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Assessing The Impact Of Camp Phever On Blood Phenylalanine Levels

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ASSESSING THE IMPACT OF CAMP PHEVER ON BLOOD PHENYLALANINE LEVELS

A

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ASSESSING THE IMPACT OF CAMP PHEVER ON BLOOD PHENYLALANINE LEVELS

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Phenylketonuria (PKU) is a metabolic disorder that results in accumulation of the amino acid, phenylalanine, throughout the body. This can result in neurocognitive complications if individuals with this disease do not follow a low-protein diet. Camp PHEver is a weeklong summer camp that gives children with PKU an opportunity to obtain skills related to diet compliance, but also enhance their confidence, relationship development, and independence. Through learned skills and the strict diet regimen at camp, campers were found to have a statistically significant drop in phenylalanine (PHE) levels within a single attendance (mean decrease per year range = 2.1 to 7.8 mg/dL; $p < 0.001$ for all). When looking at the PHE drops by year, the within year difference was higher for camp years before 2007 (mean decrease: 6.3 mg/dL; range: 5.4 to 7.8) than in camp years after 2007 (mean decrease: 3.5 mg/dL; range: 2.1 to 4.6), hypothesized to be due to the availability of the PHE-reducing drug, Kuvan. The most significant discovery was that camp is most effective at reducing PHE levels in those entering camp with levels above the recommended range. Before 2007, the drop in PHE levels over an individual camp visit was significantly higher for campers with elevated pre-camp PHE (median change: -7.6 units, IQR: -10.5 to -5.1) compared to those with PHE levels in the acceptable range (median change: -0.9 units, IQR: -2.3 to 0.6) ($p < 0.001$). Although still statistically significant, the magnitude of this difference

between campers with high versus acceptable levels of PHE was lower after 2007, with a median change in PHE levels of -4.9 units (IQR: -7.0 to -2.5) and -1.0 (IQR: -2.3 to 0.2), respectively ($p < 0.001$). Because many individuals with elevated PHE levels struggle with executive functioning, emphasis should be placed on returning these levels to the recommended range. Camp PHEver plays an instrumental role in bringing children and adolescents with PKU into the recommended range throughout the course of camp. Furthermore, camp has been reported by former campers to increase perceived long term diet compliance, independence, confidence, and relationship development and represent the first steps to long term PKU management.

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Introduction

Phenylketonuria (PKU) is a metabolic disorder caused by a biallelic pathogenic variant in the *PAH* gene. The *PAH* gene encodes for the enzyme, phenylalanine hydroxylase, that is responsible for the catabolism of phenylalanine into tyrosine. Failure of the body to produce phenylalanine hydroxylase results in PHE accumulation throughout the body. Without proper intervention, the accumulation damages neurotransmitters leading to a subset of neurological symptoms including intellectual disability, growth restriction, tremors, epilepsy, and behavioral problems including hyperactivity, stereotypy, and anxiety (Ashe et al., 2019).

Phenylalanine is an essential amino acid emphasizing the importance of early identification of PKU in newborns and swift intervention of diet modification. Screening for PKU first began in 1961 when Dr. Robert Guthrie and his laboratory began receiving filter paper specimens of blood from newborns at Jamestown hospitals (Gonzalez & Willis, 2009). At the time of identification, newborns were instructed to switch to a low-protein diet. Implementing lifelong restriction of protein intake in addition to supplementation of formula at a young age is known to avoid the sequelae of high PHE levels. Those who do not consistently adhere to the recommended guidelines may experience a decline in neurocognitive and/or neuropsychological function. Additionally, in research by Bilder et al., 2017, of 3,714 individuals diagnosed with PKU and 22,726 controls, they found that anxiety, ADHD, and depression was 1.7, 1.7 and 1.6 times more frequent in those with PKU compared to the controls, respectively, indicating increased rates of mental illness in those with PKU.

To ensure proper adherence to a low protein diet, weekly to monthly monitoring

of PHE levels, consumption of Phe-free medical formulas, diet journals, and regular appointments with a metabolic geneticist and dietitian are necessary. Due to the extensive treatment regimen impacting their daily lives, many individuals with PKU struggle to maintain their low-protein diet. Jurecki et al., 2017 revealed numerous PKU clinics reported a decline in compliance from 88% in patients ages 0-4 years to 33% for those aged 30 years and older. Another study conducted by Ahring et al., 2011 found the percentage of individuals with blood PHE concentrations meeting the individual national target ranges across 10 European centers were 89% for ages 11-16 years of age and 65% for ages greater than 16 years. Furthermore, they determined that the frequency of home blood sampling compared to the national recommendations (weekly in infancy, fortnightly in children aged 1 to 12 years, monthly in those over 12 years of age and twice weekly during pregnancy) for monitoring PHE levels declined with age from 83% in teenagers to 55% in adults. Lastly, Walter et al., 2002 found that in those younger than 10 years of age that approximately 30% had plasma PHE concentrations above the recommended levels compared to 80% of those 15 years of age and older. There is a clear inverse correlation between the decline of diet compliance with age in individuals with PKU. To combat this, studies have been conducted to determine what factors promote compliance of a nutritional plan. Cazzorla et al., 2018 found that of the 111 adults in the study, 36% (n = 33) found information about the disease and support from family as the most important factors aiding them in compliance. Nonetheless, Cazzorla et al., 2018 emphasizes the need for education and support for individuals with PKU.

Another proposed method to assist PKU patients with compliance was to increase self-efficacy. To assess the self-efficacy in the PKU population, Viau et al., 2016 utilized

a modified version of the “8-item Diabetes Self-Efficacy scale” developed by the Stanford Patient Education Research Center. In their study, they implemented phone-based motivational interviewing and found that it significantly increased self-efficacy and other self-management behaviors among PKU adults and adolescents. The same concept for diet management was applied in another study in which a summer camp was designed to help teach children with PKU proper adherence while providing them with a normal camp experience (Jennings et al., 1999). This study found post-camp PHE levels to be significantly reduced, but further research is necessary to evaluate confidence, relationship development, independence, and diet compliance gained through a camp experience in children and adolescents with PKU.

While there is ample literature providing evidence that diet compliance often wanes with age and can increase the risk for neurocognitive or neuropsychological impairments, there unfortunately remains little evidence that outlines how to enhance compliance. Although Viau et al., 2016 proposes that increasing self-efficacy is one mode to increase self-management behaviors, it fails to encompass other factors that could hinder diet-compliance. This study seeks to identify how a PKU-friendly summer camp could impact not only diet compliance, but also independence, confidence, relationship development of individuals with PKU. Furthermore, we will also evaluate the presence or absence of mental illness in campers as a factor in diet compliance. Through this research, we hope to find supporting evidence that summer camps are an important mode by which young individuals with metabolic diseases can build confidence and independence in hopes to develop skills that motivate them to live an overall healthy lifestyle. By identifying successful tools used at camp, we can develop

evidence-based practices that are translatable to the clinical setting to combat the difficulties of diet compliance.

