



Adherence to clinic recommendations among patients with phenylketonuria in the United States



E.R. Jurecki^{a,*}, S. Cederbaum^{b,c}, J. Kopesky^{d,e}, K. Perry^f, F. Rohr^g, A. Sanchez-Valle^h, K.S. Viauⁱ, M.Y. Sheinin^f, J.L. Cohen-Pfeffer^a

^a Medical Affairs, BioMarin Pharmaceutical, Inc., Novato, CA, United States

^b Department of Psychiatry, University of California, Los Angeles, CA, United States

^c Department of Pediatrics, and Human Genetics, University of California, Los Angeles, CA, United States

^d Department of Clinical Nutrition, Children's Hospital of Wisconsin, Milwaukee, WI, United States

^e Department of Genetics, Children's Hospital of Wisconsin, Milwaukee, WI, United States

^f Trinity Partners, Waltham, MA, United States

^g Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, United States

^h Division of Genetics and Metabolism, University of South Florida, Florida, United States

ⁱ Department of Pediatrics, Division of Medical Genetics, University of Utah, Salt Lake City, UT, United States

ARTICLE INFO

Article history:

Received 3 January 2017

Accepted 4 January 2017

Available online 6 January 2017

Keywords:

Phenylketonuria
Adherence
Blood phenylalanine
ACMG guidelines
Adults

ABSTRACT

Objective: Assess current management practices of phenylketonuria (PKU) clinics across the United States (US) based on the key treatment metrics of blood phenylalanine (Phe) concentrations and blood Phe testing frequency, as well as patient adherence to their clinic's management practice recommendations.

Methods: An online survey was conducted with medical professionals from PKU clinics across the US from July to September 2015. Forty-four clinics participated in the survey and account for approximately half of PKU patients currently followed in clinics in the US (Berry et al., 2013).

Results: The majority of PKU clinics recommended target blood Phe concentrations to be between 120 and 360 μM for all patients; the upper threshold was relaxed by some clinics for adult patients (from 360 to 600 μM) and tightened for patients who are pregnant/planning to become pregnant (to 240 μM). Patient adherence to these recommendations (percentage of patients with blood Phe below the upper recommended threshold) was age-dependent, decreasing from 88% in the 0–4 years age group to 33% in adults 30+ years. Patient adherence to recommendations for blood testing frequency followed a similar trend. Higher staffing intensity (specialists per 100 PKU patients) was associated with better patient adherence to clinics' blood Phe concentrations recommendations.

Conclusion: Clinic recommendations of target blood Phe concentrations in the US are now stricter compared to prior years, and largely reflect recent guidelines by the American College of Medical Genetics and Genomics (Vockley et al., 2014). Adherence to recommended Phe concentrations remains suboptimal, especially in older patients. However, despite remaining above the guidelines, actual blood Phe concentrations in adolescents and adults are lower than those reported in the past (Walter et al., 2002; Freehauf et al., 2013). Continued education and support for PKU patients by healthcare professionals, including adequate clinic staffing, are needed to improve adherence. Future research is needed to understand how to improve adherence to reduce the number of patients lost to follow-up, as the findings of this and similar surveys do not address how to keep patients in clinic.

© 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Phenylalanine hydroxylase (PAH) deficiency, commonly known as phenylketonuria (PKU), is one of the most prevalent inherited metabolic

Abbreviations: PKU, phenylketonuria; Phe, phenylalanine; PAH, phenylalanine hydroxylase; ACMG, American College of Medical Genetics and Genomics; US, United States; BH4, tetrahydrobiopterin; GMDI, Genetic Metabolic Dietitians International.

* Corresponding author.

E-mail address: ejurecki@bmrn.com (E.R. Jurecki).

disorders [1]. PAH deficiency results in elevated concentrations of Phe in the blood and brain, which, if untreated in the newborn period, can cause a range of complications, most notably severe neurocognitive and neuromotor impairments, including attention deficit symptoms, impaired mental processing, and severe intellectual disability [2–4]. The goal of PKU treatment is to lower and maintain the blood Phe concentration within the target range, preferably starting within the first 2 weeks of life. PKU patients undergo regular monitoring to ensure that Phe concentrations are controlled, nutritional

requirements are met, and patients are growing and developing appropriately [2].

PKU guideline recommendations for the appropriate target blood Phe concentrations and treatment duration have evolved over the years as the understanding of the disease has improved. Early guidelines published in the 1990s advised stricter target blood Phe concentrations for infants and young children (typically 120–360 μM), but more relaxed targets for adolescents and adults (typically up to 600–900 μM) [1,5]. In some cases dietary treatment was terminated in patients after childhood [4,6]. The National Institutes of Health issued guidelines for life-long treatment in 2000 after controlled clinical studies provided evidence that diet treatment discontinuation resulted in inferior outcomes (e.g., loss of intellectual function, higher rate of depression, neurological symptoms) [7,8]. Additional evidence [9] regarding neurotoxicities associated with elevated Phe concentrations prompted the American College of Medical Genetics and Genomics (ACMG) to update the guidelines in 2014 [2]. These guidelines recommended all patients to maintain blood Phe concentrations of 120–360 μM for life and lifetime treatment and monitoring for all patients to promote optimal outcomes [2].

