A Pilot Study on the Attitudes of Management Practices in Adults with PKU

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A PILOT STUDY ON THE ATTITUDES OF MANAGEMENT PRACTICES IN ADULTS WITH PKU

By

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A THESIS

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A PILOT STUDY ON THE ATTITUDES OF MANAGEMENT PRACTICES IN ADULTS WITH PKU

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University of Nebraska, 2012

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Phenylketonuria (PKU) is a genetic disorder caused by the deficiency of the enzyme, phenylalanine hydroxylase. Phenylalanine accumulation in brain causes cognitive impairment and behavioral problems, which can be prevented by dietary restriction of phenylalanine. People with PKU have to maintain a highly restrictive low protein diet throughout their entire life. PKU is typically diagnosed at birth through newborn screening. In order for a patient to reach their optimal IQ and health status, they need to maintain their blood phenylalanine (phe) level within the recommended range of 60-360 µmol/L.

The purpose of this study is to investigate attitudes of adults diagnosed with phenylketonuria (PKU) and how they relate to their actions of management therapy recommendations. Adults with PKU completed an online survey through Survey Monkey. After receiving consent via email, the survey link was sent to them so they completed it at their convenience. The study asked questions such as, how often they tested their blood phe level and compared that to how often their clinic recommends getting tested. Then subjects were asked on a scale of one to five (with five meaning they strongly agree) if they agreed that getting their blood phe level tested as often as their clinic recommends is important. From the data we gathered information about different management practices, the perceived importance of certain
dietary management practices, and whether certain factors, such as relationships between patient and clinic influence dietary management. There was no set universal method for counting phe intake. While there are three main methods, the two that were used the most were by counting exactly using milligrams (mg) of phe and the other was an estimation of counting in grams of protein. It was also found that the relationship with the clinic may have an impact on dietary management. Patients who had a good relationship with their clinic were more likely to follow their daily protein restriction, test their blood phe level more often, and realize the importance of testing their blood phe level as often as their clinic recommends.
Acknowledgments

I would like to start off by thanking Dr. Kaye Stanek-Krogstrand for being my advisor and providing the encouragement to foster my interests. She has always been supportive in my efforts to work in the area of phenylketonuria. I would also like to thank Dr. Wanda Koszewski for unexpectedly becoming my co-advisor. She kept me on track and was always willing to give advice. A special thanks goes to Dr. Schnepf and Dr. Rizo for being on my committee. Each person brings an area of expertise that is invaluable. I want to also thank Jill Skrabal for being willing to provide suggestions and guidance whenever I needed it.

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Table of Contents

Acknowledgements........................................................................................................ iv

List of Tables and Appendix Tables............................................................................... vi

Chapter 1: Introduction.................................................................................................... 1

Chapter 2: Review of Literature...................................................................................... 1

Management of the Disease Practices of Health Professionals................................. 1

Factors Influencing Diet Adherence.............................................................................. 3

Potential Strategies for Treatment................................................................................. 6

Summary......................................................................................................................... 9

Chapter 3: Methodology................................................................................................. 11

Chapter 4: Results.......................................................................................................... 13

Chapter 5: Discussion..................................................................................................... 20

Chapter 6: Limitations.................................................................................................... 23

Chapter 7: Future Research............................................................................................ 24

Chapter 8: Conclusion.................................................................................................... 24

References....................................................................................................................... 25
List of Tables

Table

1. Daily Phe Allowance................................................................. 17
2. Methods Use to Keep Track of Daily Phe Allowance.............. 18
3. Types of PKU Support Groups.................................................... 19

List of Appendix Tables

Appendix A: Approval from IRB....................................................... 28
Appendix B: Approval from IRB with changes.............................. 30
Appendix C: Letter Invite to PKU Electronic Mailing List .............. 31
Appendix D: Survey to Adult PKU Patients................................. 32
Appendix E: Summary of Significant Correlations....................... 37
Chapter 1: Introduction

People diagnosed with phenylketonuria (PKU) have to maintain a highly restrictive low protein diet throughout their entire life. PKU is a genetic disorder that results in a deficiency of the enzyme, phenylalanine hydroxylase. This enzyme breaks down the amino acid, phenylalanine, into another amino acid, tyrosine, making tyrosine an essential amino acid in patients with PKU. Along with a low protein diet, an amino acid formula (excluding phenylalanine) has to be consumed to provide adequate protein. If excess phenylalanine builds up, it metabolizes into toxic substances and causes problems in thinking and behavior. PKU is typically diagnosed at birth through newborn screening programs. However, if it is not caught and treated, the patient will become significantly mentally challenged for a lifetime. In order for a patient to reach their optimal IQ and health status, they need to maintain their blood phenylalanine (phe) level within the recommended range of 60-360 µmol/L. (Waisbren, 2007). As with any chronic disease PKU is very complex and successful management involves many factors.

Chapter 2: Review of Literature

Management of the Disease: Practices of Health Professionals.

Health professionals play a major role in dietary management. To increase understanding of current PKU management practices in health clinics, Blau et al. (2010) sent out a survey to a variety of health professionals who were involved in metabolic clinics all across Europe. Main focuses of the survey included general information about the center (such as number of patients, and definition of hyperphenylalaninemia), screening practices, treatment practices, follow up practices, and use of existing guidelines and protocols. In the end, 93 treatment centers from 19
countries returned the survey in which a total of 14,837 PKU patients were on record. Of these, only 12,409 PKU patients were seen per year for follow-ups. Only 12% of the 93 centers provided a full team coverage including physicians, dietitians/nutritionists, specialty nurses, psychologists and clinical biochemists. While there was a general consistency of the definition of classical PKU, moderate and mild PKU classifications were inconsistent between centers, even centers within one country. There was also a discrepancy as to at what blood phe concentration treatment should begin and only about half of the centers reported using the protocols from their center. Their results indicated an great need for a joint European guideline for the management of PKU (Blau, 2010).