Materials and Methods

This is a descriptive observational study of individuals who are diagnosed with PKU and previously attended Camp PHEver. Camp PHEver is a 6-day summer camp for children and adolescents with PKU and their unaffected siblings. This camp is an opportunity for children to not only have fun, but also to receive education about their diagnosis and management. The study was approved by the Institutional Review Boards at The University of Texas MD Anderson Cancer Center and The University of Texas Health Science Center (HSC-MS-21-0627). The first arm of this study involves evaluating and trending pre- and post-PHE levels from the Camp PHEver database. The second arm of this study was an author designed electronic survey created using the Qualtrics online software (Qualtrics, Provo, UT). Data collection was performed from August 2021 through February 2022. Every participant in the survey provided electronic consent before completing the one-time 15-minute survey.

Study Population

For the first arm of the study, the study population was collected from Camp PHEver database. The database consisted of camper profiles from 1998 through 2019. For each camper, the following variables were extracted: name, race/ethnicity, sex, blood PHE levels before and after camp, number of camp attendances, as well as medications. All data was de-identified prior to statistical analysis.

For the second arm of the study, individuals were eligible to participate if they were over the age of 18 years, had a diagnosis of PKU, and previously attended Camp

PHEver. Individuals who did not meet this criterion were excluded from the study.

Recruitment occurred via two methods: social media posts Camp PHEver group page and emails directly to former campers from their metabolic teams at The University of Texas Medical Branch, Galveston, TX, as well as The University of Texas Health Science Center at Houston. All survey data was de-identified at the point of collection.

Survey Components

Author-designed questions were crafted to measure diet compliance, independence, confidence, relationship development and camp experience. The survey components included demographic information including gender, age, race/ethnicity, number of times camp was attended, as well as approximately four questions per sub-topic evaluating: camp's impact on diet compliance, independence, confidence, relationship development and overall camp experience. To assess diet compliance, questions were designed to assess the skills developed from camp that encourage adherence to diet and regular monitoring of PHE levels. Independence was assessed by asking campers if they were able to mix their own medical formula after attending camp. Confidence was assessed by gauging campers' level of confidence before and after their camp experience, and by inquiring how comfortable they are about having a metabolic disease since attending camp. Relationship development questions were designed to understand how the camp impacted friendships as well as how campers share their personal struggles related to PKU among fellow campers and counselors. Lastly, the overall experience at camp was examined by developing questions that relate camp as a positive or negative experience, and whether they would recommend it to others.

Statistical Analysis

Stata (v.13.1, College Station, TX) statistical software was utilized for data analysis. Statistical significance was assumed at $p < 0.05$. In the first arm of the study, descriptive statistics were used to describe demographics as well as medications taken by campers. Blood PHE levels before and after camp in a single year were compared using a paired t-test. Additionally, generalized linear mixed models were used to compare blood PHE levels with other variables, including age, gender, pre-camp PHE category (Recommended PHE Level, High PHE Level), then number of attendances of camp (nth year), the calendar year of camp, as well as levels before and after 2007, the year that Kuvan, a PHE reducing agent, was FDA approved. In the second arm of the study, descriptive statistics was used to analyze the perceived impact of Camp PHEver on former campers. This analysis focused on the level of agreement or disagreement across different categories of questions across the previously outlined sub-topics. Furthermore, the Wilcoxon rank sign analysis was used to compare questions inquiring about diet compliance and confidence before first Camp PHEver attendance and after attending Camp PHEver.

Results

The Camp PHEver Database

Descriptive Data

The database was composed of 334 attendees, including campers and counselors with PKU. However, after removing counselors with PKU from the dataset, 203 of these were unique campers with an overall total of 977 camp visits amongst the cohort. Of the campers with recorded gender and ethnicity, we found half (51%) of campers were male and half (49%) were female. Additionally, 95% of campers were Caucasian, 2% were

Black, 1% were Hispanic, 0.32% Asian, 0.5% Hispanic/American, and 0.5% Not Applicable as shown in Table 1. Of all camp attendees, 67 of them took PKU related medication, 33 campers took medication for ADHD, and 10 individuals took antidepressants. These medications are listed in Table 2. Of the 203 campers, 54% (n = 110) have attended camp for 4 years or less, while 10% (n=20) of the campers have attended camp 10 or more times.

Ethnicity	Frequency	Percent
Asian	3	0.32%
Black	19	2.05%
Caucasian	884	95.46%
Hispanic	10	1.08%
Hispanic American	5	0.54%
Not Applicable	5	0.54%
Total	926	100%

Table 1: Ethnicity of Campers

Medication Type	Number of campers*	Percentage
PKU med (e.g. KUVAN or Phlexy)	67	20.06%
ADHD	33	9.88%
Allergy	23	6.89%
Vitamin	14	4.19%
Antidepressant	10	2.99%
Antipsychotic	5	1.50%
Asthma / Chronic Obstructive Pulmonary Disease	5	1.50%
Birth control	5	1.50%
Antiacid	3	0.90%
Alpha/beta Adrenergic agents	2	0.60%
NSAID	2	0.60%
Adamantanes	1	0.30%
Analgesic	1	0.30%
Antimigraine	1	0.30%
Anxiolytic	1	0.30%
Anticholinergics	1	0.30%
Anticonvulsant	1	0.30%
Antidiuretic	1	0.30%
Antispasmodics	1	0.30%
Laxative	1	0.30%
Anti-Heartburn	1	0.30%
Sedative	1	0.30%
* Total of 334 unique attendees over study period. Information on timing and duration of medication use not available		

Table 2. Frequency of various medication types used by Camp PHEver attendees, 1998-2019

Individual Camper Analysis: Within and Between Years

When comparing an individual campers' pre-camp PHE levels to their post-camp PHE level within a single year of camp attendance ("within year difference"), we found a statistically significant drop in each campers' PHE levels (mean decrease per year range = 2.1 to 7.8 mg/dL; $p < 0.001$ for all). The within year difference was higher in the camp years before 2007 (mean decrease: 6.3 mg/dL; range: 5.4 to 7.8) than in the camp years after 2007 (mean decrease: 3.5 mg/dL; range: 2.1 to 4.6). This is demonstrated in Table 3.