Patient adherence to treatment recommendations has long been a source of concern to clinicians. Poor adherence may manifest in multiple ways, such as patient-initiated relaxation of dietary restrictions; failure to take medical food, special low protein foods, and/or prescribed medications; not attending regular clinic appointments; and lack of blood Phe monitoring. While no universal quantitative definition of adherence in PKU exists, it is thought that assessment of blood Phe concentrations provides arguably the best measure of a patient's adherence to treatment [9], as blood Phe has been shown to be closely related to patient outcomes [10].

Over the last decade, PKU management in the US has evolved, both in terms of management guidelines and treatment options [2,11], though significant reimbursement issues with medical food and special low protein food exist, especially in adults [4]. However, there is a lack of data as to how these changes are impacting PKU patient adherence. Previous research on patient adherence is limited to publications preceding ACMG guidelines [5,12] or studies performed outside of the US [1,13–15]. Additionally, prior studies in the US were not national level surveys of clinics. Results of these earlier studies showed significant levels of non-adherence to clinic target Phe concentrations [1,12–15]; it is not known whether adherence has improved, declined, or remained unchanged.

In addition to blood Phe concentrations, an important component of PKU management is the frequency of blood testing, which has also been revised in the ACMG guidelines, recommending biweekly to monthly testing [2]. This aspect of adherence has been explored to an even smaller degree as compared to the blood Phe concentrations.

Given the complexity of PKU management, the presence of several specialists (e.g., dietitians, psychologists, social workers, geneticists) on the metabolic multidisciplinary care team may be beneficial to the management of PKU patients. Although several surveys have documented staffing of PKU centers in Europe [13,14,16,17], similar information for the US is lacking. Additionally, there is limited data on the association between staffing and patient outcomes, such as blood Phe control and treatment adherence.

Our study was designed to assess current PKU clinic management practices regarding target blood Phe concentrations and blood Phe testing frequency, and patient adherence to their clinic's recommendations, as well as the impact of clinic staffing on patient adherence in US clinics.

2. Methods

2.1. Survey

The survey was conducted from July through September 2015 and contained 21 questions. Data collected included the respondent's clinic characteristics (location, number of PKU patients, number of full-time staff that treat PKU), PKU treatment recommendations (target blood

Phe, target blood testing frequency), and patient adherence to clinic recommendations. Treatment recommendations and adherence were asked for specific patient groups (ages 0–4, 5–12, 13–17, 18–29, 30+ years, and pregnant or planning on becoming pregnant within 12 months). Respondents were asked to define patient adherence to target blood Phe recommendations based on the average Phe concentrations obtained over the past year. Respondents were encouraged to refer to their clinic's patient database, patient medical charts, and clinic members in order to provide accurate answers. The full text of the survey can be accessed online (Supplementary Survey Text).

This study received Institutional Review Board exemption status given minimal risk to participants and de-identified healthcare professional and patient data.

2.2. Study recruitment

A double-blinded recruitment strategy was utilized: participants were recruited by an independent third-party and were in turn blinded to the sponsor of the study. The questionnaire was sent to a total of 212 healthcare professionals from 182 PKU clinics identified by the study sponsor. Respondents from 73 unique clinics replied to the survey (40% response rate) and respondents from 44 unique clinics qualified and completed the survey. Only the first respondent per clinic was allowed to complete the full survey.

Only respondents from clinics with at least 15 actively managed PKU patients, defined as patients that have been seen in clinic within the past 3 years, qualified to complete the survey. This cut-off was selected as a compromise to ensure the representativeness of the sample while eliminating very small clinics or clinics with limited experience in treating PKU patients that could have skewed the results. The clinics meeting inclusion criteria should be the ones more knowledgeable about PKU management across broader types of patients. Respondents from 6 unique clinics were disqualified based on this criterion.

2.3. Data analysis

Initial descriptive analyses were performed by summarizing the data in Microsoft Excel. Depending on the type of variable, each analysis was performed either on a clinic level (each clinic carried a weight of 1), or on a patient level (each clinic was weighted based on the number of PKU patients).

SPSS v22 (SPSS, Inc., Chicago, IL) was used to further explore relationships among variables. Bivariate Pearson correlation was used to analyze associations between continuous variables and one-way ANOVA was used for nominal variables. A two-sided P-value <0.05 was considered significant.

3. Results

3.1. Clinic and patient demographics

The 44 clinics that participated in the survey represented all geographic regions of the US (see Supplementary Text for definitions), with the majority of clinics located in the North Central region (39%) and in the South (30%), followed by the West (20%), and the Northeast (11%). The primary practice setting was academic, either a hospital practice (59%) or specialty/multi-specialty office (32%). The majority of respondents were dietitians (45%), followed by geneticists/genetic counselors (27%), and metabolic specialists (14%). Clinics have been managing PKU patients for an average of about 22 years (range 3–50 years). The median number of actively managed patients per clinic was 78 (range 15–275 patients; note that only clinics with ≥ 15 patients with PKU were qualified to participate). In total, respondents reported on their clinics' 3772 actively managed PKU patients, 41% of which were adults (Table 1). This represents about half of all actively managed PKU patients in the US (estimated at 7180 in 2012 [4]). The total

Table 1
Total number of PKU patients by age.

