- After the child's first birthday
- Once the child turns 10 years old
- Dietary treatment is never necessary
- Don't know

18. What is considered an acceptable Phe level (mg/dL) in children with PKU?

- Less than 0 mg/dL
- Less than 1 mg/dL
- Between 2 and 6 mg/dL
- Between 6 and 10 mg/dL
- Greater than 20 mg/dL
- Don't know

19. If your child's blood Phe concentration gets too high, what happens?

- The child's IQ score increases
- The child's IQ score decreases
- Nothing happens
- Don't know

20. If your child does not eat for 2 days, what will happen to their blood Phe concentration?

- Blood Phe level increases
- Blood Phe level does not change
- Blood Phe level decreases
- Don't Know

21. Which food group should be completely avoided according to the PKU diet?

- Vegetables
- Fruits
- Meats
- Grains
- Don't know

22. If Phe levels are too high, what should the child do?

- Eat less Phe and more protein substitute
- Eat more Phe and less protein substitute
- Eat more Phe and more protein substitute
- Don't Know

APPENDIX B

Hello, my name is Lauren Ingram. I am a graduate student finishing my last semester at Middle Tennessee State University in Murfreesboro. I am conducting research for my thesis and need your help. I would greatly appreciate your participation by completing a brief survey about parental knowledge of Phenylketonuria (PKU). I chose to write my thesis on PKU because my 2 year old son was diagnosed with PKU at birth. We may have met some of you at the December 2010 and 2012 TN PKU Foundation meeting in Nashville, TN.

The survey takes less than 5 minutes to complete. There are no risks or costs associated with completing the survey. There will be no compensation for participation in this study. The information you provide will give insight into the relationship between parental knowledge of PKU and control of PKU in children.

The survey is anonymous. No one will be able to identify you or your answers. Should the data be published, no individual information will be disclosed.

If you have any questions or wish to learn more about the study, please contact me at (615) 653-7813 or at lpc2g@mtmail.mtsu.edu.

Middle Tennessee State University's Institutional Review Board has reviewed my request to conduct this project. If you have any concerns about your rights in this study, please contact The Office of Compliance at MTSU IRB at (615) 494-8918 or email compliance@mtsu.edu.

Thank you so much and I appreciate your help!

Lauren Ingram, BS Nutrition

APPENDIX C



TENNESSEE PKU
FOUNDATION

February 8th, 2011

Dr. Colson,

Lauren Ingram has the TN PKU Foundation's permission to use our contact list from the annual TN PKU Foundation meeting held December 2010 in Nashville, Tennessee for the purpose of her thesis.

Sincerely,

A handwritten signature in blue ink that reads "Heather M. Bomar". The signature is fluid and cursive, with the first name being the most prominent.

Heather Bomar
Board Member
Treasurer

P.O. Box 681914
Franklin, TN 37068
www.tennesseepku.org

APPENDIX D



January 18, 2013

College of Behavioral and Health Sciences, Dept. of Human Sciences
Lauren P. Ingram lpc2g@mtmail.mtsu.edu

Janet Colson

Protocol Title: Parental Knowledge of Phenylketonuria and the Effects of Phenylalanine Levels of Children with Phenylketonuria

Protocol Number: **13-174**

Dear Investigator(s),

The MTSU Institutional Review Board, or a representative of the IRB, has reviewed the research proposal identified above. The MTSU IRB or its representative has determined that the study poses minimal risk to participants and qualifies for an expedited review under 45 CFR 46.110 Category 7.

Approval is granted for one (1) year from the date of this letter for **32** participants.

According to MTSU Policy, a researcher is defined as anyone who works with data or has contact with participants. Anyone meeting this definition needs to be listed on the protocol and needs to provide a certificate of training to the Office of Compliance. **If you add researchers to an approved project, please forward an updated list of researchers and their certificates of training to the Office of Compliance (c/o Andrew, Box 134) before they begin to work on the project.** Any change to the protocol must be submitted to the IRB before implementing this change.