Paired difference in PHE levels before and after camp, by year					
Year	Number of campers	PHE levels, mean (sd)		Paired difference in PHE level, mean (sd)	p-value
		pre-camp	post-camp		
1998	24	11.7 (5.1)	5.3 (3.4)	-6.4 (4.5)	<0.001
1999	35	11.6 (5.9)	6.2 (3.9)	-5.4 (5.1)	<0.001
2000	40	12.9 (6.3)	6.3 (4.3)	-6.5 (4.4)	<0.001
2001	41	11.4 (6.4)	5.8 (3.9)	-5.6 (4.1)	<0.001
2002	41	11.7 (6.8)	6 (4.6)	-5.8 (5.0)	<0.001
2003	44	11.5 (6.7)	5.6 (4.8)	-6.0 (3.7)	<0.001
2004	49	14 (8.8)	6.3 (5.6)	-7.8 (5.7)	<0.001
2005	45	12.7 (7.1)	6.3 (6.1)	-6.4 (5.8)	<0.001
2006	51	13.2 (6.5)	6 (4.6)	-7.1 (5.0)	<0.001
2007	49	9.3 (5.4)	3.8 (2.8)	-5.5 (4.5)	<0.001
2008	54	7.9 (4.4)	5.2 (4.2)	-2.7 (3.7)	<0.001
2009	46	8.4 (4.8)	4.9 (4.7)	-3.5 (3.8)	<0.001
2010	52	9.1 (4.5)	4.5 (3.6)	-4.6 (3.6)	<0.001
2011	51	8.1 (5)	4.3 (3.6)	-3.8 (3.4)	<0.001
2012	49	7.6 (4.7)	4.4 (3.5)	-3.3 (2.7)	<0.001
2013	47	7.4 (4.5)	4.9 (4)	-2.5 (2.8)	<0.001
2014	47	9.5 (5.4)	5 (4)	-4.5 (3.5)	<0.001
2015	47	8.7 (5)	4.6 (3.6)	-4.1 (3.8)	<0.001
2016	46	6.7 (4)	4.6 (3.5)	-2.1 (3.6)	<0.001
2017	50	7.3 (4.2)	4.2 (3.1)	-3.1 (2.8)	<0.001
2018	26	9 (5.2)	5.4 (3.6)	-3.7 (4.3)	<0.001
2019	43	9.2 (6.1)	5.7 (4.1)	-3.5 (5.3)	<0.001

Table 3: Average Paired Differences in PHE Levels Before and After camp, By Year

Impact of Age

This adjusted analysis demonstrated that for every year increase in age, pre-camp PHE levels increased by 0.55 units (95% CI: 0.42-0.68) as seen in Figure 1. While age is associated with year-to-year pre-camp PHE levels (between year difference), it is not independently associated with within year differences in PHE level over the course of a camp attendance.

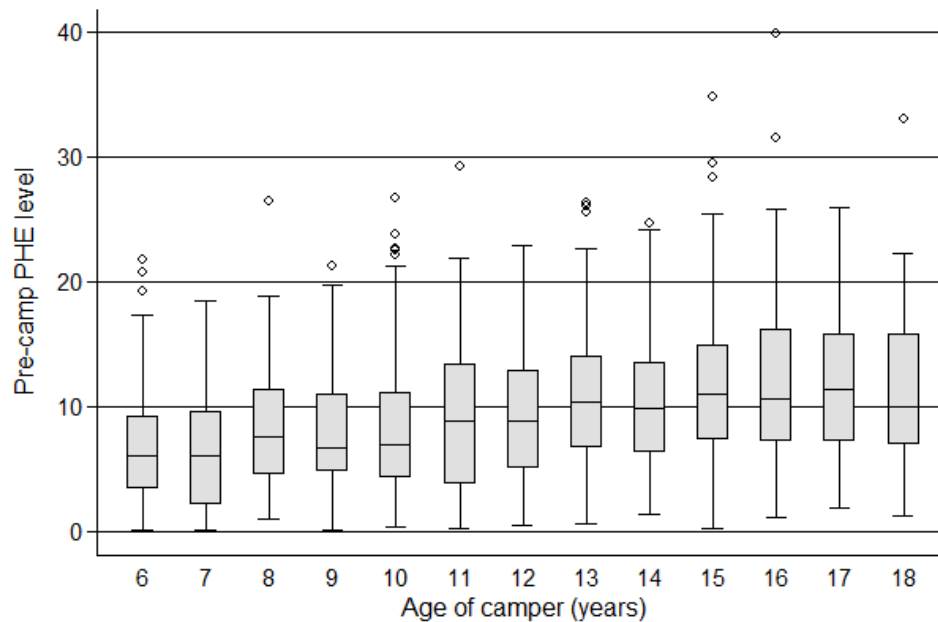


Figure 1. Pre-camp PHE levels vs. Age.

Impact of Campers' Sex

Although there was no statistically significant difference in the pre-camp or post-camp PHE levels between males and females, the average within year drop in PHE levels was 0.81 units (95% CI: 0.08-1.54) higher among female compared to male campers

Impact of Previous Camp Attendance and Calendar Year

When considering overall attendance numbers as well as the individual calendar year, there was no statistically significant difference in post-camp PHE levels based on the number of attendances at camp as well as the calendar year of attendance.

Additionally, in univariable non-adjusted analysis, there was no statistically significant change in year-to-year ("between year difference") pre-camp levels per camper who attended camp in two or more consecutive years. The average difference for each paired year comparison was near zero as demonstrated in Table 4.

Year to Year difference in baseline (pre-camp) PHE levels, stratified by year of camp		
Visit years	Number of campers	Difference in pre-camp PHE, mean (sd)
1st to 2nd	163	0.8 (4.9)
2nd to 3rd	136	0.0 (4.8)
3rd to 4th	116	-0.1 (4.2)
4th to 5th	92	1.0 (5.1)
5th to 6th	76	0.8 (5.6)
6th to 7th	59	-0.1 (4.4)
7th to 8th	49	0.3 (4.1)
8th to 9th	34	0.6 (4.8)
9th to 10th	20	1.0 (3.4)
10th to 11th	16	-0.8 (3.3)
11th to 12th	7	-2.4 (2.4)
12th to 13th	5	2.6 (5.1)
13th to 14th	1	-0.4 (n/a)

Table 4: Year to Year Difference in Pre-camp PHE levels for Repeat Campers

Impact of Pre-/Post- 2007 Time Periods

The difference in PHE levels over camp during the post-2007 period was 1.18 units (95% CI: 0.73-1.64) lower than the pre-2007 period. This is demonstrated in figure 2. Similarly, the pre-camp PHE levels were on average 3.8 units (95% CI:3.1-4.6) lower in the post-2007 period than in the pre-2007 period. There was no significant difference in average post-camp levels in the post-2007 period compared to the pre-2007 period (data not shown).