Patient group	0–4 years	5–12 years	13–17 years	18–29 years	30+ years	Total
Actively managed	641 (17)	938 (25)	657 (17)	748 (20)	788 (21)	3772 (100)
Followed in total	712 (13)	1063 (19)	838 (15)	1185 (21)	1732 (31)	5530 (100)
Lost to follow-up (as percent of total)	71 (10)	125 (12)	181 (22)	437 (37)	944 (55)	1758 (32)

Note: data shown as number of patients (%). Percentages may not add up to 100 due to rounding.

number of patients followed by the clinics was 5530 (52% adults), including those not seen in the last 3 years and thus possibly lost to follow-up. The proportion of total patients considered lost to follow-up increased with age, from 10% for the 0–4 years age group to 55% in the 30+ age group. Overall, an estimated 32% of all PKU patients in respondent's clinics were lost to follow-up.

We found that approximately 3% of the actively managed patients (and 7% of adults) were described as pregnant or planning to become pregnant in the next 12 months. These numbers highlight the importance of maternal PKU management [2].

3.2. PKU clinic staffing

Respondents were asked how many full-time healthcare professionals staffed within their clinic treat PKU patients (Table 2). All clinics reported having at least one physician and one dietitian on staff, and most (73%) reported having at least one genetic counselor. On average 2.7 physicians, 1.8 dietitians and 1.7 genetic counselors were reported per 100 actively managed PKU patients, with ranges varying by an order of magnitude, though it should be noted that these specialists are likely caring for patients with other diseases in addition to the PKU patients. 34% of clinics reported a nurse practitioner, 32% reported a social worker, and 16% reported a psychologist or neuropsychologist on the PKU care team.

3.3. Blood Phe: clinic recommendations and patient adherence

Forty-three out of 44 clinics recommended specific target blood Phe concentrations (Table 3). There was consensus regarding the lower threshold for target blood Phe concentration with approximately 95% of clinics recommending 120 μM , aligned with the ACMG guidelines [2]. There was greater variability in the clinic-recommended upper threshold for target blood Phe concentration, ranging from 360 to 600 μM . Clinics set the most stringent recommendations for younger patients and relaxed them for older patients. Nearly half of clinics

(48%) set especially strict upper target blood Phe thresholds for patients who are pregnant or are planning to become pregnant, most often 240 μM , a target that has been mentioned in the ACMG guidelines but not explicitly recommended [2].

Non-adherence to clinic recommended target Phe concentrations increased with age (Fig. 1A). The majority of adults had blood Phe concentrations above 360 μM , with 15% of those aged 18–29 years and 20% of those aged 30+ years reported to have elevated blood Phe > 1200 μM (Fig. 1B). It is important to note that this estimate is limited to actively managed patients with non-missing blood Phe concentrations and may be higher for those not checking Phe concentrations between visits, not actively managed in clinic, or lost to follow-up.

Since clinic-recommended target blood Phe did not always align with the ACMG guidelines, the percentage of non-adherent patients (with blood Phe above the target range) was determined in two separate comparisons using the ACMG guidelines as well as the clinic targets (Supplementary Table 1). Referring to either the ACMG guidelines or clinic targets had little impact on the percentage of non-adherent patients.

As a subset of clinics relaxed their target blood Phe recommendations for adults, we investigated whether using more “realistic” target Phe ranges translates into improved patient adherence (based on the clinic's definition). Surprisingly, clinics that used a higher upper Phe target (600 μM vs 360 μM) for adult patients 18–29 years old and ≥ 30 years old did not show better adherence even when judged by the clinic's own recommended targets (Fig. 2). When evaluated against a single adherence criterion of 360 μM , clinics with a higher upper target of 600 μM had more non-adherent patients compared to clinics that set a 360 μM target ($P < 0.05$ for both age groups).

3.4. Blood Phe testing frequency: clinic recommendations and patient adherence

Eighty-nine percent of clinics that participated in the survey (39/44) indicated that they have a protocol in place to recommend a certain

Table 2
PKU clinic staffing.

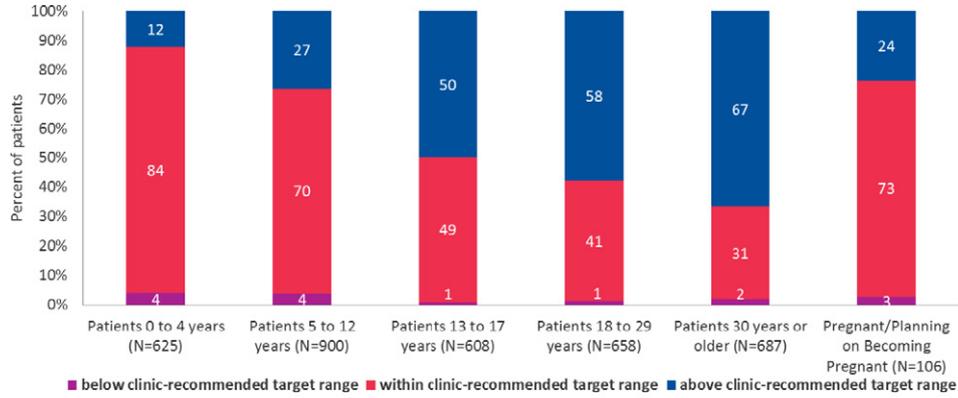
	Clinics with specialists N (%)	Mean (per clinic)	Range (per clinic)	Mean (per 100 patients)	Range (per 100 patients)
Physicians	44 (100)	2.3	1–5	2.7	1–13
Dietitians	44 (100)	1.5	1–3	1.8	1–7
Genetic counselors	32 (73)	1.5	0–7	1.7	0–13
Nurse practitioners	15 (34)	0.4	0–2	0.4	0–4
Social workers	14 (32)	0.3	0–1	0.4	0–5
Psychologists/neuropsychologists	7 (16)	0.2	0–2	0.3	0–6

Table 3
Clinic target blood Phe recommendations.