While there needs to be an established international set of guidelines for treating patients with PKU, it should also include guidelines for infants with PKU as well. Portnoi et al. 1999 sent out a survey to experienced dietitians who work with PKU patients from nine clinics in the United Kingdom (UK) and four in Australia. These dietitians were overseeing a total of 63 infants. Questions from the survey included topics of quantity of amino acids given, the type of protein substitute used, use of breast milk versus normal infant formula, energy requirements, use of energy supplements and weaning practices. Twenty eight percent of the infants with PKU in the UK (n=14) were breast fed while 41% (n=8) of infants were breast fed in Australia. According to the UK Medical Research Council, recommendations for amino acids in a phenylalanine free formula for normal infants are 3.0 grams/kilogram per day. Twenty-eight percent of the dietitians surveyed reported prescribing less amino acid than recommended. About half of the dietitians, 45 percent, suggested solids by three months of age as the volume of regular infant formula had to be maintained and infants had increasing appetite. Dietitians varied in the method by which they introduced a concentrated protein supplement with 25 percent using
a protein substitute with no added vitamins and minerals, half of the dietitians using a protein substitute with increased carbohydrates, vitamins, and minerals, and 25 percent of dietitians using both methods. This study emphasizes the need to have a universal guideline for management practices of PKU.

It seems that clinicians around the world use similar, but not exact, recommended phe levels however; these levels are only a snapshot of that point in time. Health professionals often focus on overall mean lifetime blood levels. There is little to no research investigating effects of the stability of blood phe levels. A study by Anastasoaie and associates (2008) looked at the possible correlation between Full Scale IQ (FSIQ) and (1) average blood phe levels for each participant and (2) consistency of blood phe levels determined by the set standard deviation of blood phe level for each subject. Anastasoaie et al. (2008) asked if stability of blood phe is related to cognitive outcome in early and continuously treated PKU. Measurements that were taken from 46 children included the Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children, and Wechsler Abbreviated Scale of Intelligence. There was not a significant correlation between standard deviation of blood phe levels and most recent FSIQ, but it was closely related at \( p = .06 \). This showed a closer relationship than the relationship with mean lifetime blood phe level and cognitive outcome. These results may suggest the need for an increase in frequency of testing patients’ blood phe levels to monitor fluctuations.

**Factors influencing diet adherence.**

A number of factors affect how well a patient will be compliant. One component of dietary management that Olsson, Montgomery, and Alm (2007) looked at was family influence. A total of 41 Swedish patients completed a postal questionnaire regarding this topic. There were two questions for patients focusing on frequency of amino acid formula intake per day and eating
foods on the diet. Questions for parents focused on how parents helped their child; if they take time to prepare special food for traveling, celebrations, sickness, and if they planned the diet carefully when blood test results arrive. Additional background variables were also in the analysis, such as parent’s marital status and education level. Parents’ marital status was the only significant relation to phe levels where patients tended to have higher phe levels when their parents were separated or divorced. This shows that family roles may have an influence on dietary compliance.

Another study by Crone et al. (2005) explored parental dynamics that may relate to PKU patients and their adherence to the diet. A questionnaire was sent out to parents in the Netherlands with children, up to age 22, having PKU. It focused on factors such as parent’s attitudes, beliefs, subjective norms, emotional reactions, and self-efficacy that may affect the patient’s behavior. Before the questionnaire was sent out, the average phe concentrations for the children were collected from the previous three years. Out of the 238 questionnaires sent out, 170 parents filled it out and returned it. Significant results showed decreased average phe concentration was seen when parents reported that their child followed the diet, despite infrequent higher phe levels and the reported ease of providing the amino acid formula three times a day. Increased mean phe concentrations were seen in children with parents reporting disapproval from relatives when the child did not follow the diet. This might suggest that caregivers and family should be firm with the child’s adherence to the diet but not be harsh.

Bilginsory, Waitzman, Leonard, & Ernst (2005) were also interested in investigating barriers to the diet according to patients and caregivers. A survey was mailed to PKU patients and their caregivers in Utah focusing on management of the disease and difficulties of compliance. Caregivers were asked to complete each question and children over 10 years of age
were asked to complete a division of questions. A total of 32 surveys were returned. There were 13 subjects over the age of ten who filled out a portion of the survey. With the recommended frequency of blood phe testing at once a month, the older cohort of respondents had an average number of tests of 6.6 per year. Compliance habits were frequently changed before a blood test was taken in 47% of families. Slightly less than half (45%) of subjects agreed that PKU was not “a substantial financial burden on their household.” (Bilginsory et al., 2005) Insurance for the majority of the families (83%) did not cover the expensive low protein foods. Two main sources of strain for caregivers dealt with planning/preparation of meals, and social implications of the diet.

Women of child bearing age particularly need to control their levels in order to prevent complications for the fetus. Using focus groups, Kemper et al. (2010), wanted to identify barriers and motivators in girls and women in regards to adhering to the diet. The study included 19 women attending a camp for women with metabolic diseases. Out of the 19 women, 15 women had PKU, two had methylmalonic academia (MMA) and the last two had Maple Syrup Urine Disease (MSUD). Each focus group was semi-structured and open ended questions covered perception of the diet, experience with medical providers and medical home services, and transition to adult medical services. Major barriers that were noted were insurance coverage, temptation to go off the diet, and potential lack of social support from family and friends. This suggests that interventions to help with dietary control need to be customized for each person due to the variability of symptoms when the diet is not followed. Other recommendations are difficult to improve due to type of insurance coverage. Suggested improvements that can be implemented are “educating school officials, expanding roles of metabolic RDs, and assisting with transition from pediatric to adult health-care providers” (Kemper et al., 2010).
Potential strategies for treatment

Knowledge of one’s disease may increase successful management of that disease. Bekhof et al. (2003) investigated caregivers and patient’s knowledge of PKU and the possible relation to average blood phe levels, which indicates level of adherence to the low protein diet. A questionnaire was completed by 62 PKU patients (aged 12-22 years old) and parents of 161 children with PKU (aged 1-22 years old). To measure dietary compliance, the mean blood phenylalanine of three years was taken. Out of the 14 total questions, just a little over half of the parents and 29 percent of the patients themselves got over 11 correct. Higher knowledge of the parents was significantly associated with lower phe levels of their children. This was no longer significant after accounting for other confounders, such as severity of the disease, patient’s age, education level of the parent, and ethnicity. Psychological and emotional factors may have an additional role as knowledge alone did not hold a significant association with diet compliance.