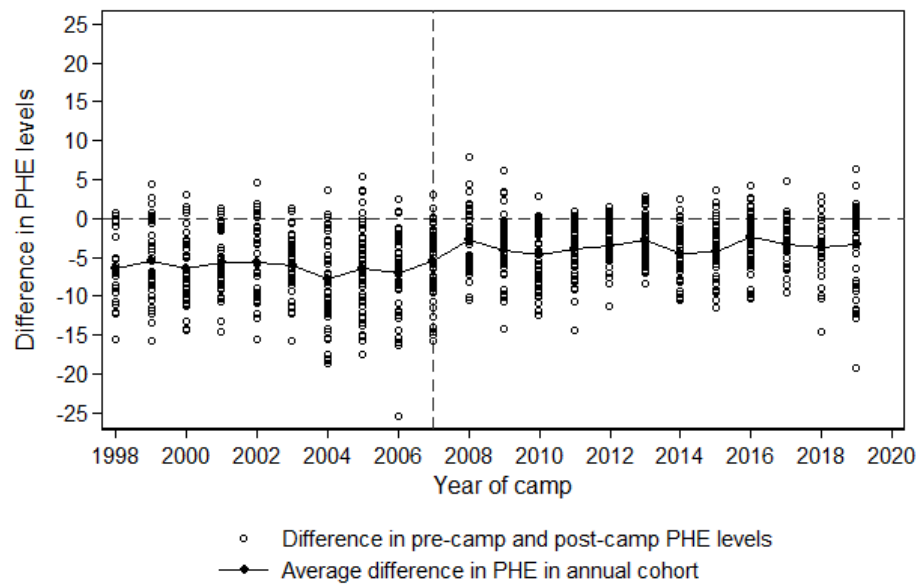


Figure 2: Difference in PHE Levels Pre- and Post- 2007

When analyzing levels from year to year (between year differences), there was no statistically significant difference in pre-camp PHE levels (Figure 3). There was also no change when comparing pre-camp levels from year to year (Table 5) even after adjusting for the pre- and post- 2007-time frames (data not shown).

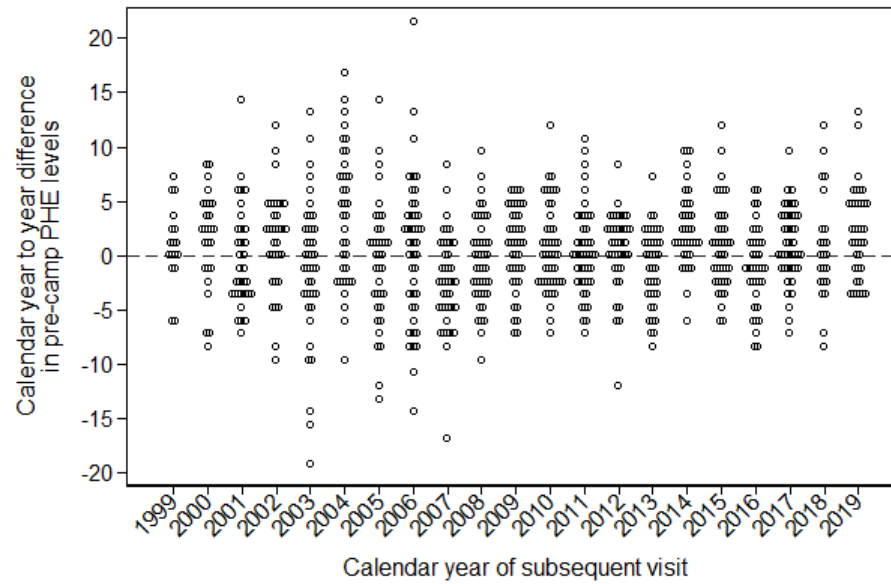


Figure 3: Calendar Year to Year Differences in Pre-Camp PHE Levels by Year

Year to Year difference in baseline (pre-camp) PHE levels, stratified by year of camp		
Visit years	Number of campers	Difference in pre-camp PHE, mean (sd)
1998 to 1999	17	1.0 (3.5)
1999 to 2000	26	1.4 (4.6)
2000 to 2001	33	-0.1 (4.8)
2001 to 2002	33	1.3 (4.6)
2002 to 2003	41	-1.1 (6.5)
2003 to 2004	37	3.5 (6.2)
2004 to 2005	37	-0.8 (5.6)
2005 to 2006	43	0.4 (6.7)
2006 to 2007	40	-2.3 (4.6)
2007 to 2008	44	-0.5 (4.0)
2008 to 2009	42	0.8 (3.8)
2009 to 2010	46	0.6 (3.9)
2010 to 2011	44	0.3 (4.0)
2011 to 2012	38	0.5 (3.5)
2012 to 2013	39	-1.1 (3.5)
2013 to 2014	36	2.4 (3.5)
2014 to 2015	40	0.7 (4.0)
2015 to 2016	37	-1.1 (3.7)
2016 to 2017	41	1.0 (3.4)
2017 to 2018	23	0.6 (5.0)
2018 to 2019	37	2.1 (4.1)

Table 5: Year to Year Difference in Pre-camp PHE Levels

Impact of Pre-Camp PHE Levels

Pre-camp PHE levels were associated with the magnitude of the difference between the pre- and post-camp PHE levels, with higher pre-camp levels resulting in, on average, a greater drop in PHE levels over camp. For every unit increase in pre-camp PHE levels, the drop in blood PHE levels from pre- to post-camp were higher by 0.50 units (95% CI 0.47- 0.54).

This association led to the stratification of campers into two sub-cohorts: 1) campers entering with a high PHE level (HPL) defined as greater than 6mg/dL 2) campers with PHE levels within the national recommended range (RPL, recommended PHE level) defined as less than or equal to 6mg/dL. Of the 977 total visits, 70% (n=688) of camp visits started with HPL and the remaining 30% (n=289) of camp visits entered camp with RPL. Of the 688 camp visits with HPL, half of them (51%, n=353) ended camp with post-camp PHE at RPL. In the sub-cohort with pre-camp PHE levels at RPL, only 6% (n=17) had a post-camp PHE level that was HPL. Before 2007, the change in PHE levels over an individual camp visit was significantly greater for campers with HPL at pre-camp (median change: -7.6 units, IQR: -10.5 to -5.1) compared to those that had RPL (median change: -0.9 units, IQR: -2.3 to 0.6) ($p<0.001$). Although still statistically significant, the magnitude of this difference between campers with HPL versus RLP was lower after 2007, with a median change in PHE levels of -4.9 units (IQR: -7.0 to -2.5) and -1.0 (IQR: -2.3 to 0.2), respectively ($p<0.001$). Comparing the pre-2007 to the post-2007 PHE levels within each pre-camp PHE strata, there was no difference in the change in PHE levels over camp for campers that were RPL , but the change in Phe levels over

camp was smaller after 2007 among campers with pre-camp HPL ($p<0.01$). This is demonstrated in Figures 4A and 4B.

