

# Management of adult patients with phenylketonuria: survey results from 24 countries

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**Abstract** Phenylketonuria (PKU) is no longer considered merely a pediatric concern; current guidelines recommend life-long treatment. However, information on the adult PKU patient population is scarce. A survey was initiated on behalf of the European PKU Group (EPG) that focused specifically on early-treated adult patients diagnosed by neonatal screening. The online survey was sent via email to 204 healthcare professionals (HCPs) in 33 countries. Eighty-one HCPs from

24 countries responded. The main findings were that the majority of adult patients with PKU in active follow-up are under 30 years of age and are managed in centers that also treat children. Seventy-eight percent of adult PKU patients in follow-up receive treatment, mainly by diet (71 %), with BH4 treatment rarely used in adulthood. Only 26 % of responding HCPs perform routine neurocognitive testing in all their adult patients. There was little consensus regarding target blood

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phenylalanine (Phe) concentrations, although the majority of respondents reported that their patients achieved blood Phe concentrations below 1200  $\mu\text{mol/l}$ .

**Conclusion:** This survey highlights the need for blood Phe concentration target recommendations and consensus guidelines, more research into adult PKU patient management, and the need to identify those patients lost to follow-up to ensure PKU is managed for life.

**Keywords** Phenylketonuria · Phenylalanine · Survey · Adults · Diet

### Abbreviations

HPA Hyperphenylalaninemia  
 IMD Inherited metabolic disease  
 Phe Phenylalanine  
 PKU Phenylketonuria

### Introduction

Phenylketonuria (PKU) is no longer considered merely a pediatric concern; current guidelines recommend life-long treatment [16, 14, 23]. Recently, strict dietary control with target levels between 120 and 360  $\mu\text{mol/l}$  also for adult PKU was suggested [24]. As PKU patients continue to make the transition from pediatric to adult care, the adult PKU patient population consequently expands. Adult PKU patients have complex needs that include neuropsychological and psychosocial problems, risk of maternal PKU syndrome in an offspring, adherence issues and deteriorating blood Phe control [8, 13, 26, 11, 23, 1, 9, 10, 22].

Information on treatment practices and a management consensus for the adult patient group is limited and has not been systematically investigated. To establish optimal guidelines for adult PKU management, there is much to be gained from increased and documented knowledge of the current status of adult PKU patient-treating centers, the number of patients making the transition to adult care, patient distribution, treatment practices, adherence, neurocognitive tests, and motivation. In response to this need, an adult PKU management survey was initiated and sent to healthcare professionals (HCPs).

### Materials and methods

#### Survey

The survey was developed by the authors of this manuscript in 2011 and was performed in January and February 2012. It consisted of a total of 24 closed (answer choices provided) and open (no answer choices provided) questions (Table 1). Questions concerned characteristics of respondent's centers that

treat adult patients with PKU/hyperphenylalaninemia (HPA). Characteristics of respondent's adult patients with PKU/HPA such as demographics, blood phenylalanine (Phe) concentrations, follow-up, treatment, adherence, and neurocognitive testing were also included. Information was requested of early-treated patients diagnosed by neonatal screening only.

An initial email was sent on behalf of the European PKU Group (EPG) to describe the purpose of the survey project, to give the opportunity to recommend alternative individuals, or to decline further participation. A second email containing a link to the online survey (using the tool [surveymonkey.com](http://surveymonkey.com)) was sent and a reminder 2 weeks later.

#### Participants

Emails were sent to 204 HCPs who treat adults with PKU in 33 countries, Arab Emirates, Argentina, Australia, Austria, Belgium, Brazil, Chile, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Japan, Lebanon, Netherlands, Norway, Poland, Portugal, Saudi Arabia, Singapore, Spain, Sweden, Switzerland, Taiwan, Turkey, UK, and Uruguay. The email addresses were provided by the EPG.

#### Data analysis

The responses were compiled in a spreadsheet, and descriptive analyses were performed in the form of additions and means. Center names and exact addresses were not requested in the survey. The majority of responses ( $n=65$ ) came from different cities; therefore, there was no risk of over-reporting of centers or patients in these responses.

Many respondents had not answered the survey in its entirety; thus, the number of responses per individual question was stated ( $n$ ). Responses from 2 HCPs ( $n=2$ ) from the same city had responded to different questions within the survey with no overlap, therefore were treated as separate responses.

It was clear from the responses given in the general information and patient distribution sections that HCPs from three cities ( $n=8$ ) were reporting different centers. These were treated as separate responses as we believe there is no over-reporting in these cases.

HCPs from two cities ( $n=6$ ) had multiple responses that were very similar (per city), which created the risk that the responding HCPs in these cities may have reported data from the same center. When the respondents had responded to the same question (as previously mentioned, it was often the case that respondents did not complete the survey in its entirety), one response was retained and repeated responses were removed.

