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# Access to Low Protein-Modified Food Associated with Clinical Biomarkers in Patients with Phenylketonuria

By

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Master of Public Health

Epidemiology

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B.A., Franklin & Marshall College, 2018

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## Abstract

Access to Low Protein-Modified Food Associated with Clinical Biomarkers in Patients with Phenylketonuria

By Ellen Jordan

Background: Low protein-modified foods (LPMF) are thought to provide satiety and variety to patients diagnosed with Phenylketonuria (PKU) who have more severe phenylalanine (Phe) restrictions. We aim to understand whether there is an association between access to LPMF and metabolic control in patients with PKU. Additionally, we hope to evaluate whether there are differences in control by frequency of one's interaction with the Metabolic Nutrition Therapy 4 Prevention (MNT4P) LPMF bridge program.

Methods: We used invoice data from MNT4P's novel LPMF bridge program to identify a cohort of patients with PKU and quantify the number of times each patient accessed LPMF in their first year participating in the program. A retrospective chart review of biomarker data and anthropometrics was then completed for eligible patients. The association between LPMF orders and log-transformed median blood Phe levels was quantified through multivariable fixed-effects linear regression, as was that between frequency of interaction with the program and blood Phe levels.

Results: A total of 37 patients were included in the analysis. The median age of the study population was 3.8 years (IQR 0.8 – 15.1), 9 (24%) were receiving concurrent treatment with sapropterin dihydrochloride, and the median number of LPMF orders during the follow-up period was four (range 1 – 12). When adjusting for filter paper submission adherence and age, participation in the LPMF program was associated with median blood Phe levels 0.70 times those recorded in the baseline year (95% CI 0.38 – 1.31; adjusted $R^2$ 0.67, $p < 0.001$). Frequency of LPMF ordering also was associated with differences in median blood Phe levels (adjusted $R^2$ 0.66, $p < 0.001$). Among patients ordering 1-4 times, there was a 29% reduction compared baseline (95% CI 0.38 – 1.33); those ordering 5-12 times saw a 34% reduction (95% CI 0.33 – 1.32).

Conclusion: Access to LPMF was associated with reduced median blood Phe levels in patients with PKU. This indicates that improving access to LPMF may have clinical utility and public health salience in the management of PKU.

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# Contents

# Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder resulting from a mutation of the phenylalanine hydroxylase (*PAH*) enzyme gene, seen annually in approximately 1 in every 15,000 newborns in the United States.[1] Affected individuals are unable to convert phenylalanine (Phe), an essential amino acid, to tyrosine (Tyr), which results in a build-up of Phe in the blood. Patients are diagnosed by measuring the plasma concentrations of Phe, which is generally done at birth through the US Newborn Screening program.[1] Patients with unmanaged or poorly controlled Phe levels can develop pigment dilution, eczema, seizures, hyperactive behavior, delayed speech, and low intelligence.[2]

Due to the severity of the potential mental deterioration and impairment, treatment must begin at birth and be maintained throughout the lifetime of the patient. Pharmaceutical therapies, such as sapropterin dihydrochloride (Kuvan, BioMarin Pharmaceutical) and pegvaliase-pqpz (Palynziq, BioMain Pharmaceutical), are available; however, sapropterin dihydrochloride is only effective in tetrahydrobiopterin-responsive patients, and pegvaliase requires daily injections.[3–5] Dietary management remains the primary method of treatment for most patients with PKU.

Successful diet management requires patient compliance in avoiding regular foods (i.e., those with very high levels of protein such as meat, fish, eggs, and cheese[6]) that could elevate the concentration of Phe in the blood beyond recommended limits and instead supplementing the diet with medical foods. Once patients reach adolescence, the frequency of blood Phe concentrations recorded outside threshold recommendations begins to rise for many patients, suggesting that the patients are no longer adhering to their diets as strictly.[7–9] Phe concentrations in adult patients with PKU, especially those with “classic” PKU (the phenotype characterized by the most severe PAH enzyme restriction), are often chronically above the recommended blood thresholds of 360 µmol/L.[3] Structural factors, such as cost of medical foods[10] and general food insecurity,[11] can impede patients from adhering to treatment. Social influences can also impact adherence. For example, embarrassment at needing to consume medical foods - either socially or in the workplace - begins to be more acutely felt by patients as they grow older.[12,13] As patients

mature, they may also seek fewer restraints and gravitate toward foods that taste better or provide more satiety.[13]