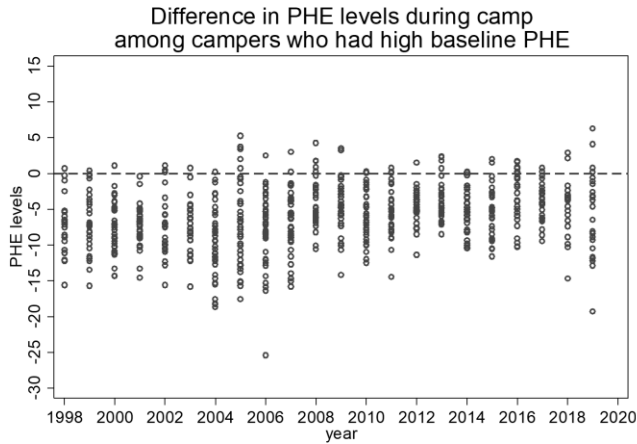


Figure 4A: Difference Amongst Campers with HPL Pre-camp

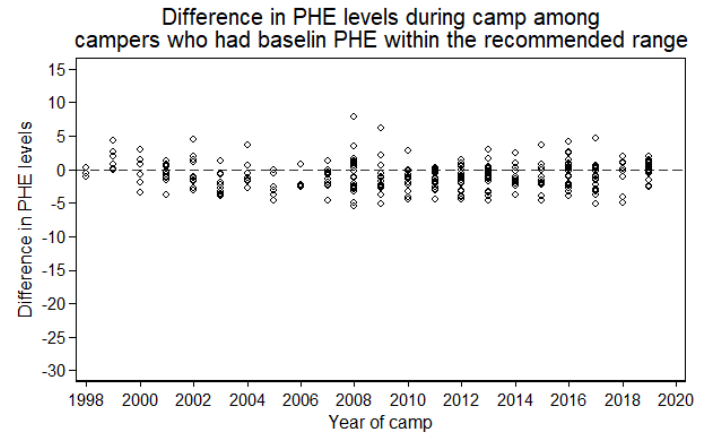


Figure 4B: Difference Amongst Campers with RPL Pre-camp

Impact of Camp PHEver-The Survey

Here, we received 34 completed surveys. Of the 34 respondents, 3% ($n=1$) were gender non-conforming, 71% ($n=24$) were female, and 26% ($n=9$) were male. The median age of respondents was 28 years of age. Additionally, 3% ($n=1$) of respondents were Black or African American, and 97% ($n=33$), identified as white. Lastly, 24% ($n=8$) of respondents attended camp 5 times or less, 44% ($n=15$) of respondents attended between 6-10 times, and 32% ($n=11$) of respondents attended camp more than 10 times.

An overall average of 78% of campers expressed agreement with questions related to improved diet compliance. Similarly, with questions related to improved independence, 89% expressed agreement. Lastly, overall, there was a 90% agreement with improved confidence, 100% with a positive camp experience, and 94% with improved relationship development. This is indicated in Figure 5.

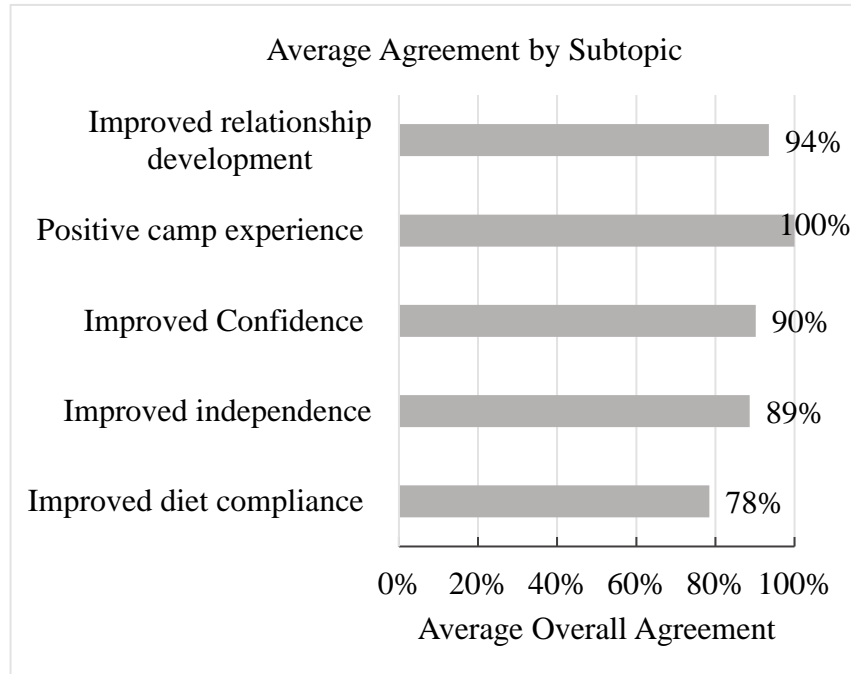


Figure 5: Overall Agreement by Subtopic

Of the paired questions related to diet compliance and confidence, there was a statistically significant increase in one's perceived diet compliance ($n=18$, $p=0.002$) and confidence ($n=20$, $p=0.003$) after attending camp, as seen in table 6.

Confidence Scores			Diet Compliance Scores		
Score Difference	Frequency	Percent	Score Difference	Frequency	Percent
-3	1	2.94	-3	0	0
-2	1	2.94	-2	1	2.94
-1	5	14.71	-1	3	8.82
0	7	20.59	0	12	35.29
1	4	11.76	1	8	23.53
2	12	35.29	2	8	23.53
3	2	5.88	3	1	2.94
4	2	5.88	4	1	2.94
Change in score			Change in score		
Type	Number		Type	Number	
Positive	20		Positive	18	
None	7		None	12	
Negative	7		Negative	4	

Table 6: Confidence and Diet Compliance Scores Pre- and Post- Camp PHEver

Discussion

This study aimed to describe the impact of Camp PHEver on PHE levels as well as diet compliance, confidence, independence, and relationship development. The results of the study elucidate the benefits of summer camps as they relate to PKU management but provide additional assistances in identifying other factors that camp improves that may be targeted to develop and implement new strategies to enhance diet compliance.

PKU is a metabolic condition that requires life-long low protein diet, intake of medical foods and formulas, and frequent monitoring of PHE levels and metabolic appointments. When PHE levels are out of control, adverse neurocognitive and psychiatric outcomes can occur emphasizing the importance of maintaining levels in the recommended ranges (Vockley et al., 2013). Our study identified that a summer camp for children with metabolic conditions such as PKU can have an immediate and long-term impact on health within one attendance. On average, there was a statistically significant

drop in PHE levels over the 4 days of camp. This is likely a result of Camp PHEver providing only low-protein food options, set time frames for each camper to prepare their own medical formulas, and hands-on cooking classes exposing the campers to new low-protein recipes. In addition, campers interact directly with metabolic dietitians who can reinforce these behaviors and ensure they maintain the appropriate PHE intake. While decreases of PHE levels during camp were identified, there was no change in levels from year to year in repeat campers. One possible explanation for these results is the relapse to a less strict regimen between camp attendances, resulting in pre-camp levels that fluctuate regardless of previous drops in PHE levels during camp.