Durham-Shearer, Judd, Whelan, & Thomas, (2008) expanded on the idea that knowledge can be a tool in dietary adherence. They hypothesized that a patient-focused written education resource would be more effective as it would be tailored to patients based on their individual needs. An educational packet was formed based on a survey that was mailed to all 177 PKU patients seen at the adolescent and adult metabolic clinic at University College London Hospital in England. This survey inquired about preference of packet format, such as a booklet, folder, etc., and obtained a baseline of knowledge and compliance. A total of 71 surveys were returned and subjects who were compliant with the diet, concluded by self-responses and blood phe levels from the past six months, were invited to the second phase of the study. Out of the 32 compliant subjects, 22 received the custom educational resource, a filofax-style folder with removable
inserts. Ten of these subjects were put into a control group and received the resource after the completion of the study. All subjects were asked to return a follow up questionnaire after one and again after six months. After one month, 23 subjects returned the questionnaire and 22 subjects returned the questionnaire after six months. Knowledge level significantly increased after one month in the intervention group, but the difference was not maintained at six months. There was no significant difference in reported intake of protein formula at either follow up. Compliance with following prescribed phe intake was significantly greater in the control group at one month. This may mean that this resource may be useful as a supportive tool rather than a purely educational resource.

Another potential strategy to help with diet adherence may be to foster positive feelings and attitudes in children. Evans et al., 2009 hypothesized that supporting children’s cooking skills by providing educational materials might help develop positive attitudes regarding their diet. A group of children from one UK metabolic center helped put together an instructional cooking DVD along with a low protein cookbook. Effectiveness of the teaching aids was evaluated by a questionnaire containing mostly closed-ended questions and two open-ended questions. A total of 102 questionnaires were returned representing 88 families and 105 children. About 75 percent of caregivers and children who responded agreed that the resources motivated them to explore new recipes. No correlation was observed between median phenylalanine levels or number of blood samples along with any of these parameters: frequency of the low protein cooking, how useful caregivers found the DVD and book, whether they had tried the recipes, or the number of recipes tried.

To help patients stay motivated to follow the diet, health professionals should also be able to understand what the disease is like from the patient’s point of view. Vegni, Fiori, Riva,
Giovannini, & Moja, (2009) looked at how various age groups of patients who have PKU experience their disease. Forty patients with PKU from the Pediatric Department of the San Paolo Hospital of Milan volunteered for the study and were separated into three age groups with ten participants in each; 10-year-old age range, 15-year-old age range, 20-year-old and a 25-year-old age range. Open-ended question interviews conducted by trained psychologists were used to collect data. There were two major themes revealed throughout the groups; the internal representation of PKU and the understanding of PKU. Each age group had its own challenges, but appeared to be going through appropriate development stages. Respondents also showed a lack of knowledge about the disease. Vegni et al. (2009) suggested patient education needs to be improved and tailored to age as knowledge of the patient may be taken for granted. Suggestions for health care professionals were also expressed. Participants wished physicians were more personable and understood what having PKU was like.

Barriers of management have been a main focus in previous studies and there is a need to highlight helpful strategies for patients. Van Rijn et al. (2008) studied the preferred method of tracking phe intake in PKU patients. Two main methods include exact measurement or estimation. Out of the 327 surveys sent out, 189 were included in the data after returns and inclusion criteria. Patient’s responses were divided into three age groups: < 10 years old, 10-15 years old, and 16-29 years old. Questions looked into attitudes, subjective norms, and perceived behavioral control of the patients. Exact and estimation methods were defined for the patients. Younger groups tended to use exact measuring methods, and estimation was seen more frequently in older patients with only 20% of adult patients reporting using exact methods of measurements. There was no association between method of measuring phe intake and blood phe levels, although in the 10-15 year old group lower phe levels were seen in patients that used
exact methods of measurement. Clinicians may be able to recommend tailored methods for their patients in order to control their phe levels.

Until recently, strategies only involved what could be done to improve current treatments. Developments of new treatments have been advancing faster than ever. A review by van Spronsen and Enns (2010) discussed new medical treatments that show promise to increase compliance with the diet. It is now general knowledge that the low protein diet needs to be followed throughout life, but management methods are inconsistent throughout the world. One development in treatment was the discovery of glycomacropeptide (GMP). This is a natural protein, derived from goat’s milk, which contains minimal phe. This can potentially be used instead of the traditional formula as it has a more palatable taste and may be more effective in lowering phe levels. Limitations to this include the need to supplement tyrosine, tryptophan, vitamins and minerals. Another promising treatment is an injectable form of the enzyme, phenylalanine-ammonia lyase. This enzyme is responsible for breaking down phenylalanine into non-toxic compounds, preventing high levels of phe in the body. A recently FDA and EMEA approved drug, Kuvan®, works in patients who are responsive to a substance, (6R)-L-erthro-5,6,7,8-tetrahydrobiopterin or BH4, which aids in the breakdown of phenylalanine and potentially lowers phe levels significantly allowing for a more liberalized diet. The development of these treatments has been long anticipated and will significantly impact patients with PKU.