To address the last of these concerns, dietitians encourage the incorporation of low protein-modified foods (LPMF) for patients with classical PKU who may have a difficult time keeping their Phe levels within the target range.[14,15] LPMF are made with the starch protein of grains, instead of higher-protein flour, and are meant to replace foods such as bread and pasta. Introduced early in the diets of patients with classical PKU, they are thought to provide energy and diet variety, which can prevent weight loss (catabolism releases Phe into the bloodstream) and elevated blood Phe levels from ingesting Phe-containing foods.[15] In the UK, LPMF was found to, on average, contribute to a third of the daily energy intake of patients with PKU.[16] Patients have confirmed that LPMF allows them to manage their PKU more effectively, specifically by providing variety and increasing satiety.[17] However, little is known about how LPMF is quantitatively related to patient compliance and outcomes, especially in American patient populations who face variable insurance coverage which can act as an additional barrier to accessing LPMF.[18,19]

To address compliance issues related to the social determinants of health, bridge programs such as the Medical Nutrition Therapy 4 Prevention (MNT4P) program have been established to provide education and support to patients who need assistance in managing their inherited metabolic disorders (IMDs). This support includes insurance navigation and the emergency provision of medical supplies, including medical food, to assist patients with the financial burden of managing their disorders. In 2018, this program began a LPMF provision program that subsidizes the cost of Ajinomoto Cambrooke LPMF ordered by interested patients. By quantifying the effect of uninterrupted access to LPMF on clinical parameters, we hope to understand if this program improves patient outcomes. Given that insurance coverage and the cost of specialized medical foods – which are not considered by the Food and Drug Administration (FDA) to be therapies in the way that pharmaceutical interventions are[19] – are considered barriers to patient compliance,[10] we are hoping to better understand the context of diet management compliance for PKU patients in the United States.

In this study, we aim to quantitatively understand whether LPMF access through participation in this program is associated with improved patient compliance with dietary management of PKU. Our first objective was to evaluate whether participation in this program is associated with changes in blood Phe concentrations in the first year after initial order. Blood Phe levels are a practical and valid method to monitor metabolic status, specifically as it they correlate with IQ in patients with PKU.[20] Since patients could opt into the program at their own choosing, our second objective was to understand whether frequency of ordering in the first year (high versus low) is associated with a treatment effect.

Nutrition management plays a critical role in preventing the progression of severe outcomes in patients with PKU. However, this management strategy is only effective when patients can adhere to it. Understanding the role LPMF plays in the management of PKU can better assist clinicians in counseling their patients. It can also illuminate current disparities in socioeconomic status and state policy and contextualize patient non-compliance to diet in the United States.

# Methods

## Study population

To be eligible for the LPMF program, patients had to first be enrolled in MNT4P. Patients who indicated need of LPMF through this enrollment were then connected to the subsidy program, which covers LPMF items manufactured and provided by Ajinomoto Cambrooke. Through MNT4P, each patient was eligible to request a set dollar amount worth of food ($200 per month prior to 2019 and $150 per month after 2019) every month, based on patient interest. Invoices provided to MNT4P from Ajinomoto Cambrooke were used to identify MNT4P patients who interacted with the intervention at least once between the inception of the program (February 2018) and the date of the chart review (December 2021). All patients were concurrently receiving treatment and counseling at the Emory University Hospital outpatient clinic for PKU.

Patients identified through MNT4P enrollment who both stated a need for LPMF and were included in at least one of the invoices provided by Ajinomoto Cambrooke were considered eligible for

this study if they had a clinical diagnosis of PKU and had interacted with the LPMF program at least one calendar year prior to the chart review. Patients who began PKU treatment with sapropterin dihydrochloride or pegvaliase during the two-year period of interest were excluded from the study. Also excluded were patients who did not have outcome (biomarker) or covariate (dietary Phe tolerance) data for both study periods. This second category includes patients who began ordering LPMF upon initial contact with MNT4P and those who were still establishing optimum diet control, either through lack of patient education or adherence or from having been lost to follow-up by the clinic, by the time of their first order.