Our data demonstrates that some groups struggle with diet compliance more than others. Though diet may subtly fluctuate in middle childhood, PHE levels less often fall out of range due to the guidance from guardians and pediatricians. However, teens and young adults struggle as a result of the transition of care away from parents, lack of structure, as well as the surge of independence, rebellious nature, and peer pressure (Vockley et al., 2013). Our current study is consistent with the previously published literature as the data identified that with every year of increased age the pre-camp PHE levels increased by 0.55 mg/dL. This is perhaps due to more independence in food choices and affected individuals' desire to fit in with their peers outside of camp, resulting in decreased diet compliance.

Our study also revealed that females may benefit more from an educational summer camp. This is consistent with the research of Kenneson & Singh, 2021, in which they found that women were more likely to participate in PKU initiatives and reported adherence to a prescribed diet in comparison to males. The findings of increased diet

compliance were echoed in the current study with larger drops in PHE levels over camp. This is perhaps caused by the higher likelihood of participation of females in educational activities, leading to overall increased improvement. Another possible explanation is that males with PKU have been shown to have higher rates of neophobia than females (Tonon et al., 2019) . Neophobia, or the fear of novel foods, is an instinct that may prevent male campers from trying foods outside of their typical diet at camp. This possibility, in conjunction with the increased physical exertion at camp, may lead to the observed relatively smaller changes in PHE levels in male campers during Camp PHEver. However, though there was also no statistically significant difference between either the pre-camp or the post-camp levels between males and females. This could be due to the large degree of inter-individual variability in terms of the PHE levels they have at arrival at camp as well as the inter-individual variability in how much of change occurs over camp.

Because certain groups may be more susceptible to poor diet compliance, targeted education may be necessary for early intervention. While camp is successful at lowering PHE levels temporarily, it does not seem to have long-term impacts at this time. Furthermore, the number of camp attendances per camper does not play a significant role in fluctuations of PHE levels. However, medication has proven to be a successful means to reduce PHE levels. Kuvan (sapropterin dihydrochloride), a synthetic form of BH4 which helps stimulate residual activity of phenylalanine hydroxylase, received FDA approval on December 13th, 2007, (Drug Approval Package: Kuvan (Sapropterin Dihydrochloride) NDA #022181, n.d.) . Kuvan has been demonstrated to increase the tolerance for phenylalanine and reduce blood PHE levels. In the SPARK phase IIIb trial,

they found that at week 26, those taking Kuvan with a low protein diet had a Phe tolerance 30.5 mg/kg/day higher than those on a low protein diet alone (Muntau et al., 2017) . In this same study, they also found that the individuals taking Kuvan had a decrease in blood concentrations before gradually returning to concentrations like those in Phe-restricted diet only due to increased Phe consumption. In the present study, the PHE levels pre- and post- 2007 (year Kuvan was approved) support the efficacy of the drug as pre-camp PHE levels were lower during the post-2007 period. There was no difference in post-camp levels in the post-2007 period compared to the pre-2007 period, indicating that regardless of the pre-camp PHE level those that attend camp leave with levels in or near the recommended range because of the camp's structure. Lastly, the difference in PHE levels over camp during the post-2007 period was smaller than in the pre-2007 period. Pre-camp levels were more elevated during the pre-2007 period, therefore, the strict adherence to a low-protein diet in these individuals lead to a larger drop in PHE levels over the course of camp.

As the difference in PHE levels before and after 2007 indicated, pre-camp levels could be a good predictor of the reduction of blood PHE. Additionally, when classifying individuals entering camp as having high PHE or within the recommended range, the average PHE drop for those with high pre-camp levels was significant as well as greater than those entering camp with PHE levels in the recommended range. Campers with elevated levels at the start of camp may not be diet compliant at home, and therefore benefit greatly from the strict diet at camp. While Camp PHEver is particularly efficient at reducing blood PHE for those beginning camp with elevations, further information is

needed to identify factors that can allow camp to have a more lasting impact, and in turn, prevent fluctuations between attendances.

Another goal of this study was to identify Camp PHEver's impact on perceived diet compliance, as well as other factors that could promote health management between camp attendances. As identified by Viau et al., 2016, phone-based motivational interviewing, that occurs once monthly, significantly increased self-efficacy. Like the effects of phone-based, motivational interviewing, we found that Camp PHEver had a positive impact on perceived confidence, independence, diet compliance, and relationship development in former campers. The questions that compare pre- and post-camp diet compliance and confidence found that there was a significant increase in one's perceived diet compliance and confidence after attending Camp PHEver. This indicates that not only do camp levels improve during the week, but some campers feel as though Camp PHEver had a lasting impact on their diet compliance. Another notable find was that 94% of former campers who on average, expressed agreement with positive relationship development since attending Camp PHEver. Cazzorla et al., 2018 identified that many of the top reported factors that influence poor diet adherence in PKU, include embarrassment, support from family as well as impact on socializing. Our results indicate that attending Camp PHEver can increase confidence as well as improve relationship development both of which are instrumental in combating the barriers that individuals encounter maintaining compliance. Furthermore, 89% of former campers felt an increased sense of independence since attending Camp PHEver. This is important, as adolescents with PKU have previously been noted to struggle during the transition into adulthood (Vockley et al., 2013). Therefore, a summer camp, such as Camp PHEver, can

instill independence prior to adulthood and might prevent a decline in diet adherence. Lastly, 100% of former campers reported having a having an overall positive experience with Camp PHEver. Not only do individuals with PKU gain confidence, independence, relationship development, and diet compliance, they also have report enjoying the overall experience and leads to the individuals attending again in the future.

Though Camp PHEver is not currently successful at preventing campers from relapsing to poor management between attendances, encouraging campers to return is very important. For example, Jahja et al., n.d. found that those with PHE levels <360 mmol/L had better cognitive flexibility and executive control than those with levels above 360 mmol/L. Executive functioning and cognitive flexibility are required for proper management of PKU. Lack of these qualities could send an individual with PKU into an uncontrolled cycle if there is no external intervention. Therefore, for those with elevated Phe levels, it can be even more important to return to camp as a method of returning to a recommended range while having a traditional camp experience. This opportunity becomes possible due to summer camps like Camp PHEver.

Camp PHEver does an excellent job at reducing PHE levels over the course of a camp attendance, as well as giving individuals with PKU an opportunity to regain executive and cognitive flexibility. However, while camp does promote skills that can improve long-term management, such as confidence, independence, and relationship development, it is clear further measures must be taken, as PHE levels still fall out of range between camp attendances. Perhaps implementation of monthly motivational interviewing during the interim of camp attendances could improve PHE fluctuations, as outlined in Viau et al., 2016. Another possibility is providing individuals with PKU a

secure webpage that updates them consistently with their levels (ten Hoedt et al., 2011).