Summary

Successful management involves many complex issues such as overcoming barriers to diet adherence while finding what methods work to maintain that adherence, coping with social effects that the disease may entail, and being supported by peers and health care professionals. Several studies have explored the main barriers to the diet as perceived by patients, caregivers,
and clinicians. Main barriers include cost, knowledge of the disease, and inconsistent treatment methods.

There have also been studies on patients’ attitudes and other factors about dietary influence. Multiple factors include family dynamics, social support, and knowledge. There is minimal research on what patients are doing that they find helpful in managing their diet and how important these behaviors are to them. Another point that will influence a patient’s behavior is their daily phenylalanine tolerance. If one has a higher tolerance than they may not fully comply with their clinic’s recommendations. Someone with a lower tolerance may be aware of the consequences of having a high blood phe level and will feel that management practices are always important.

Another essential aspect is relating these behaviors to clinic recommendations. As mentioned above, there are inconsistent management guidelines. Patient’s behaviors may be related to what their clinic recommends. This may also show healthcare professionals what patients are doing and how they feel about it.
Chapter 3: Methodology

The goal of the present study was to discover attitudes of patients with PKU and how they relate to their actions of management therapy. The first hypothesis was adult patients will agree that it is important for them to keep track of their phe consumption daily, but they may actually keep track of their phe less often. The second hypothesis is that adults will also feel it is important to test their blood phe level as recommended but may actually test their blood phe level less frequently. An adult with PKU may feel they are familiar with following the diet through years of practice, and therefore may not feel the need to test their blood phe levels as much as their clinic recommends. The third hypothesis is that patients who feel they have a good relationship with their clinic will be more likely to follow the clinic’s recommendations. They are more likely to test their blood phe level per clinic recommendations and follow their daily restriction every day. If patients feel like their doctor or dietitian really cares about them, then they will be more motivated to follow their diet and other recommendations.

After obtaining approval from the Institutional Review Board (IRB) and changes in protocol (see Appendix A and B), a survey invitation was sent out to select adult patients with PKU in the United States. These select patients served to pilot test the survey. Health care professionals, which included three registered dietitians and one metabolic disease physician, also helped test the survey. After the survey was tested, a survey invitation was sent out to the main PKU electronic mailing list that reaches over 1,000 people, although the number of adults who actually have PKU on the list is unknown. The invitation also encouraged recipients to send the invitation to other possible participants. Possible subjects were also recruited from a PKU gathering held in Massachusetts in May 2011. However, there was limited gathering of PKU patients in attendance. Participants that qualified had to be diagnosed with PKU, be over the age
of 19 years and live in the United States. If someone was interested in participating, they emailed the primary researcher with their consent. Once patients responded with consent, a link to an online survey was sent to them. After four weeks, a reminder message was sent out to the original electronic mailing list. Subjects had two months, from October 2011 to December 2011, to complete the survey.

Questions on the survey revolved around management practices such as: what their daily phe allowance is, how patients keep track of their phe intake, how often they keep track of phe intake, how often they typically have their blood phe levels tested, and how often they are seen for a PKU checkup (Appendix D). Then the surveys asked about their attitudes towards these practices. These questions used a Likert type scale and asked the participant to scale how strongly they agree with a statement such as: “I feel it is important for me to get tested frequently.”

There were a total of 17 participants, who responded, ten of which were female. Participants lived across the United States from the following regions: Midwest (n=6), Northeast (n=6), Southeast (n=2), Southwest (n=2), and West coast (n=1). The youngest subject was 19 years old and the oldest two people were 42 years old.

Statistical analysis of the data included descriptive statistics in which means, standard deviations, ranges, and frequencies were calculated. Inferential statistics were used to determine Pearson correlations and possible significant correlations. Significances were determined at p < 0.05. Hypothesis testing was performed to find possible significant relationships between the following: importance of tracking daily phe intake and actual frequency of tracking daily phe consumption, importance of testing blood phe levels often and actual frequency of blood phe
level testing, and agreement of a good relationship with one’s clinic and frequency of following one’s daily protein restriction.

**Chapter 4: Results**

A table showing subjects’ daily phenylalanine allowance is shown below (Table 1: Daily Phe Allowances). Five of the 17 subjects had a daily phenylalanine allowance of 300-315 milligrams (mg) of phenylalanine per day. The common rough estimation is 50 mg of phe per one gram of protein (Schuett, 2011). Seven subjects had a daily phenylalanine allowance of 350-700 mg (around seven to fourteen grams of protein). Three subjects had allowances over 1000 mg of phe. One person had allowance of 3750 mg of phe which is approximately 75 grams of protein. Being able to have 75 grams of protein is unusual for someone with PKU. One explanation is that this subject has a form of PKU called benign hyperphenylalanemia when phenylalanine levels were tested through newborn screening; they were higher than normal, but not high enough for a diagnosis of Classical PKU. Patients with hyperphenylalanemia may not even need a restricted diet. (Arnold, 2009) Two of the responses of the question were taken out. One person responded “Unknown” to the question and one person answered the question “18.” This answer was unclear and could mean different things such as 18 grams of protein or 18 phe exchanges. In the United States, one phe exchange is equal to 15 mg of phe. By computing the Pearson correlation, the amount of phenylalanine allowed per day negatively and significantly correlated with subjects who agreed that meeting with a support group will help manage the diet (r = -0.589, p = .044).