## Data Collection

Upon enrolling in MNT4P, patients have the option to provide informed consent (and assent, for children between the ages of six and eighteen) for their patient data to be used in studies evaluating the program. This has been approved by the Emory University Institutional Review Board (IRB), and receipt of MNT4P's services is not contingent on the provision of this consent. Invoice data provided by Ajinomoto Cambrooke was used to determine the number and frequency of LPMF orders per participant starting with their first point of contact with the program and ending 12 months later. Biomarker and covariate data were collected retrospectively from electronic medical records, with each patient's baseline set to one calendar year before they first interacted with MNT4P's LPMF program. In this first, baseline, year, patients were not yet ordering LPMF through MNT4P, so data collected for this period were used as control data to assess whether engagement with the program is associated with biomarker levels. Medical chart data were collected from baseline through the end of 2021. For the purposes of this study, only patient data pertaining to the two-year window of interest were included in analysis. Data collected included the patient's birthdate, chart date, sex, height, weight, *PAH* genotype, dietary prescription (for daily energy, Phe tolerance, protein equivalent, and brand/dose of medical food, if available), hospitalizations, and biomarker (Phe and Tyr) concentrations and measurement dates. From the anthropometric data, body mass index (BMI) was calculated. Per the American College of Medical Genetics and Genomics (ACMG) guidelines, blood Phe levels between 120-360 μmol/L (2-6 mg/dL)

were considered within the treatment threshold.[21] The proportion of within-threshold Phe results was calculated using the biomarker results for each participant's study periods. Participant age was averaged for each study period.

Since chart data were only captured during routine visits with dietitians and physicians, anthropometric, medical food protein equivalents per day, and daily Phe tolerance collected and prescribed at these visits were assumed to remain stable until the next visit. Chart addenda and ad-hoc updates (i.e., height/weight updates and changes in medical food/dietary Phe intake) were included when available; these changes were considered as taking effect on the date of the chart update unless a specific date of initiation or change was provided in the chart note. Biomarker data were collected from both lab results filed in the patient's clinical chart and MNT4P records. To mitigate any potential biasing effect from lack of regular filter paper submissions, biomarker measurements from both filter papers and plasma amino acid results were included.

The number of biomarker measurements was calculated for each participant's study period and included as a potential confounder; we considered patients who submitted filter paper data and attended clinic visits for blood draws more frequently to be more adherent to preventative measures, which could affect both their engagement with MNT4P's LPMF program and their overall metabolic control. MNT4P covers postage for these filter paper submissions. Patients are routinely reminded of the frequency at which they should be submitting these samples (alongside diet records) to dietitians, especially if there is a history of Phe values that demonstrate low metabolic control. These results then inform daily Phe tolerance, medical food, and (if applicable) sapropterin dihydrochloride prescription.

## Data Analysis

This was a retrospective chart review of existing medical records, so there were no fixed timepoints at which patients submitted samples for Phe and Tyr lab values. To analyze trends in Phe levels, we aggregated the blood Phe (µmol/L) biomarker values over one-year periods and calculated the median. For each participant, we also calculated the proportion of Phe results which were within the

recommended treatment range, 120-360 μmol/L (2-6 mg/dL). To assess whether the frequency of interaction with MNT4P's LPMF program imparted a treatment effect, participants were grouped into one of two cohorts (Low Use versus High Use) based on the number of times they ordered LPMF during their first calendar year in the program, using the median frequency as the cut point.

We fit multivariable fixed effects linear regression models to evaluate the average treatment effect of participation in the program by comparing Phe levels during the treatment year to those Phe levels in the baseline year. This same analysis was repeated by cohort, which was included as a dummy variable in the model, to assess whether the average effects differed by order frequency. Prior to linear analysis, median Phe values were log-transformed to minimize potential effects from the skewed nature of the biomarker results. In both models, we explicitly adjusted for time-varying confounders, including age, the number of biomarker measurements submitted (which we considered a proxy for general adherence), and daily dietary Phe tolerance.[22] Through use of this model, each participant served as their own control, thereby adjusting for potential time-invariant confounders[23] which include both the use of other treatment methods (sapropterin dihydrochloride, since no patients included were concurrently prescribed or taking pegvaliase; true/false) and other unmeasured confounders, such as socioeconomic status or family structure,[24,25] that were assumed not to change over the study period.