Patient group		0–4 years	5–12 years	13–17 years	18–29 years	30+ years	Pregnant/planning on becoming pregnant
Lower target	<120 μM	2 (5)	1 (2)	1 (2)	1 (2)	1 (3)	2 (5)
	120 μM	41 (95)	42 (98)	42 (98)	41 (98)	37 (95)	38 (95)
	>120 μM	–	–	–	–	1 (3)	–
Upper target	<360 μM	6 (14)	2 (5)	–	–	–	19 (48)
	360 μM	36 (84)	39 (91)	38 (88)	30 (71)	25 (64)	20 (50)
	361–599 μM	–	1 (2)	2 (5)	2 (5)	1 (3)	–
	600 μM	1 (2)	1 (2)	3 (7)	10 (24)	13 (33)	1 (3)

Note: data shown as number of clinics (% of clinics that responded). Percentages may not add up to 100 due to rounding.

A.



B.

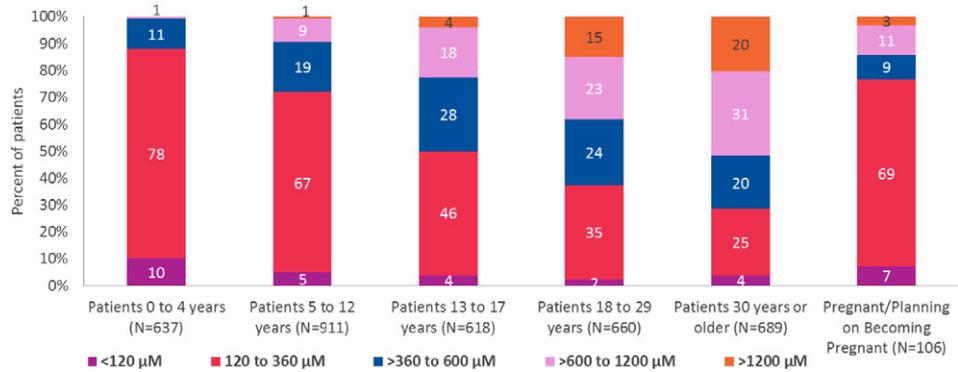


Fig. 1. Blood Phe concentrations. Then show text for A. and B. below. Note: figures exclude patients for whom adherence or actual Phe concentration was unknown: 1–3% of children and 12–13% of adults. A. Patient adherence to clinic-recommended blood Phe target concentrations. B. Patient distribution according to actual blood Phe concentrations.

frequency of blood Phe testing, which includes blood tests obtained on clinic days and blood tests obtained between appointments. Most clinics recommended weekly testing for infants (<1 year old) and pregnant/planning to become pregnant women, and monthly for all other patients (Table 4), which aligned with the ACMG guidelines [2].

Patient adherence to clinic-recommended blood Phe testing frequency decreased with age (Supplementary Fig. 1), mirroring the findings on adherence to blood Phe recommendations. Fig. 3 shows actual Phe testing frequency; notably, 37% of patients 30 years and older check blood Phe concentrations once a year or less. Testing frequency

is low in younger patients as well – 31% of adolescents (13–17 years) test only once or twice a year.

Adherence to clinic-recommended blood Phe concentrations was not significantly correlated with either the adherence to blood frequency testing recommendations or to actual blood frequency testing, with the exception of the subset of patients who are pregnant/planning to become pregnant (Supplementary Tables 2 and 3). This lack of correlation has been observed previously [12]. Similarly, actual frequency of clinic visits and staffing were not correlated (Supplementary Fig. 2 and Supplementary Table 4).

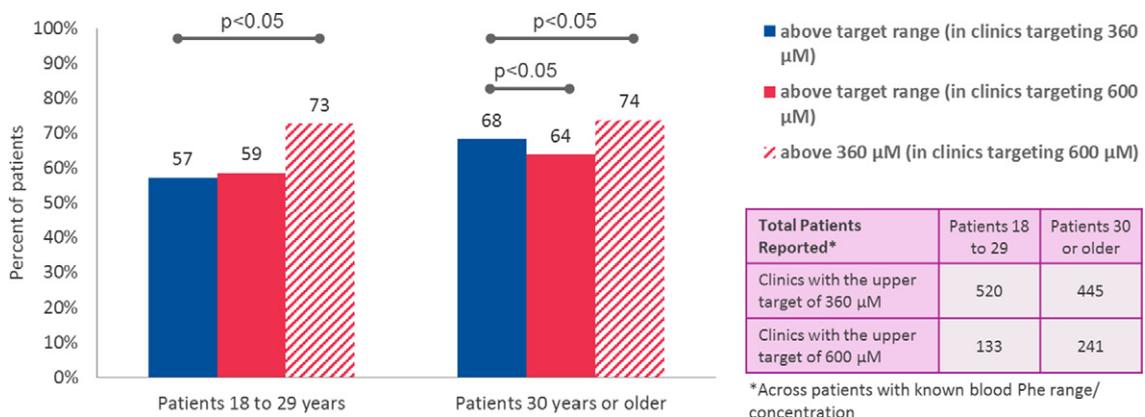


Fig. 2. Relationship between clinic target blood Phe concentration and patient adherence.