“Table 2: Methods Used to Keep Track of Daily Phe Intake” shows how subjects keep track of their phe intake and if their clinic supports them in their choice of tracking phe. Methods used to track phe included; counting milligrams (mg) of phe in foods, using exchanges,
and counting by grams of protein. Using the exchange method, 15 mg of phe is equal to one exchange. In counting phe by grams of protein the common estimation is that there is 50 mg of phe per one gram of protein (Schuett, 2011). Counting phe by grams of protein is less exact than directly counting mg of phe in foods or using the exchange method. In the sample, eight subjects reported counting mg of phe in food, three subjects reported using phe exchanges, and seven subjects reported counting in grams of protein. Seven people felt that their metabolic clinic will support them in whatever method they feel comfortable with. Seven people agreed that the method they use is the method that their clinic recommends. Two people disagree that their reported method is one that their clinic recommends and one subject did not know what tracking method their clinic recommends.

Subjects reported sometimes to how often of keeping track of their phenylalanine consumption where keeping track of their phe consumption everyday = 5 and rarely = 1 (M = 3, SD = 1.54). Using Pearson's correlation, subjects keeping track of their phe consumption was positively correlated, although not significant, with the agreement that it is important to keep track of phe consumed (r = .491, p= .179). This result does not support the research hypothesis that adult patients will agree that it is important for them to keep track of their phe consumption daily but will keep track of their phe intake less often. The correlation between how often patients test their blood phe level and how often their clinic recommends doing it was insignificantly positive (r = .481, p = .051). A post-hoc test was performed to determine the chance of Type II error occurring between how often patients test their blood phe level and how often their clinic recommends getting tested. Power was 0.566 with a 43% chance of a Type II error occurring. Subjects reporting testing their blood phe level on average once every three months. Where 9 = once a week and 1 = once every two years the average was 5.41 (SD = 2.57).
The importance of following their clinic’s recommendations for frequency of testing where 5 = strongly agree and 1 = strongly disagree averaged to be 4.41 (SD = .618). The correlation between subjects actual frequency of testing and the importance of following their clinic’s recommendations for how often they test blood phe levels was not significant (r = .319, p = .213). This result does not support the research hypothesis that adult patients will agree that it is important for them to test their blood phe level as recommended, but may actually test their blood phe level less often.

Subjects who agreed that they have a good relationship with their clinic where 5 = strongly agree and 1 = strongly disagree had an average of 3.88 (SD = 1.11). There was a significant, positive correlation between subjects who agreed that they have a good relationship with their clinic and how frequently they test their blood phe level (r = .629, p = .007). There was also a significant correlation with these subjects and how often they follow their daily restriction (r = -.699, p = .002). In other words, the more they agreed that they had a good relationship with their clinic, the more often they followed their daily phe restriction. These subjects also felt that it was important to get tested as frequently as their clinic recommends (r = .530, p = .029). However, there was an insignificant positive correlation with how often they keep track of their phe (r = .474, p = .054). A post-hoc test was performed on this correlation and power was .561. There was a 44% chance that a Type II error occurred.

A significant and positive correlation was seen between how often patients keep track of their phe intake and how often they get their blood phe level tested (r = .724, p = .001). Subjects that tracked their phe intake more often tended to follow their daily protein restriction more often (r = -.642, p = .005) as in the coding, 1 = subjects follow the daily protein restriction every day. These subjects also felt it was important to get tested as often as their clinic
recommends \( r = .590, p = .013 \). Age was also tested against how often phe intake is tracked and how often blood phe level is tested \( (r = .107, p = .684; r = -.081, p = .946 \), respectively). In addition, there were no other significant correlations when focusing on age.

All participating subjects belonged to one or more support groups for PKU, as shown in Table 3: Types of PKU Support Groups. A support group could be any place (whether online or in person) where patients can go and communicate with other PKU patients about PKU issues. Thirteen subjects belonged to the electronic mailing list, 11 subjects belonged to a facebook group related to PKU, ten subjects belonged to an online PKU site such as www.pku.com, five subjects belonged to a local PKU organization, and six subjects reported belonging to a clinic support group. Being a part of a clinic support group was defined as attending regular PKU events and talking to their metabolic dietitians and/or physicians regularly. Nine participants belonged to at least three of the different types of support groups. On average, subjects reported that they sometimes interact with other people in these groups. There were no significant correlations between how often subjects interact with their support groups and any aspects of their diet management practices.
Table 1: Daily Phe Allowances

<table>
<thead>
<tr>
<th>Participant</th>
<th>Daily Phe Allowance (mg)</th>
<th>Actual response if not originally in “mg”</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td></td>
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<td>5</td>
<td>450</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>315</td>
<td>21 exchanges</td>
</tr>
<tr>
<td>9</td>
<td>450</td>
<td>75 grams of protein</td>
</tr>
<tr>
<td>10</td>
<td>Aprox. 3750</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>475</td>
<td>40 grams of protein</td>
</tr>
<tr>
<td>14</td>
<td>Aprox. 2000</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>700</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Methods Used to Keep Track of Daily Phe Intake

<table>
<thead>
<tr>
<th>Participant</th>
<th>Method used to keep track of phe</th>
<th>Does clinic support this method?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mg</td>
<td>Any method that helps</td>
</tr>
<tr>
<td>2</td>
<td>grams</td>
<td>Any method that helps</td>
</tr>
<tr>
<td>3</td>
<td>exchanges</td>
<td>Agree</td>
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Table 3: Types of PKU Support Groups

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<th>Participant</th>
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<th>Local Org.</th>
<th>Clinic</th>
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</table>

**Email** = electronic mailing list; **Facebook** = any PKU related group on facebook; **Site** = any website dedicated to PKU and allows users to interact with each other; **Local Org.** = any local PKU organization where people get a chance to meet; **Clinic** = regularly talking to metabolic physician and/or dietitian and attending events regularly hosted by the clinic.
Chapter 5: Discussion

When assessing the amount of phenylalanine one can have daily, the only significant association was seen when looking at whether subjects thought meeting in person with a support group will helped manage their diet. The lower the subject’s daily phe allowance, the more likely they will think that meeting in person with a PKU support group will help them manage their diet. This is expected because the lower someone’s daily phe allowance is, the more difficult it would be for them to come up with acceptable menu plans. Meeting with a support group could make determining a healthy, balanced meal plan easier.