## Results

We identified 93 patients with PKU who had provided informed consent through the MNT4P enrollment process and ordered LPMF at least once between February 2018 and December 31, 2021. Of these initial 93 patients, 76 had a program start date on or before December 31, 2020, one calendar year prior to the chart review, and were eligible to be included in the study. Twenty patients began receiving treatment outside of dietary management (e.g., sapropterin dihydrochloride or Palynziq) during the study period and were excluded. Outcome and/or covariate data were missing for an additional four patients,

further restricting our eligible population to 52 participants. Finally, 37 participants had data for both the baseline and follow-up period and comprised the final analytic population.

The median age of the study population during the first year they interacted with the LPMF program was 3.8 years (IQR 0.8 – 15.1) and 19 (51%) were male. 9 (24%) patients received concurrent sapropterin throughout the study period. No patients were treated with pegvaliase during the study. Patients were prescribed a median of 21 g (IQR 12 – 46) of protein equivalents during their baseline year and 30 g (IQR 19 – 50) during the second year. During the first and second year of the study, the median daily Phe goal was 275 mg (IQR 223 – 380) and 315 mg (IQR 255 – 423), respectively. Before ordering LPMF, the average BMI of this study population was 19.9 (SD 4.6). In the second year, the average BMI was 20.4 (SD 4.4). The median number of biomarker measurements (filter paper and plasma amino acid) submitted by each patient was 11 (IQR 3 - 33) during baseline and 10 (IQR 3 - 14) the second year. The median number of LPMF orders placed during the first year was four (range 1 – 12). Per order, patients bought an average of 8.7 LPMF items (SD 1.6). From Year 1 to Year 2, was also a slight increase in the median proportion of filter paper test results that were within the recommended treatment levels (Table 1, Figure 1D).

Average and median values of blood Phe levels remained stable throughout the study and fell within to the ACMG's uppermost acceptable limit, 360 μmol/L[21] (Table 1; Figure 1A). The fixed effects model indicated there was a moderately strong within- subject linear association between participation in the LPMF program and changes in median blood Phe (adjusted $R^2$ 0.67, $p < 0.001$). When adjusting for age, the number of biomarker levels submitted by the patient, and daily Phe tolerance, participation with the program was associated with lower median blood Phe levels that were 0.70 times (95% CI 0.38 – 1.31) those recorded during baseline. Age was highly correlated with BMI; given the existing research supporting the role of age in diet adherence in this population[8,9,13], we opted to adjust for age and not include BMI in the model.

Cohorts were determined using the median number of interactions with the LPMF program. Those who interacted with the program one to four times in their first year were considered low-frequency users, and those who had five to twelve interactions in their first year were high-frequency users. While the median ages, sex distributions, and average BMI of the patients did not differ considerably between the two cohorts, seven of the nine patients being treated with sapropterin were low-frequency users, while the other two were high-frequency users (Table 1). The median daily Phe goal of the high use cohort was higher during both periods when compared to the low use cohort (350 mg/day and 380 mg/day versus 256 mg/day and 289 mg/day, respectively). Over the study period, the median daily protein equivalent (PE) prescription was the same at baseline and increased slightly in both cohorts.

The median biomarker submissions per patient were similar across both cohorts and over both study periods, with a median of 71% of these baseline submissions within the recommended treatment range of 120-360 μmol/L (2-6 mg/dL) among low-frequency users, compared to an initial median of 47% among high-frequency users. While the median within range decreases slightly among low-frequency users between the two years, there was an increase from 47% to 60% in high-frequency users over the study period (Table 1; Figure 1E). There were slight, parallel increases in the median blood Phe levels and increased interquartile ranges of blood Phe levels among both high- and low-frequency users in Year 2 (Figure 1C and 1B). When evaluating the association between the frequency of participation in the LPMF program and median blood Phe levels (on the logarithmic scale), we observed associations similar to that of the overall population (Table 2). After accounting for age, the number of biomarker measurements submitted by the patient, and daily Phe tolerance, there was a moderately strong within-patient linear association between frequency-use cohort and median blood Phe (adjusted $R^2$ 0.66, $p < 0.001$). Low-frequency use in the first year of participation was associated with median blood Phe levels 0.71 times (95% CI 0.38 – 1.33) those recorded in the baseline year. High-frequency use of the program was associated with blood Phe levels that were 0.66 times (95% CI 0.33 – 1.32) those recorded in the baseline year.