Table 4
Clinic target blood Phe testing frequency.

Patient group	<1 years	1–4 years	5–12 years	13–17 years	18–29 years	30+ years	Pregnant/planning on becoming pregnant
Weekly or more often	27 (69)	7 (18)	3 (8)	2 (5)	2 (5)	1 (3)	30 (88)
Twice a month	9 (23)	15 (38)	11 (28)	4 (10)	1 (3)	2 (6)	2 (6)
Monthly	2 (5)	15 (38)	23 (59)	25 (64)	24 (63)	22 (61)	2 (6)
Once in 2–4 months	1 (3)	2 (5)	2 (5)	8 (21)	9 (24)	8 (22)	–
Twice a year	–	–	–	–	2 (5)	1 (3)	–
Annually	–	–	–	–	–	2 (6)	–

Note: data shown as number of clinics (% of clinics that responded within a given patient age group). Percentages may not add up to 100 due to rounding.

3.5. PKU clinic staffing and patient adherence

Staffing resources (defined as number of specialists per 100 actively managed PKU patients) were correlated with the proportion of non-adherent patients (those not following clinic recommendations for blood Phe concentrations) in different age groups (Table 5). The 5–12 and 18–29 years age groups had more significant associations with increased staffing compared to other age groups. In terms of specialties, statistically significant correlations were observed more frequently between the total number of staff and number of social workers and psychologists. The negative association between number of social workers and non-adherence was observed in the 5–12 and 18–29 years age groups, and for psychologists the association was significant for three age groups (5–12, 13–17, 18–29 years). Finally, genetic counselors were the only specialty that had a statistically significant impact on the older patients (30+ years). In contrast, no patient group showed a significant association with the number of dietitians or nurse practitioners.

4. Discussion

This is the first national-level US survey documenting clinic recommendations on target blood Phe concentrations and the frequency of blood testing in PKU, as well as PKU patient adherence to these recommendations. Patient adherence to treatment recommendations is a very important consideration in the management of PKU, since elevated blood Phe concentrations have been associated with cognitive and neuropsychological impairment in children, adolescents, and adults [2,6,7,10]. These impairments may also be affecting the ability of patients to understand and follow their clinic's recommendations. Adherence to treatment may also be affected by adult patients' lack of perceived PKU burden, especially among the lost to follow-up patients. As the PKU treatment paradigm is continuously evolving, the clinical community needs to understand how these changes (e.g., introduction of the ACMG guidelines) are impacting PKU practices and patients' clinical outcomes across the country.

We found that clinic recommendations on blood Phe concentrations are fairly uniform, with almost all clinics in our sample setting the lower

threshold at 120 μM and a majority setting the higher threshold at 360 μM for all age groups. A minority of clinics relaxes the upper threshold to 600 μM for adults. These findings suggest a tightening of standards compared to that reported in the previous 1–2 decades, when the majority of US clinics targeted 600–900 μM for patients >12 years [5,12]. This tightening can be attributed to a combination of factors, including advances in our knowledge about the effects of elevated Phe concentrations as well as the issuance of ACMG and Genetic Metabolic Dietitians International (GMDI) guidelines [2,18] recommending universal 120–360 μM targets. Additional research is needed to investigate the differences in outcomes of patients maintaining blood Phe below 360 μM vs below 600 μM throughout their lifespan, particularly throughout adulthood.

Results of our study also indicated that approximately 40% of the US sample clinics set tighter guidelines (120–240 μM) for women that are pregnant or planning to become pregnant, consistent with stricter international guidelines [19] as opposed to ACMG recommendations [2]. Of note, there have been reports of compromised outcomes and behavioral issues in offspring of women with elevated Phe concentrations [20]. It may be of interest to investigate whether outcomes in clinics using a 360 μM threshold differ from clinics using a 240 μM threshold.

Consistent with previous findings, both in the US and in other countries [1,12,15], we found adherence to be strongly dependent on age. This illustrates that, despite the availability of a larger selection of medical foods, special low protein foods, and an approved medication, adherence to recommended Phe goals remains challenging, especially for older patients. Importantly, the drop-off in adherence starts in young children (5–12 years). Given the importance of improving adherence during the formative years of brain development, our findings suggest that intervention at an earlier age could be critical to improving blood Phe control over the longer term.

Compared to prior research, new adherence levels in children <12 years appear to be similar or slightly higher [1,12,15]. Since guidelines have not changed significantly over the past 20 years in this age group [1,5], comparable levels of adherence also indicate that blood Phe control has remained the same or improved slightly for these patients.