As seen in Table 2: Methods Used to Keep Track of Daily Phe Intake, there is a variety of ways in which subjects kept track of their phe intake. Eight of the 17 subjects measure in mg of phe, seven subjects measured in grams of protein, and three used phe exchanges. This shows that different clinics may be recommending different methods of tracking. Each clinic may be only recommending one method for all of their patients or they could suggest tracking methods based on the patient’s preferences. In this study, the age of the subject did not significantly correlate with how they keep track of their phe intake. Van Rijn et al. (2008) found that subjects under ten years of age tended to use more exact counting methods. Subjects older than ten years of age and younger than 29 years old used estimation methods. The questions used in their study asked about specific situations, such as how would you measure phe if you were at a restaurant, where this study asked subjects about how they typically measure phe.

As the results show, seven subjects reported that they feel that their clinic would support them in whatever method they found the most beneficial. Two subjects disagreed that it was the method that their clinic recommends. This shows that metabolic health care professionals need to be more aware of what works for their patients. However, one subject who reported that they
disagree also reported that their clinic recommends getting blood phe levels tested once every three months, whereas they test themselves once every four months. This subject also reported they are neutral/ambiguous on how good they feel their relationship is with their clinic.

Results did not support the hypothesis that when someone agrees to the importance of keeping track of their daily phe intake, they may actually keep track of their phe consumption less often. The reasoning was that adults would be more comfortable with the diet and would have developed habits to manage their phe level, meaning they would not need to keep track of their daily phe consumption regularly. This study found that there was no significant correlation between the two factors. In this study, subjects reported, on average, testing their blood phe level once every three months. This is slightly lower than findings by Bilginsory, Waitzam, Leonard, & Ernst (2005) as they had results that showed children between the ages of ten and eighteen tested themselves on average 6.6 times per year. More research needs to be done to determine if habits change from childhood to adulthood. There also was no association between how often subjects test their blood phe level and how often their metabolic clinic recommended getting tested. There was a 43% chance of a Type II error occurring in the correlation between subjects agreeing to the importance of keeping track of their daily phe intake and how often they actually kept track of it. This means that while the results did not show a correlation, there was a 43% chance that there is one. More research needs to be done to determine any possible significance.

The second hypothesis was that adult patients will agree it is important for them to test their blood phe level as often as their clinic recommends, but they actually tested their blood phe level less often. The reason may be that adults who have grown up on the diet have developed familiar patterns and, when they have a routine, may feel more in control. This in turn may
make getting their blood level tested not as big a priority. The results did not support this as the correlation was found insignificant.

Having a good relationship with their clinic may be an important factor to dietary management in those that have PKU. The third hypothesis was that subjects who feel they have a better relationship with their clinic are more likely to follow recommendations. The results from this study showed subjects that agreed that they have a good relationship were more likely get their blood phe levels tested more often and per clinic recommendations. This study also found that subjects who have a good relationship with their clinic were more likely to follow their daily restriction. These findings suggest that those who trust their metabolic health care providers are more likely to follow recommendations. However, the correlation was barely insignificant with subjects reporting a better relationship with their clinic and how often they keep track of their daily phe intake. Type II error could have occurred due to a small sample size. More research needs to be done in order to determine a more definite correlation.

In this study, it was found that if a subject kept track of their phe intake more often, they were more likely to feel it is important to test their levels per clinic recommendations. These subjects may also be more likely to get their blood phe level tested more often and follow their daily phe restriction more often. Seeing as how patients who feel that they have a good relationship with their clinic may keep track of their phe intake more often, having a good relationship with their metabolic clinic could be an important factor in dietary management. However, more research would be needed to confirm it.

It appears that subjects were more likely to belong to an internet support group than one that meets in person. As areas of the United States may not have a local organization or support group available, patients will seek groups on the internet or the main PKU electronic mailing list.
Nine subjects reported to be in at least three types of support groups and all but two subjects were in more than one support group. As mentioned before, there was an inverse relationship between belonging to a support group that met in person and subject’s phe allowances. This suggests that subjects with lower dietary phe allowances were more likely to seek a support group that meets in person. Even though there were no other significant correlations, more research should be done in this area as the majority of patients may belong to multiple support groups.

Chapter 6: Limitations

A limitation of this study was the small sample size. The exact number of adults with PKU in the United States is unknown due to a number of adults being off the diet for so long and not returning to their clinics. It is estimated that 1 in every 10,000 newborns in the United States are diagnosed with PKU and hundreds require a low protein diet to keep their blood phe levels normal (Schuett, 2008). There could have been a few reasons why there was little participation. Perhaps the channels used for recruiting were not enough and in the future it would best to contact clinics around the country and involve health professionals. Patients’ attitudes could possibly affect participation as well. Some patients do acknowledge their situation, but may do everything they can to be normal and they are not involved with anything PKU related. In the end, having a small sample size could have resulted in some of the correlations to be insignificant. More research needs to be done in this area as a larger sample size may impact these results.
Chapter 7: Future Research

This pilot study opens the door for future research that gives more insight for metabolic healthcare professionals. The results begin to show how important the relationship between the clinic and patient can be. Healthcare professionals can use this information to better understand what their patients are going through. These results also raise more questions such as: what can metabolic clinicians do to improve their relationship with patients and why don’t patients follow their diet management regularly even though they know it is important? More research will be able to further confirm findings in this study and will be able to expand on them.