Table 1. Demographic characteristics, LPMF program interactions, and biomarker results of the study population at baseline (Year 1) and during the intervention year (Year 2).

| | *All (N = 37)* | | *Low Use (N = 19)* | | *High Use (N = 18)* | |
|---|---|---|---|---|---|---|
| | **Year 1** | **Year 2** | **Year 1** | **Year 2** | **Year 1** | **Year 2** |
| **Demographic** | | | | | | |
| Age (years) | 3.8 (0.8-15.1) | 4.7 (1.7-15.7) | 5.6 (1.0-15.3) | 6.5 (2.0-16.1) | 1.1 (0.7-12.5) | 2.0 (1.7-13.6) |
| Adult (n, %) | 7 (19) | 7 (19) | 4 (21) | 4 (21) | 3 (17) | 3 (17) |
| Male (n, %) | 19 (51) | 19 (51) | 10 (53) | 10 (53) | 9 (50) | 9 (50) |
| BMI (mean ± SD) | 19.9 ± 4.6 | 20.4 ± 4.4 | 20.2 ± 5.3 | 20.7 ± 5.1 | 19.7 ± 3.9 | 20.2 ± 3.7 |
| **Prescription** | | | | | | |
| PHE (mg/day) | 275 (223-380) | 315 (255-423) | 350 (254-608) | 380 (300-503) | 256 (201-315) | 288 (235-370) |
| PE (g/day) | 21 (12-46) | 30 (19-50) | 21 (15-43) | 28 (20-47) | 21 (11-50) | 30 (20-50) |
| Sapropterin (n, %) | 9 (24) | 9 (24) | 7 (37) | 7 (37) | 2 (11) | 2 (11) |
| **LPMF Orders** | | | | | | |
| N (median, range) | 0 | 4 (1-12) | 0 | 2 (1-4) | 0 | 8 (5-12) |
| Items (mean ± SD) | 0 | 8.7 ± 1.6 | 0 | 8.2 ± 1.8 | 0 | 9.1 ± 1.2 |
| **Biomarker** | | | | | | |
| Results per Patient | 11 (3-33) | 10 (3-14) | 9 (4-25) | 10 (3-13) | 9 (3.8-25.3) | 8.5 (3.3-35.3) |
| Phe (µmol/L, mean ± SD) | 325 ± 196 | 340 ± 213 | 310 ± 208 | 327 ± 213 | 340.2 ± 186.9 | 353 ± 218 |
| % in range | 59 (33-78) | 62 (33-78) | 71 (51-87) | 67 (38-79) | 47 (33-61) | 60 (17-72) |

*Note:* PHE denotes the daily Phe goal and protein equivalents (PE) are those in prescribed medical food. Median (IQR) is reported unless otherwise specified.