This survey found lower adherence in adolescents (13–17 years) compared to younger children, while prior authors observed higher

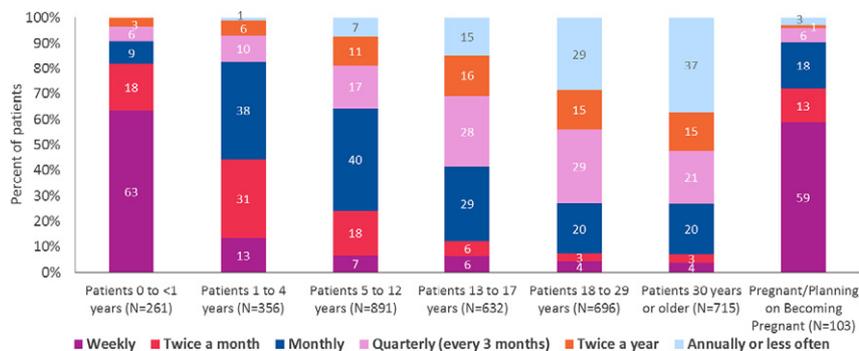


Fig. 3. Patient distribution according to actual blood Phe testing frequency. Note: figure excludes patients for whom actual Phe testing frequency was unknown: 4% of children and 7–9% of adults. Patient distribution according to actual blood Phe testing frequency.

Table 5
Correlations between clinic staffing and patient adherence.

		Patients non-adherent to clinic blood Phe recommendations					
		Age 0–4 (N=44)	Age 5–12 (N=44)	Age 13–17 (N=42)	Age 18–29 (N=42)	Age 30+ (N=39)	Pregnant/ planning to become pregnant (N=35)
Total number of HCPs per 100 patients	r	-0.196	-0.431	-0.283	-0.427	-0.204	0.059
	P-value	0.203	0.004	0.069	0.005	0.212	0.736
Number of full-time physicians per 100 patients	r	-0.125	-0.409	-0.157	-0.247	0.079	0.200
	P-value	0.418	0.006	0.322	0.115	0.633	0.249
Number of full-time dietitians per 100 patients	r	-0.098	-0.265	-0.185	-0.257	-0.137	0.106
	P-value	0.526	0.082	0.242	0.100	0.406	0.543
Number of full-time social workers per 100 patients	r	-0.067	-0.460	-0.204	-0.471	-0.162	-0.074
	P-value	0.664	0.002	0.195	0.002	0.324	0.672
Number of full-time psychologists / neuropsychologists per 100 patients	r	-0.163	-0.350	-0.370	-0.315	-0.153	-0.102
	P-value	0.292	0.020	0.016	0.042	0.354	0.560
Number of full-time nurse practitioners per 100 patients	r	-0.117	0.067	0.011	-0.106	0.144	-0.044
	P-value	0.448	0.666	0.946	0.503	0.381	0.800
Number of full-time genetic counselors per 100 patients	r	-0.189	-0.205	-0.253	-0.342	-0.479	-0.007
	P-value	0.219	0.183	0.106	0.027	0.002	0.967

Pearson correlations computed between the number of specialists per 100 actively managed PKU patients in a given clinic and the proportion of patients of a given age group within this clinic that have blood Phe above clinic-recommended target.

Relevant P-values are highlighted in light yellow, significant ($p < 0.05$) correlations are highlighted in orange and bolded. No correction for multiple comparisons was made.

r – Pearson correlation coefficient

adherence in adolescents [12,15]. This discrepancy may largely be due to the fact that almost all clinics in our survey recommend 360 μM as a threshold for both younger children and adolescents, while previous studies reported higher thresholds (600–900 μM) [12,15]. Importantly, actual blood Phe concentrations among adolescents are lower today than in the past [1,12].

Finally, we find adherence for adults followed in clinic to be very similar to more recent reports [12,15] and higher than that reported in the early 2000s [1]. However, since guidelines today are significantly stricter than before for older patients, similar adherence rates indicate lower actual blood Phe concentrations in adults today. This improvement is noteworthy, especially because many older patients have been used to a more lax Phe target of 600 μM .

Our adherence data was consistent with results from a recent patient survey conducted by the National PKU Alliance [21]. This self-selected, non-randomized survey of 625 PKU patients found that about 68% of patients younger than 18 years and about 23% of adults had Phe concentrations in the 120–360 μM range. In comparison, we

find 62% and 26% of the respective age groups fall within the same range. The similarities between patient- and physician-reported outcomes provide additional validation to the applicability of both approaches to the study of PKU treatment adherence.

Despite some reduction in adolescent and adult blood Phe concentrations, we still find that >60% of adolescents (age 13–17) and >70% of adult PKU patients in clinics are non-adherent to target Phe concentrations. This is concerning, as many of the patients that are not able to follow the recommendations may become lost to follow-up.

To summarize, while patient adherence to clinic recommendations and national guidelines on blood Phe concentrations is still low (especially in older adults), actual blood Phe concentrations have improved (especially in adolescents and adults). This apparent paradox is explained by the fact that recommendations themselves are stricter today as our understanding of the disease and the detrimental impact of high blood Phe has advanced. It is also supported by our observation that, if evaluated against the ACMG recommended guideline of 360 μM , clinics with a higher upper target have more non-adherent patients

(Fig. 2). This suggests that being adherent can be influenced by both the patient and physician expectations (i.e., target Phe) in addition to PKU-related limitations. In other words, tighter guidelines may contribute to better control of blood Phe concentrations.