Chapter 8: Conclusion

One of the major findings from this study is just how important the relationship between the patient and their metabolic clinic is. The greater their relationship was, the more likely they will keep better track of their phe intake. These subjects may test their blood phe level more often and follow their restriction more often. A stronger relationship may also help with other areas in management such as handling difficult situations and motivation to follow the diet. There also seems to be a variety of methods used to count phe intake. Perhaps there is no specific method that is best; each clinic needs to work with each patient individually to see what counting method will be most effective. The results also show that it would be beneficial if there were a uniform guideline of management as frequency of recommended testing blood phe levels seem to vary.
References


Appendices

Appendix A: Approval from IRB
Appendix B: Approval from IRB with changes
Appendix C: Letter Invite to PKU Electronic Mailing List
Appendix D: Survey to Adult PKU Patients
Appendix E: Summary of Significant Correlations
Appendix A: Approval from IRB

IRB Number: 20110711827 EX

Project ID: 11827

Project Title: Attitudes of Management Practices in Patients with Phenylketonuria across the United States

Dear Elizabeth:

This letter is to officially notify you of the approval of your project by the Institutional Review Board (IRB) for the Protection of Human Subjects. It is the Board’s opinion that you have provided adequate safeguards for the rights and welfare of the participants in this study based on the information provided. Your proposal is in compliance with this institution’s Federal Wide Assurance 00002258 and the DHHS Regulations for the Protection of Human Subjects (45 CFR 46) and has been classified as Exempt Category 2.

You are authorized to implement this study as of the Date of Final Approval: 07/01/2011.

1. Please include the IRB approval number (IRB# 20110711827 EX) in the email consent document. Please email a copy of these messages to irb@unl.edu for our records. If you need to make changes to the messages please submit the revised messages to the IRB for review and approval prior to using them.

We wish to remind you that the principal investigator is responsible for reporting to this Board any of the following events within 48 hours of the event:

* Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths, or other problems) which in the opinion of the local investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures;
* Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur;

* Any publication in the literature, safety monitoring report, interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research;

* Any breach in confidentiality or compromise in data privacy related to the subject or others; or

* Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the research staff.

This project should be conducted in full accordance with all applicable sections of the IRB Guidelines and you should notify the IRB immediately of any proposed changes that may affect the exempt status of your research project. You should report any unanticipated problems involving risks to the participants or others to the Board.

If you have any questions, please contact the IRB office at 472-6965.

Sincerely,

Becky R. Freeman, CIP
For the IRB
Appendix B: Approval from IRB with changes

October 5, 2011 Elizabeth Vlock Department of Nutrition and Health Sciences 909 S 181st Ave Elkhorn, NE 68022
Kaye Stanek Krogstrand Department of Nutrition and Health Sciences 202J LEV, UNL, 68583-0806 IRB Number:
Project ID: 11827 Project Title: Attitudes of Management Practices in Patients with Phenylketonuria across the
United States

Dear Elizabeth:

The Institutional Review Board for the Protection of Human Subjects has completed its review of
the Request for Change in Protocol submitted to the IRB. 1. It has been approved to recruit participants via word of
mouth. You will contact as many people as you can and they will be encouraged to contact others. Those people
who are interested will then contact you. 2. It has been approved to send the invitation to the PKU list-server as well.
3. The revised recruitment messages have also been approved. We wish to remind you that the principal investigator
is responsible for reporting to this Board any of the following events within 48 hours of the event: * Any serious
event (including on-site and off-site adverse events, injuries, side effects, deaths, or other problems) which in the
opinion of the local investigator was unanticipated, involved risk to subjects or others, and was possibly related to
the research procedures; * Any serious accidental or unintentional change to the IRB-approved protocol that
involves risk or has the potential to recur; * Any publication in the literature, safety monitoring report, interim result
or other finding that indicates an unexpected change to the risk/benefit ratio of the research; * Any breach in
confidentiality or compromise in data privacy related to the subject or others; or * Any complaint of a subject that
indicates an unanticipated risk or that cannot be resolved by the research staff. This letter constitutes official
notification of the approval of the protocol change. You are therefore authorized to implement this change
accordingly. If you have any questions, please contact the IRB office at 472-6965.

Sincerely,

Becky R. Freeman, CIP for the IRB

Sincerely,

Becky R. Freeman, CIP for the IRB
Appendix C: Letter Invite to PKU Electronic Mailing List

Hello,

My name is Elizabeth Vlock and I am a Master’s student in Nutrition and Health Sciences at University of Nebraska at Lincoln.

Adults (ages 19 and older) with PKU are invited to participate in a research survey entitled “Attitudes of Management Practices of Adult Patients with Phenylketonuria across the United States.” The purpose of this study is to investigate attitudes of adults diagnosed with phenylketonuria (PKU) and how they relate to their actions of management therapy recommendations. This information will provide an insight to health care professionals who work with these patients. The results could be published in journals, books, or presented at conferences.

The study will consist of filling out a short online survey. It should take between 15-20 minutes and you will be able to take it at your convenience. The first part of the survey will ask about various management behaviors and the second part will ask about your attitudes towards those behaviors.

Please be assured that all of your response will be confidential and cannot traced back to you. Participation is voluntary and there is no known risk for taking it.

If you know of anyone else who could participate in this survey please forward this message to them so they will have the opportunity to participate. Everybody’s perspective is important and will help healthcare professionals better understand the people they are treating.

If you have any questions at all about the survey please call or e-mail me or Dr. Stanek-Krogstrand. If you have questions or concerns about the research please contact the Institutional Review Board at 402-472-6965 or email them at irb@unl.edu. If you would be interested in participating please call or respond to this email saying you are willing to participate and a link to the survey will be sent to you. Thank you so much.