Although this study did not find a significant difference in those given a graph of their PHE values, camp administration received feedback that a virtual notification was helpful. Overall, Camp PHEver is instrumental in paving the way for management of children with metabolic diseases, however more strategies could be identified to translate increased confidence, independence, and relationship development to long-term management.

Appendix

Copy of Survey

Start of Block: Informed Consent Block

Page Break

Are you 18 years and older?

☐ Yes (1)

☐ No (2)

Skip To: End of Survey If Are you 18 years and older? = No



INFORMED CONSENT FORM TO TAKE PART IN RESEARCH
Title: Assessing the Impact of Camp PHEver on Serum Phenylalanine Levels
Letter of Information
HSC-MS-21-0627
Primary Investigator: Michelle Zelnick

You are invited to take part in a research study called, "Assessing the Impact of Camp PHEver on Serum Phenylalanine Levels", conducted by Michelle Zelnick, of the University of Texas Health Science Center at Houston. For this research project, she will be called the Principal Investigator or PI.

The purpose of this study is to see if Camp PHEver has an impact on serum phenylalanine levels, as well as other factors, such as diet compliance, confidence, and relationship development. If you decide to take part in the study the total time commitment is 20 minutes. You are invited to take part in this study because you have Phenylketonuria and have attended Camp PHEver in the past. You can refuse to answer any questions asked or written on any forms. Participation in this study is voluntary. A decision not to take part in this study will not change the services or opportunities offered to you by UTHealth or Camp PHEver.

If you agree to take part in this survey you will agree to a 20-minute survey.

Upon agreeing to partake in this survey, you will have the option to participate in a drawing with a 1 in 100 chance of winning a \$25 Target gift card. You will be asked to provide your e-mail to be entered into the drawing. The e-mail will not be linked to your survey. You may receive no benefit from taking part in this study. The information gained may help provide us with a better understanding of the impact of Camp PHEver on Serum Phenylalanine levels, independence, diet compliance, confidence, and relationship development. There are no known risks to take part in this study. The only possible risk may be breach of confidentiality. This information collected will not contain identifying information with the survey. You have the alternative to choose to not take part in this study and can withdraw at any time.

There is no cost, and you will not be paid to take part in this study. You will not be personally identified in any reports or publications that may result from this study. Any personal information about you that is gathered during this study will remain confidential to every extent of the law.

If you have any questions about this project, please contact Michelle Zelnick at (937)-524-3414.

If you agree to take part in the study your agreement is completion of the survey.

This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. IRB NUMBER: HSC-MS-21-0627. IRB APPROVAL DATE: 07/30/2021. For any questions about research subjects rights call CPHS at (713) 500-7943.

Page Break

- ☐ Yes, I agree to participate (1)
- ☐ No, I do not agree to participate (2)

Skip To: End of Survey If = No, I do not agree to participate

Page Break

End of Block: Informed Consent Block

Start of Block: Demographics

Which best describes your gender?

- ☐ Female (1)
- ☐ Male (2)
- ☐ Transgender Female (3)
- ☐ Transgender Male (4)
- ☐ Gender variant/non-conforming (5)
- ☐ Not listed/Prefer to self-describe (6)

-
- ☐ Prefer not to answer (7)
-

What is your current a
Years-old (9)

☐ 1 (1)

☐ 2 (2)

☐ 3 (3)

☐ 4 (4)

☐ 5 (5)

☐ 6 (6)

☐ 7 (7)

☐ 8 (8)

☐ 9 (9)

☐ 10 (10)

☐ 11 (11)

☐ 12 (12)

☐ 13 (13)

☐ 14 (14)

☐ 15 (15)

☐ 16 (16)

☐ 17 (17)

☐ 18 (18)

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☐ 21 (21)

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☐ 32 (32)

☐ 33 (33)

☐ 34 (34)

☐ 35 (35)

☐ 36 (36)

☐ 37 (37)

☐ 38 (38)

☐ 39 (39)

☐ 40 (40)

☐ 41 (41)

☐ 42 (42)

☐ 43 (43)

☐ 44 (44)

☐ 45 (45)

Do you identify yourself as Hispanic or Latino?

☐ yes (1)

☐ no (2)

☐ Prefer not to answer (3)

Please specify the racial group(s) that best describe you. Select all that apply.

☐

White (1)

☐

Black or African American (2)

☐

American Indian or Alaska Native (3)

☐

Asian (including East Asian, Southeast Asian, Middle Eastern, etc.) (4)

☐

Native Hawaiian or Pacific Islander (5)

☐

Not listed, please specify (6)

☐

Prefer not to answer (7)

How many times have you attended camp as a camper?

1 2 3 4 5 6 7 8 9 10 11 12 13



End of Block: Demographics

Start of Block: Camp PHEver

I feel I have followed my diet prescription closely before attending Camp PHEver.

Disagree

Agree

1 2 3 4 5



I feel that Camp PHEver gave me the skills to follow my diet more closely.

Disagree

Agree

1 2 3 4 5



I feel I have followed my diet more closely since attending Camp PHEver.

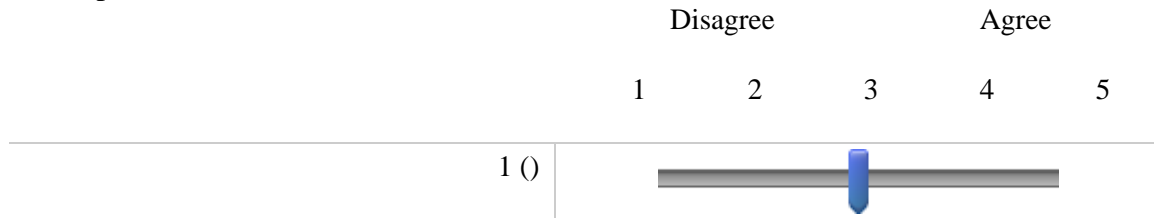
Disagree

Agree

1 2 3 4 5



My experience at Camp PHEver has helped me manage my phenylalanine levels outside of camp.



Page Break

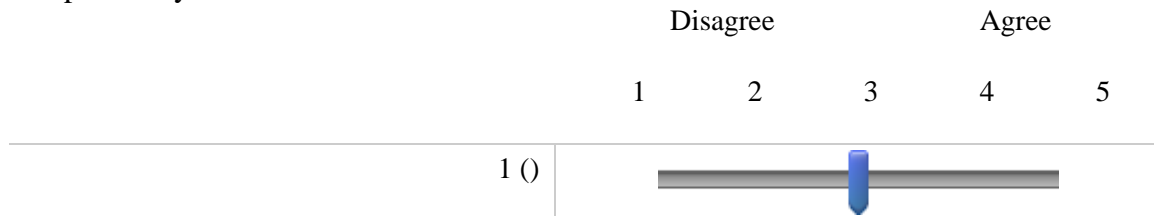
While you attended Camp PHEver, did your medical food (formula) require that you mix it yourself?