#### Definitions

After reference to the literature [5] and discussion within the author group, the following Phe-level definitions were agreed

**Table 1** Survey questions

<p><b>General Information</b></p> <p>1. Which one of the following statements applies to your center (one answer only):  <input type="checkbox"/> We treat adults and children (all age categories) <input type="checkbox"/> We only treat adults (<math>\geq 18</math> years of age)</p> <p>2. Where is your center located? Town/City: _____ Country: _____</p> <p>3. In your center, how many medical doctors treat adult patients with PKU - please express your answer in a) total number of doctors and b) whole time equivalent positions (e.g. 2.5) a) Total number of doctors: _____ b) Whole time equivalent doctors: _____</p> <p>4. In your center, how many dieticians treat adult patients with PKU - please express your answer in a) total number of doctors and b) whole time equivalent positions (e.g. 2.5) a) Total number of dieticians: _____ b) Whole time equivalent dieticians: _____</p> <p>5. Are there any other professionals (other than medical doctors and dieticians) treating adult patients with PKU?  <input type="checkbox"/> None <input type="checkbox"/> Nurse <input type="checkbox"/> Psychologist <input type="checkbox"/> Neuropsychologist <input type="checkbox"/> Social worker <input type="checkbox"/> Other (please specify): _____</p>
<p><b>PKU Patient Distribution</b></p> <p>6. In your center, what are the approximate numbers of PKU/HPA patients?  Total patient number (all ages): _____ Adult female patients: _____ Adult male patients: _____</p> <p>7. Who usually refers your adult patients to your center (several answers are possible)?  <input type="checkbox"/> Patients were already treated at your center when they were teenagers/children <input type="checkbox"/> Another pediatrician <input type="checkbox"/> Adult physician e.g. obstetrician/ gynecologist/ endocrinologist/ neurologist/general practitioner <input type="checkbox"/> Dietitian <input type="checkbox"/> Self-referral <input type="checkbox"/> Other (please specify): _____</p> <p>8. What is the percentage of adult patients with classical PKU (untreated blood Phe level <math>&gt;1200</math> <math>\mu\text{mol/l}</math>) (%): _____ mild PKU (untreated blood Phe level between 600 and 1200 <math>\mu\text{mol/l}</math>) (%): _____ HPA (untreated blood Phe level <math>&lt;600</math> <math>\mu\text{mol/l}</math>) (%): _____</p> <p>9. What percentage of your adult patients has mean blood Phe concentrations of  <math>&lt;240</math> <math>\mu\text{mol/l}</math> (%): _____ 240-600 <math>\mu\text{mol/l}</math> (%): _____ 601-900 <math>\mu\text{mol/l}</math> (%): _____  901-1200 <math>\mu\text{mol/l}</math> (%): _____ <math>&gt;1200</math> <math>\mu\text{mol/l}</math> (%): _____</p> <p>10. What is the target range of blood Phe levels for your adult (non-pregnant) patients? (<math>\mu\text{mol/l}</math>): _____</p> <p>11. What is the age distribution of your adult patients (%)? 18-29 years: _____ 30-39 years: _____ 40-49 years: _____ <math>\geq 50</math> years: _____</p> <p>12. What is the gender distribution of your adult patient sample (%)?  Females <math>&gt;12</math> and <math>&lt;45</math> years (child bearing age): _____ Females <math>\geq 45</math> years: _____ Males: _____</p> <p>13. What proportion of your adult patients have you lost contact with (definition of lost for follow-up: <math>\geq 3</math> times no show for outpatient evaluation and/or no blood samples sent for Phe analysis)? Adult women (%): _____ Adult men (%): _____</p> <p>14. On average, how frequently do you have contact with your adult patients (please count a blood Phe measurement sent in by the patient as one contact)? <input type="checkbox"/> More than 10x/year <input type="checkbox"/> 6-10x/year <input type="checkbox"/> 2-5x/year <input type="checkbox"/> 1x/year <input type="checkbox"/> Less than 1x/year</p>
<p><b>Treatment</b></p> <p>15. What % of your adult patients are treated by (please provide proportions)?  No treatment: _____ Phe-restricted diet: _____ BH4 alone: _____ Phe-restricted diet in combination with BH4: _____ Other: _____</p> <p>16. Overall, how would you rank the adherence to treatment of your adult FEMALE patients who are treated with a Phe-restricted diet alone?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with a Phe restricted diet alone</p> <p>17. Overall, how would you rank the adherence to treatment of your adult MALE patients who are treated with a Phe-restricted diet alone?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with a Phe-restricted diet alone</p> <p>18. Overall, how would you rank the adherence to treatment of your adult FEMALE patients who are treated with BH4 alone?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with BH4 alone</p> <p>19. Overall, how would you rank the adherence to treatment of your adult MALE patients who are treated with BH4 alone?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with BH4 alone</p> <p>20. Overall, how would you rank the adherence to treatment of your adult FEMALE patients who are treated with a Phe-restricted diet in combination with BH4?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with a combination of Phe restricted diet + BH4</p> <p>21. Overall, how would you rank the adherence to treatment of your adult MALE patients who are treated with a Phe-restricted diet in combination with BH4?  <input type="checkbox"/> Very good <input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Very poor <input type="checkbox"/> Not applicable, no patients are treated with a combination of Phe restricted diet + BH4</p>
<p><b>Neurocognitive Tests</b></p> <p>22. Do you perform neurocognitive tests in your adult patients?  <input type="checkbox"/> Yes, for all patients <input type="checkbox"/> Yes, for some patients <input type="checkbox"/> No</p>
<p><b>Motivation</b></p> <p>23. What are the main reasons motivating your MALE adult patients to pursue their treatment? (several answers are possible)  <input type="checkbox"/> Improved quality of life <input type="checkbox"/> Improved neurocognitive function <input type="checkbox"/> Improved nutritional status <input type="checkbox"/> Maintenance of a good metabolic control <input type="checkbox"/> Improved behavior <input type="checkbox"/> They do because they have been told to do it <input type="checkbox"/> Other (please specify) _____</p> <p>24. What are the main reasons motivating your FEMALE adult patients to pursue their treatment? (several answers are possible)  <input type="checkbox"/> Improved quality of life <input type="checkbox"/> Improved neurocognitive function <input type="checkbox"/> Improved nutritional status <input type="checkbox"/> Maintenance of a good metabolic control <input type="checkbox"/> Improved behavior <input type="checkbox"/> They do because they have been told to do it <input type="checkbox"/> Other (please specify) _____</p>