Please note that any unanticipated harms to participants or adverse events must be reported to the Office of Compliance at (615) 494-8918.

You will need to submit an end-of-project form to the Office of Compliance upon completion of your research located on the IRB website. Complete research means that you have finished collecting and analyzing data. **Should you not finish your research within the one (1) year period, you must submit a Progress Report and request a continuation prior to the expiration date.** Please allow time for review and requested revisions. Your study expires **January 18, 2014.**

Also, all research materials must be retained by the PI or faculty advisor (if the PI is a student) for at least three (3) years after study completion. Should you have any questions or need additional information, please do not hesitate to contact me.

Sincerely,

Shelley C. Moore, PhD(c), MSN, RN
IRB Committee Member

APPENDIX E



To Whom It May Concern:

We are writing a letter of medical necessity regarding the treatment of (patient first name & last name). (patient name) has been under the consultative care of the (clinic name). He/She has an inborn error of metabolism, a genetic disorder, known as phenylketonuria (PKU, ICD 9 270.1). We are writing to request that low protein modified food products be covered by his/her current medical insurance.

PKU is a lifelong problem that requires a phenylalanine-restricted diet including low protein modified food products and the prescription of medical foods/formulas by a licensed physician with the support of a registered dietitian in order to control the blood phenylalanine level. Low protein modified food products are defined as manufactured products that will deliver no more than one gram of protein per serving. Low protein modified food products supply needed additional calories (to help prevent catabolism, which in itself can cause phenylalanine levels to rise), without supplying additional phenylalanine containing protein. Use of low protein modified food products, especially when used consistently, greatly improves adherence to the treatment program.

PKU results from a deficiency of the enzyme responsible for metabolizing the amino acid phenylalanine. This results in the build-up of phenylalanine to toxic levels. An untreated child with PKU will suffer irreversible brain damage as well as severe and progressive neurological disorders. Normal growth and development are possible if an infant with PKU is treated appropriately. In adolescents and adults, neurological deterioration, phobias, difficulty in concentration and impulse control, and loss of IQ points can occur if treatment is not sustained.

Patients are treated with prescribed medical foods/formulas, as well as a phenylalanine-restricted diet which includes low protein modified food products. This diet excludes all foods high in protein (i.e. meat, poultry, fish, dairy, nuts and legumes) and markedly restricts all grains, including rice, breads, and pastas. Medical foods/formulas provide the primary protein constituent (80-85% of RDA protein) for the PKU dietary treatment regimen. Low protein modified food products provide other nutrients which includes additional calories to prevent catabolism which can cause a rise in phenylalanine levels. Use of these products is medically supervised by a physician and implemented by a registered dietitian specially trained in the nutrition management of inborn errors of metabolism. Nutrition therapy must also

provide a sufficient and balanced intake of other nutrients to avoid nutritional deficiencies. Nutrition therapy of PKU solely via protein restriction is not possible, because it will result in protein malnutrition, calorie deprivation, vitamin and mineral deficiency, failure-to-thrive, and potentially death.

The standard of care for PKU requires the use of the medical food/formulas and a phenylalanine-restricted diet which includes the use of low-protein modified food products, as well as routine nutrition follow-up with a specially trained registered dietitian. The two primary goals of treatment are:

1. To maintain the blood phenylalanine at a level that is not toxic, but still allows for normal growth and development.
2. To ensure that the individual's overall nutritional requirements are met, allowing for normal growth and development, and the avoidance of nutritional deficiencies.

The recommended treatment range of blood phenylalanine levels for individuals with PKU is between 2 and 6mg/dL (120 and 360 μ mol/L). There is good correlation of cognitive function and maintenance of blood phenylalanine levels in this treatment range. Elevated blood phenylalanine in patients has been associated with behavior and learning problems which can reverse when the blood levels return to the treatment range. Currently, indefinite continuation of dietary management is recommended to all patients with PKU. These recommendations are based on a growing body of evidence indicating there is a decline in average IQ and development of difficulties in school performance after diet discontinuation.