Blood-testing frequency is an important measure of adherence for PKU patients, and specific recommendations are provided by ACMG guidelines [2]. We found that most clinics set their recommendations to be similar to the guidelines, though there's a tendency for less frequent monitoring in older patients. Adherence as judged by blood testing frequency is similar to adherence as judged by blood Phe concentrations. Our data indicates that there is a lack of correlation between the two measures of adherence, which was also documented previously [12]. It should be noted, however, that patients who test infrequently may “prepare” for their blood test and thus show a lower blood Phe concentration upon testing, but may suffer from higher blood Phe concentrations between tests.

We found that higher staffing intensity was associated with higher adherence to clinic blood Phe recommendations (i.e., lower blood Phe concentrations) in specific age groups. The magnitude of the effect was dependent on patient age group and type of healthcare professional. Greater adherence in young children (5–12 years) and young adults (18–29 years) was associated with increased clinic staff. These patients are undergoing a great change (e.g., starting school, leaving home) and as they become more independent they will encounter different outside influences; additional support offered by the clinic may serve as an extra buffer. In contrast, no significant associations were observed for the youngest children (0–4 years) and pregnant/planning to become pregnant women. This is not surprising, as they attract the most attention from the staff and tend to have very high adherence.

In terms of specialist types, the positive impact of psychologists/neuropsychologists was pronounced. Importantly, only seven clinics (16% of all) had any psychologists on staff. The availability of social workers was also associated with improved metabolic control. This suggests that increasing the availability of psychological and social support may help to improve patient adherence. Interestingly, no statistically significant impact of the dietitian staffing on patient adherence was observed, though there was an apparent trend and a larger sample size may have revealed a significant correlation. It is possible that since diet is a key aspect of the management of PKU, dietitians are generally present on staff in the majority of the clinics. It is also important to note that diet is just one component of PKU management: adherence is impacted by other modes of support, e.g., help with scheduling, travel to and from clinic, follow-up calls. Finally, a significant correlation in staffing intensity of genetic counselors with adherence was noted in adult patients. Presence of additional genetic counselors is likely reflective of clinics that are generally better staffed, potentially allowing for more time with adult patients and more availability for appointments.

Our survey has several limitations. Only a subset of US clinics participated in the survey, thus potentially introducing bias due to non-respondents and clinic distribution that may overrepresent some regions of the country. However, these caveats are mitigated by the observations that (1) participating clinics reportedly account for about half of all actively managed patients in the US; (2) no significant differences by region in key variables (e.g., adherence) have been found (data not shown). Another potential confounding factor is the possibility of differing definitions of PKU severity between clinics. This may lead to differences of blood Phe concentrations between subsets of clinics. However, additional analyses did not find this to be the case, suggesting that clinics may be using comparable definitions of severity (data not shown).

The study relied on medical professionals reporting of patient outcomes (e.g., adherence). While we encouraged the respondents to consult their internal databases and patient charts, additional verification steps were not part of the design. Respondents may have reported on their better performing patients since they likely visit the clinic more often; additionally, poorly controlled patients are more likely to be lost to follow-up. These concerns are partially mitigated by the close

agreement between our results and the patient survey data reported by Brown & Lichter-Konecki [21].

Except where noted, no statistical analyses were performed to compare results between groups; therefore, comparative results reported should be considered observational. We did not investigate treatment paradigms (e.g., whether patients were on a special diet or used sapropterin dihydrochloride). Finally, we did not investigate the potential impact of different state policies on medical/special low protein food coverage on the variations in adherence between clinics.

We find that recommendations of target blood Phe concentrations in the US are now stricter compared to prior years, and largely reflect recent guidelines by the American College of Medical Genetics and Genomics [2]. Adherence to recommended Phe concentrations remains suboptimal, especially in older patients. However, despite remaining above the guidelines, actual blood Phe concentrations in adolescents and adults are lower than that reported in the past [1,12]. Continued education and support for PKU patients by healthcare professionals, including adequate clinic staffing, are needed to improve adherence. In addition, future research is needed to understand how to improve adherence to reduce the number of patients lost to follow-up, as the findings of this and similar surveys do not address how to keep patients in clinic.

Conflict of interest

ERJ and JLCP are employees and shareholders of BioMarin Pharmaceutical Inc.

KP and MYS have received compensation from BioMarin Pharmaceutical Inc. for their consulting services.

JK, FR, ASV, and KSV have received compensation from BioMarin Pharmaceutical Inc. for serving as consultants for other departments of the company. ASV is also a principal investigator for several multicenter clinical trials sponsored by BioMarin Pharmaceutical Inc.

SC declares no conflict of interest.

Acknowledgements

The authors thank Mr. B. Spera and Ms. Q. Zhang for contributing to questionnaire development, data collection and analysis, Dr. J. Breck, Mr. N. Dunn, Mr. H. Sanchez and Ms. G. Chiu for helpful discussions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ymgme.2017.01.001>.