☐ Yes (1)

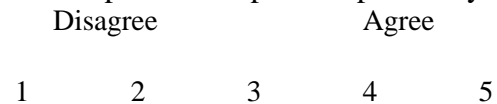
☐ No (2)

Skip To: Q7 If While you attended Camp PHEver, did your medical food (formula) require that you mix it yourself? = No

My experience at Camp PHEver helped me learn to prepare my medical food (formula) independently.



My experience at camp helped me learn to prepare low protein recipes independently.



1 ()	
------	--

Given that there are no issues with accessibility of ingredients, my experience at Camp PHEver helped me feel more comfortable trying low protein recipes outside of camp.

Disagree

Agree

1

2

3

4

5

1 ()	
------	--

I have made lasting friendships with fellow campers from Camp PHEver.

Disagree

Agree

1

2

3

4

5

1 ()	
------	--

I have kept in contact with individuals I have met at Camp PHEver.

Disagree

Agree

1

2

3

4

5

1 ()	
------	--

During camp, I felt comfortable sharing my struggles with PKU with campers and counselors.

Disagree

Agree

1

2

3

4

5



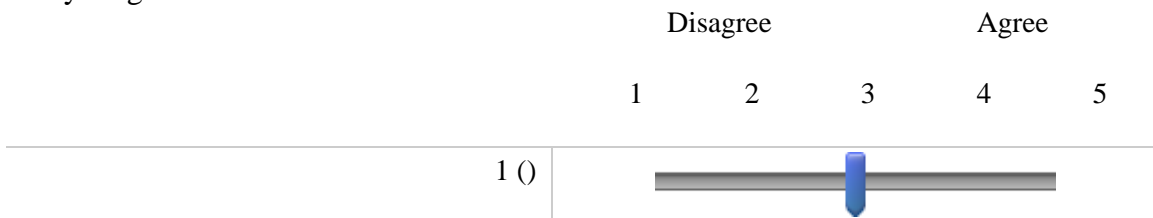
Since attending camp PHEver, I feel more comfortable sharing my struggles with PKU with people I know.



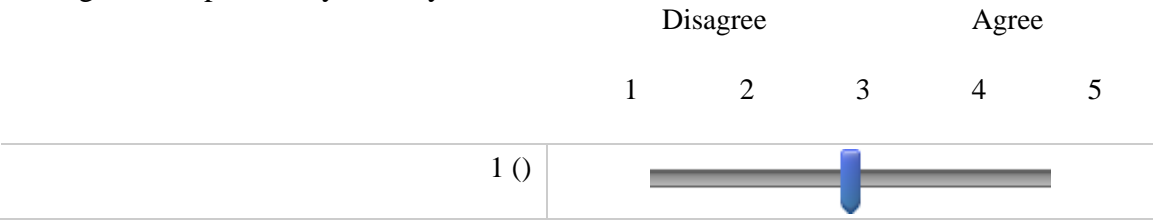
Camp PHEver encouraged me to build a stronger relationship with my healthcare team (i.e. metabolic dietician, geneticist).



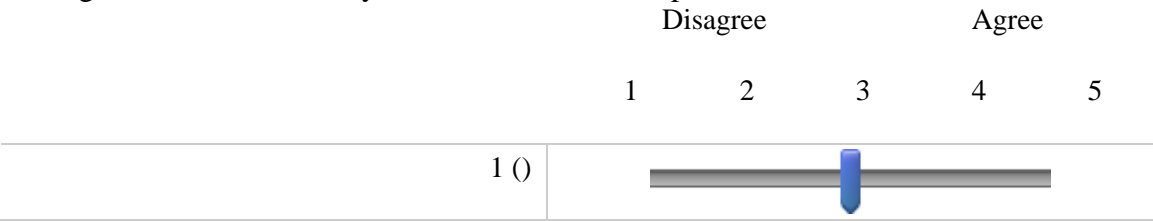
Camp PHEver has increased my feelings of independence and self-confidence in regard to my diagnosis of PKU.



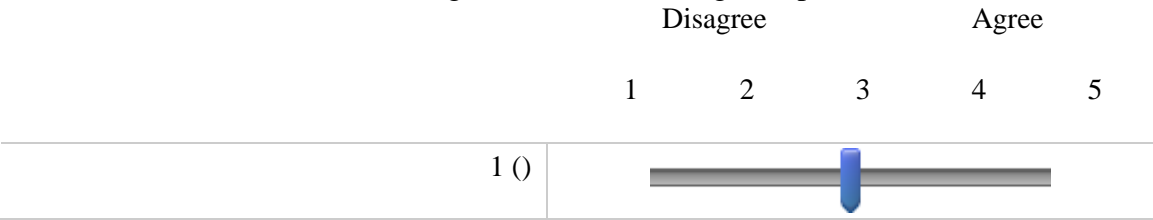
Having PKU is part of my identity.



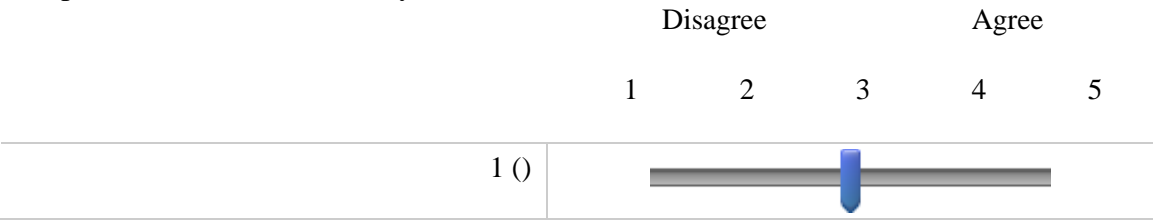
Having PKU has lowered my self-confidence in the past.



I feel more comfortable with having PKU after attending Camp PHEver.



Camp PHEver has increased my self-confidence.



I would recommend attending Camp PHEver to others with PKU.

Disagree

Agree

1

2

3

4

5

10



End of Block: Camp PHEver

Start of Block: Raffle

If you are interested in being entered in a raffle to win the \$25 gift card, please enter your email address below.

End of Block: Raffle

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Vita

Michelle Zelnick was born in Ohio, the daughter of Peter and Judy Zelnick. After completing her work at Troy High School, Troy, Ohio in 2015, she began school at Tulane University in New Orleans Louisiana. It was here that she received the degree of Bachelor of Science with two majors in Neuroscience and Psychology in May of 2019, as well as a Master of Science in Cellular and Molecular Biology in May of 2020. In August of 2020, she entered the University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences Genetic Counseling Program.

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