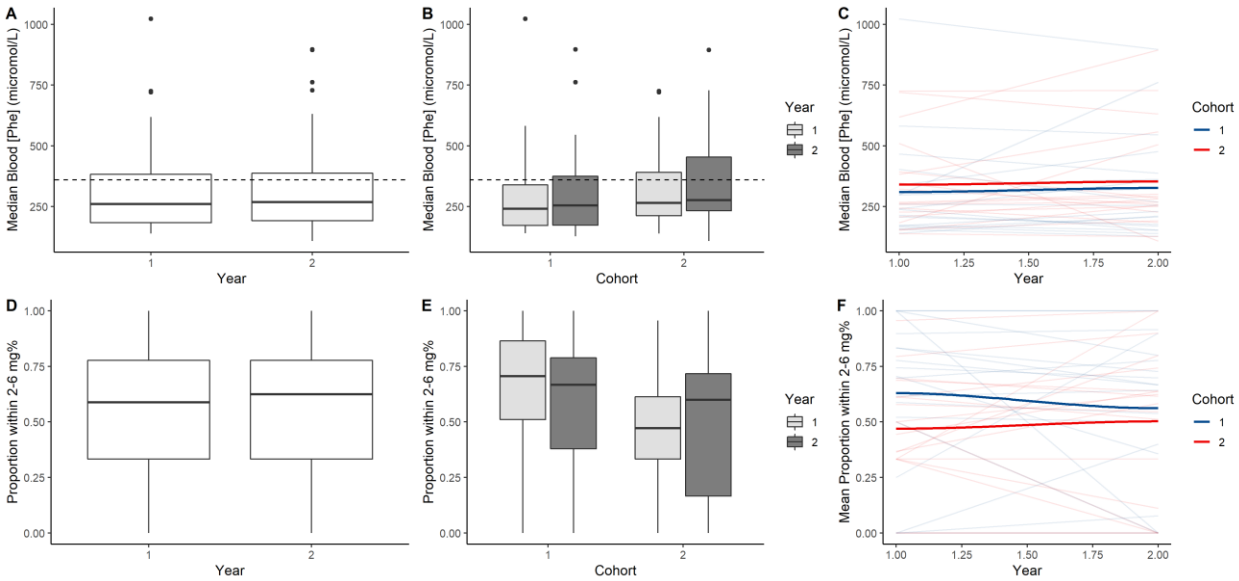


Figure 1. Change in blood Phe biomarker results. Distribution of median Phe levels overall (A) and within cohorts (B), compared to the ACMG recommended limit, 360 µmol/L. Spaghetti plot summarizing individual-level and cohort-level changes in median Phe (C). Distribution of Phe results within range, overall (D) and by cohort (E), at Year 1 and Year 2. Spaghetti plot summarizing individual and cohort-level changes in the average proportion of Phe results within range between Years 1 and 2 (F).

Table 2**.** Average association between interacting with the LPMF program and change in median blood Phe levels in the first year of patient participation, overall and by cohort.

| | *Overall Effect* | | *Effect by Cohort* | |
|---|---|---|---|---|
| **Coefficient** | **Estimate (95% CI)** | **P-value** | **Estimate (95% CI)** | **P-value** |
| Intercept | 315.10 (157.25 – 631.37) | <0.001 | 214.80 (85.18 – 541.69) | <0.001 |
| Year | 0.70 (0.38 – 1.31) | 0.25 | -- | -- |
| Low Use | -- | -- | 0.71 (0.38 – 1.33) | 0.28 |
| High Use | -- | -- | 0.66 (0.33 – 1.32) | 0.24 |
| $R^2$ (within) | 0.67 | <0.001 | 0.66 | <0.001 |

*Note*: Patient identification dummy variables not shown. Age, number of biomarker submissions, and daily Phe tolerance were included as time-varying confounders within each model.

# Discussion

We observed a strong within-subject association between joining MNT4P's LPMF program and log-transformed median blood Phe results in the first year of program participation. Specifically, access to LPMF among patients with PKU living in the Southeastern United States appears to be associated with a reduction in median blood Phe levels, which is consistent with preliminary research on the effect of LPMF in other patient populations.[26] However, this estimate is imprecise and lacks statistical significance. This association persisted when we evaluated the average effects by frequency-use cohort, with both low- and high-frequency participation associated with a reduction in median blood Phe in the second year. There appeared to be a slightly stronger protective effect in those high-frequency users of the program, despite the apparent lack of change in this cohort's – and the overall cohort's – median blood Phe results between the two years. Stability of population-level Phe concentrations over time have been observed in another cohort in the United States,[3] but this, in conjunction with the results from the regression, suggests that access to LPMF, at the very least, may not result in worsened outcomes in this patient population.

The slight differences in trends observed by cohort may suggest differential effects of LPMF not by frequency alone, but by patient population. Not only were those low-frequency users also those with higher initial proportions of results within treatment range (Figure 1E), the median Phe levels at baseline were slightly lower than the corresponding median among high-frequency users. There were also

relatively more patients receiving concurrent treatment with sapropterin in the cohort of low-frequency users. Sapropterin is an effective treatment for the management of PKU precisely because it assists *PAH* in the conversion of Phe to Tyr. Due to this increase in enzyme function, average Phe levels remain lower and dietary Phe tolerance increases.[4] Thus, that we would expect to see the observed differences in median daily Phe goal and prescribed protein equivalents between the cohorts given the difference in number of sapropterin-treated patients, since increases in dietary Phe tolerance allow patients to consume more non-modified (regular) foods. While daily Phe goal and treatment with sapropterin were both controlled for through use of fixed-effects regression (as a time-varying covariate and as a constant patient attribute, respectively),[23] these characteristics might account for the higher proportions of biomarker results returned within 120-360 μmol/L (2-6 mg/dL) and the lower variability in results compared to those in the high-frequency use cohort.