References

- [1] J.H. Walter, F.J. White, S.K. Hall, A. MacDonald, G. Rylance, A. Boneh, et al., How practical are recommendations for dietary control in phenylketonuria? *Lancet* 360 (9326) (2002) 55–57.
- [2] J. Vockley, H.C. Andersson, K.M. Antshel, N.E. Braverman, B.K. Burton, D.M. Frazier, et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, *Genet. Med.* 16 (2) (2014) 188–200.
- [3] N. Al Hafid, J. Christodoulou, Phenylketonuria: a review of current and future treatments, *Translat. Pediatr.* 4 (4) (2015) 304–317.
- [4] S.A. Berry, C. Brown, M. Grant, C.L. Greene, E. Jurecki, J. Koch, et al., Newborn screening 50 years later: access issues faced by adults with PKU, *Genet. Med.* 15 (8) (2013) 591–599.
- [5] R. Wappner, S. Cho, R.A. Kronmal, V. Schuett, M.R. Seashore, Management of phenylketonuria for optimal outcome: a review of guidelines for phenylketonuria management and a report of surveys of parents, patients, and clinic directors, *Pediatrics* 104 (6) (1999), e68.
- [6] F. Trefz, F. Maillot, K. Motzfeldt, M. Schwarz, Adult phenylketonuria outcome and management, *Mol. Genet. Metab.* 104 (Suppl) (2011) S26–S30.
- [7] R. Koch, B. Burton, G. Hoganson, R. Peterson, W. Rhead, B. Rouse, et al., Phenylketonuria in adulthood: a collaborative study, *J. Inherit. Metab. Dis.* 25 (5) (2002) 333–346.
- [8] National Institutes of Health Consensus Development P, National Institutes of Health Consensus Development Conference Statement: phenylketonuria: screening and management, October 16–18, 2000, *Pediatrics* 108 (4) (2001) 972–982.

- [9] A. MacDonald, M. van Rijn, F. Feillet, A.M. Lund, L. Bernstein, A.M. Bosch, et al., Adherence issues in inherited metabolic disorders treated by low natural protein diets, *Ann. Nutr. Metab.* 61 (4) (2012) 289–295.
- [10] Agency for Healthcare Research and Quality (AHRQ), Adjuvant treatment for phenylketonuria (PKU), *Comp. Eff. Rev.* 56 (2012).
- [11] R.H. Singh, F. Rohr, D. Frazier, A. Cunningham, S. Mofidi, B. Ogata, et al., Recommendations for the nutrition management of phenylalanine hydroxylase deficiency, *Genet. Med.* 16 (2) (2014) 121–131.
- [12] C. Freehauf, J.L. Van Hove, D. Gao, L. Bernstein, J.A. Thomas, Impact of geographic access to care on compliance and metabolic control in phenylketonuria, *Mol. Genet. Metab.* 108 (1) (2013) 13–17.
- [13] F.K. Trefz, F.J. van Spronsen, A. MacDonald, F. Feillet, A.C. Muntau, A. Belanger-Quintana, et al., Management of adult patients with phenylketonuria: survey results from 24 countries, *Eur. J. Pediatr.* 174 (1) (2015) 119–127.
- [14] F.J. van Spronsen, K.K. Ahring, M. Gizewska, PKU-what is daily practice in various centres in Europe? Data from a questionnaire by the scientific advisory committee of the European Society of Phenylketonuria and Allied Disorders, *J. Inherit. Metab. Dis.* 32 (1) (2009) 58–64.
- [15] K. Ahring, A. Belanger-Quintana, K. Dokoupil, H. Gokmen-Ozel, A.M. Lammardo, A. MacDonald, et al., Blood phenylalanine control in phenylketonuria: a survey of 10 European centres, *Eur. J. Clin. Nutr.* 65 (2) (2011) 275–278.
- [16] M. Gizewska, A. MacDonald, A. Belanger-Quintana, A. Burlina, M. Cleary, T. Coskun, et al., Diagnostic and management practices for phenylketonuria in 19 countries of the South and Eastern European Region: survey results, *Eur. J. Pediatr.* 175 (2) (2016) 261–272.
- [17] N. Blau, A. Belanger-Quintana, M. Demirkol, F. Feillet, M. Giovannini, A. MacDonald, et al., Management of phenylketonuria in Europe: survey results from 19 countries, *Mol. Genet. Metab.* 99 (2) (2010) 109–115.
- [18] GMDI. Genetic Metabolic Dietitians International PKU guidelines, [July 27th, 2016]. Available from: <https://southeastgenetics.org/ngp/guidelines.php/87/PKU%20Nutrition%20Guidelines/Version%201.112015>.
- [19] P.J. Lee, D. Ridout, J.H. Walter, F. Cockburn, Maternal phenylketonuria: report from the United Kingdom Registry 1978–97, *Arch. Dis. Child.* 90 (2) (2005) 143–146.
- [20] F. Maillot, M. Lilburn, J. Baudin, D.W. Morley, P.J. Lee, Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine, *Am. J. Clin. Nutr.* 88 (3) (2008) 700–705.
- [21] C.S. Brown, U. Lichter-Konecki, Phenylketonuria (PKU): a problem solved? *Mol. Genet. Metab. Rep.* 6 (2016) 8–12.