We appreciate your attention to this request for (patient's name)'s low protein modified food products to be covered by his/her current medical insurance. Please do not hesitate to contact us if you have any questions at (clinic contact info).

Sincerely,

(dietitian name), RD, LDN
(physician credentials, clinic name)

(Physician name), M.D.

cc: (parents name)

SAMPLE LETTER FOR INSURANCE COVERAGE OF MEDICAL FOODS

(Date)

RE: (patient name)

D.O.B: (patient date of birth) To Whom It May Concern:

We are writing a letter of medical necessity regarding the treatment of (patient first name & last name). (patient name) has been under the consultative care of the (clinic name). He/ She has an inborn error of metabolism, a genetic disorder, known as phenylketonuria (PKU, ICD 9 270.1). We are writing to request that medical food/formula be covered by his/her current medical insurance.

PKU is a lifelong problem that requires a phenylalanine-restricted diet and the prescription of special medical foods/formulas by a licensed physician with the support of a registered dietitian in order to control the blood phenylalanine level. The term medical food/formula as defined in section 5(b) of the Orphan Drug Act {21 U.S.C. 360ee (b) (3)} is a "food which is formulated to be consumed or administered internally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles are established by medical evaluation."

PKU results from a deficiency of the enzyme responsible for metabolizing the amino acid phenylalanine. This results in the build-up of phenylalanine to toxic levels. An untreated child with PKU will suffer irreversible brain damage as well as severe and progressive neurological disorders. Normal growth and development are possible if an infant with PKU is treated appropriately. In adolescents and adults, neurological deterioration, phobias, difficulty in concentration and impulse control, and loss of IQ points can occur if treatment is not sustained.

Patients are treated with prescribed medical foods/formulas (in a variety of forms powder, capsule, liquid, bar etc.), special low-protein modified food products as well as a phenylalanine-restricted diet. This diet excludes all foods high in protein (i.e. meat, poultry, fish, dairy, nuts and legumes) and markedly restricts all grains, including rice, breads, and pastas. Currently, (patient name) is prescribed (name of medical formula) which is a medical formula used to manage PKU. Medical foods/formulas provide the primary protein constituent (80-85% of RDA protein) for the PKU dietary treatment regimen. Use of these products is medically supervised by a physician and implemented by a registered dietitian specially trained in the nutrition management of inborn errors of metabolism. Nutrition therapy must also provide a sufficient and balanced intake of other nutrients to avoid nutritional deficiencies. Nutrition therapy of PKU solely via protein restriction is not possible, because it will result in protein malnutrition, calorie deprivation, vitamin and mineral deficiency, failure-to-thrive, and potentially death.

The standard of care for PKU requires the use of the medical food/formulas and a phenylalanine-restricted diet, as well as routine nutrition follow-up with a specially trained registered dietitian. The two primary goals of treatment are:

1. To maintain the blood phenylalanine at a level that is not toxic, but still allows for normal growth and development.
2. To ensure that the individual's overall nutritional requirements are met, allowing for normal growth and development, and the avoidance of nutritional deficiencies.

The recommended treatment range of blood phenylalanine levels for individuals with PKU is between 2 and 6mg/dL (120 and 360 μ mol/L). There is good correlation of cognitive function and maintenance of blood phenylalanine levels in this treatment range. Elevated blood phenylalanine in patients has been associated with behavior and learning problems which can reverse when the blood levels return to the treatment range. Currently, indefinite continuation of dietary management is recommended to all patients with PKU. These recommendations are based on a growing body of evidence indicating there is a decline in average IQ and development of difficulties in school performance after diet discontinuation.

We appreciate your attention to this request for (patient's name)'s medical formula, (name of medical formula) to be covered by his/her current medical insurance. Please do not hesitate to contact us if you have any questions at (clinic contact info).

Sincerely,

(dietitian name), RD, LDN
(physician credentials, clinic name)
cc: (parents name)

(Physician name), M.D.