Given the diversity of ages represented and the longitudinal nature of the study, it was imperative to adjust for this known confounder in our linear model. Notably, our study population is younger than that featured in a recent PKU chart review completed in the United States.[3] Increases in age have elsewhere been associated with worsened metabolic control in PKU patients.[7–9,27] The strong positive association between age and Phe levels might explain the relative overall stability of the outcomes observed in this study and could potentially indicate that, while access to LPMF might not completely override this relationship, it could be mitigating the detrimental effects of age within this patient population. Conceptually, this could be due to the role LPMF is meant to play in providing calories and a sense of normality to the diets of patients.[15] As children age and begin to choose their own snacks and meals, having LPMF as a readily accessible option might obviate choosing between formula and high protein, harmful foods.[12]

Improving access to LPMF may also resolve barriers to diet adherence that are imposed by social factors.[13,25,28] Our study featured patients who reside in the Southeastern United States, where insurance coverage of LPMF and medical food is variable and not mandated by state legislation,[2,19] and where the

cost of LPMF items is often greater than it is for their non-modified, higher protein counterparts.[21] Considering the known financial burden of LPMF (and of dietary management of PKU generally[10]), a program that subsidizes the cost of LPMF may improve the ability of patients to remain 'on diet.' Socioeconomic status, family structure, food insecurity, immigration status, and other social variables[11,24,25,29] were assumed to remain constant for each patient and thus were adjusted for through use of the fixed-effects linear models. The protective effect of LPMF observed through use of these models may not refer strictly to the nutritional effects of LPMF – participation in this program might confer additional benefit through providing patients with support and education, which have been indicated to influence metabolic control.[14,26] Interacting with this program might also require patients to be in closer contact with the clinic as they age,[30] which could holistically improve metabolic control.

## Limitations

This study had several limitations. There could be myriad reasons that patients would indicate need for LPMF upon enrollment in MNT4P (thereby becoming eligible to receive assistance). For example, these could be patients struggling to maintain control of their disorder, those who require the financial assistance, or those who have educated themselves on LPMF (or who have had particularly motivating conversations with clinicians regarding this intervention). Once within the program, patients then could choose to interact with the program as much or as little as they desired, and these decisions, as seen in our discussion addressing the unequal distribution of patients being treated with sapropterin between the two cohorts, might be due to inherent differences between patients. While within-subjects analysis using each patient as their own control attempts to address these potential between-subjects differences,[23] this could complicate any inferences regarding the effect of LPMF ordering frequency on metabolic control. Further research characterizing motivators of LPMF consumption would assist in clarifying these points.

We also do not know whether patients were consuming the LPMF they ordered, or to what extent LPMF were being incorporated into the patients' diets. This is especially pertinent for patients who

ordered only once or twice in the first year. There is some concern regarding the palatability of LPMF,[13] and patients who ordered once might have tried the foods and found them not to their taste, leading to non-consumption. Ease of preparation has also been identified as a barrier to consumption of LPMF[13] – to address this, MNT4P provides recipes and support from registered dietitians alongside the monetary subsidies. Despite this accommodation, high frequency users may reflect a patient population for whom these are not barriers and whose diet composition may be different from low-frequency users.

### Conclusion

This is one of the first studies evaluating the association between access to LPMF and metabolic control of PKU among patients living in the Southeastern United States. Biomarker data is widely considered a reliable predictor of clinical outcomes[15]; additionally, the observational nature of the study allowed us to incorporate the frequency of biomarker submissions as a proxy for general adherence.[22] Using each patient as their own control through both the study design and analysis of the results allowed us to evaluate within-subjects effects. In doing so, we identified that access to LPMF is associated with improved clinical outcomes in patients with PKU, which is consistent with preliminary research on the effect of LPMF provision in other countries.[26] Further research is warranted to evaluate the extent to which patients are consuming the LPMF they order and what might motivate the frequency with which patients interact with programs such as MNT4P's LPMF bridge program. Given that this patient population experiences variable insurance coverage and potentially needs to pay out-of-pocket for foods to assist in the management of their lifelong disease, these findings have implications for policy and clinical practice in the United States.

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