Elizabeth Vlock, RD
University of Nebraska
Elizabeth.vlock@gmail.com
(402) 212-6154

Dr. Kaye Stanek Krogstrand, RD, LMNT
Associate Professor
Nutrition and Health Sciences
133 HECO
University of Nebraska
Lincoln, NE  68583
402-472-5285
Fax 402-472-1587
email: kstanek1@unl.edu
Appendix D: Survey to Adult PKU Patients

1) Age: _____________

2) Gender (circle one): Male Female

If you are female:
Are you pregnant? (Circle one) Yes / No
Weeks gestation? ______
What is your current daily phenylalanine prescription? ______

Have you ever been pregnant? (Circle one) Yes / No

For the next question, think about the time before your first pregnancy.

1 2 3 4 5
(Strongly disagree) (Strongly agree)

I feel that managing my low protein diet (getting blood phe level tested frequently, tracking daily phe intake, following the low protein diet, etc.) is more important during pregnancy

1 2 3 4 5
(Strongly disagree) (Strongly agree)

During pregnancy, I strictly followed my clinic’s recommendations, followed the low protein restrictions, tested blood phe levels frequently, and improved my overall management of PKU

3) In which region of the United States do you live in? (Check the box that applies)

- [ ] West Coast
- [ ] Southwest
- [ ] Midwest
- [ ] Northeast
- [ ] Southeast

4) What is the recommended amount of phenylalanine you are allowed per day?

__________________________
5) How often do you follow your recommended daily protein restriction?
   a) Everyday
   b) Often – most days of the week
   c) Sometimes
   d) Rarely
   e) Never
   f) Only around the days that I test my phe level

6) Which method is your preferred method of keeping track of the amount of phenylalanine you consume per day?
   a) I count my phes in milligrams (mg)
   b) I count by grams of protein
   c) I count by phe exchanges
   d) I count by another way: ___________________________

7) This is the method that I feel my clinic recommends.
   a) Agree
   b) Disagree
   c) Unknown
   d) I feel my clinic supports any method that helps me

8) How often do you keep track of your phe intake?
   a) I keep track of my phe intake everyday
   b) I keep track of my phe intake most days
   c) I keep track of my phe intake sometimes
   d) I keep track of my phe intake rarely
   e) I only keep track of my phe intake around the days that I get my phe level tested

9) How often do you typically get your blood phe level tested?
   a) Once per week
   b) 2-3 times per month
   c) Once per month
   d) Once every 2-3 months
   e) Other: ________________
10) How often does your clinic normally recommend you get your blood phe level tested?
   a) Once per week
   b) 2-3 times per month
   c) Once per month
   d) Other: ___________________
   e) Unknown

11) In the last 6 months, how many times have you gotten your blood phe level tested?
   a) 0-2 times
   b) 3-6 times
   c) 7-10 times

12) How often do you see your clinic physician, registered dietitian, or other healthcare professional for a “PKU checkup”?
   a) Two or more times a year
   b) Once a year
   c) Once every two years
   d) Other: ________________

13) Check all the types of healthcare professionals that meet with you during your PKU checkup.
   - Physician
   - Dietitian
   - Nurse
   - Psychologist
   - Other: ________________

For the following questions, a support system is a group of people that talk regularly about PKU and offers help or advise to others who need it.

14) Check which support groups or systems you belong to (check all that apply):
   - PKU list serv
   - Facebook group (or other internet groups, such yahoo groups)
   - Online PKU site (such as, but not limited to, www.pku.com or www.cookforlove.org)
   - A local PKU organization
   - Your PKU clinic (attending regular events, talking to healthcare professionals regularly, etc.)
   - Other (you may list more than one) : _____________________________
15) How often do you interact with other people in these support systems (such as asking questions or responding to comments or questions)?
   a) Very often
   b) Often
   c) Sometimes
   d) Rarely
   e) Never

For the next set of questions, circle the number that best represents how you feel with one meaning you strongly disagree and five meaning you strongly agree.

16) It is important for me to keep track of my phe intake everyday
   1   2   3   4   5
   (Strongly disagree) (Strongly agree)

17) It is important for me to follow my protein restriction daily
   1   2   3   4   5
   (Strongly disagree) (Strongly agree)

18) It is important for me to get tested frequently (as often as my clinic recommends)
   1   2   3   4   5
   (Strongly disagree) (Strongly agree)

19) I feel I have a good relationship with my PKU clinic (includes relationship with registered dietitian, physician, and other healthcare professionals)
   1   2   3   4   5
   (Strongly disagree) (Strongly agree)

20) It is important to have a good relationship with my PKU clinic to maintain healthy phe levels
21) I believe that belonging to a support group helps me manage my diet and maintain healthy phe levels.

22) Belonging to a support group that meets in person will help me manage my diet more than one that does not meet in person.
## Appendix E: Summary of Significant Correlations

<table>
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<tr>
<th>Correlations</th>
<th>r values</th>
<th>p values</th>
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<td>Patients who feel they have a good relationship with their clinic are more likely to test their blood phe level more often</td>
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<td>0.007</td>
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<td>Patients who feel they have a good relationship with their clinic are more likely to follow their daily protein restriction</td>
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<td>0.002</td>
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<td>Patients who feel they have a good relationship with their clinic are more likely to see the importance of getting their blood phe level tested per clinic recommendations</td>
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<td>The lower a subject’s daily phe allowance, the more likely they will feel that meeting with a support group in person will help them manage their diet</td>
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<td>0.044</td>
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<td>The more often subjects keep track of their daily phe intake the more often they will get their blood phe level tested</td>
<td>0.724</td>
<td>0.001</td>
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<td>The more often subjects keep track of their daily phe intake the more often subjects will follow their daily protein restriction</td>
<td>-0.642</td>
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<tr>
<td>The more often subjects keep track of their daily phe intake the more they will realize the importance of getting their blood phe level tested per clinic recommendations</td>
<td>0.590</td>
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