PKU phenylketonuria, HPA hyperphenylalaninemia, Phe phenylalanine

upon: classical PKU was defined as untreated blood Phe level  $>1200$   $\mu\text{mol/l}$ , mild PKU as untreated blood Phe level

between 600 and 1200  $\mu\text{mol/l}$ , and HPA as untreated blood Phe level  $<600$   $\mu\text{mol/l}$ .

Definition of lost to follow-up: three or more failures to attend an outpatient appointment (written as “no show for outpatient evaluation” in the survey) and/or no blood samples sent for Phe analysis. A blood Phe measurement sent by the patient was counted as one contact with a patient.

## Results

Eighty-one HCPs from 24 countries sent survey responses: Argentina (1), Australia (2), Austria (4), Belgium (2), Brazil

(1), Canada (1), Chile (1), Czech Republic (4), Denmark (1), France (7), Germany (10), Hungary (1), Ireland (1), Italy (8), Netherlands (7), Norway (1), Poland (1), Portugal (3), Spain (7), Sweden (2), Switzerland (2), Taiwan (1), Turkey (6), and UK (7).

The majority of respondents reported that their centers treated both adults and children, with the minority treating adults only (Table 2). The adult-only treating centers were in Australia, France, the Netherlands, and the UK. Twenty-six percent stated that only medical doctors and dietitians treated adult patients in their center. Additional professionals involved in some centers were psychologists, social workers,

**Table 2** Characteristics of respondent’s centers that treat adult PKU patients

Which one of the following statements applies to your center? (one answer only)							<i>n</i> (%)
Treatment of adults and children (all age categories)							65 (88)
Treatment of adults only ( $\geq 18$ years of age)							9 (12)
In your center, how many medical doctors and dietitians treat adult patients with PKU?							
a). Total number							
	0	1	2	3	4	>4	
Medical doctors ( <i>n</i> , (%))	0 (0)	22 (35)	19 (31)	10 (16)	6 (10)	5 (8)	
Dietitians ( <i>n</i> , (%))	1 (2)	22 (35)	29 (47)	8 (13)	1 (2)	1 (2)	
b). Whole time equivalent							
	Mean (standard deviation)						
Medical doctors	1.4 (1.2)						
Dietitians	0.985 (0.8)						
Are there any other professionals (other than medical doctors and dietitians) treating adult patients with PKU? (multiple answers possible, 74 respondents answered this question)							
	<i>n</i> (%)						
Psychologist	37 (47)						
Social worker	32 (41)						
Nurse	28 (36)						
Neuropsychologist	15 (19)						
Other (responses included: geneticist, counselor, neurologist, pharmacist, dietetic assistant, molecular biologist)	14 (18)						
No other experts	20 (26)						
Who usually refers your adult patients to your center? (multiple answers possible, 57 respondents answered this question)							
	<i>n</i> (%)						
Patients already treated at center as teenagers/children	52 (91)						
Self-referral	20 (35)						
Adult physician, e.g., obstetrician/gynecologist/endocrinologist/neurologist/general practitioner	19 (31)						
Pediatrician (from another center)	16 (28)						
Other (responses included the following: social worker, other metabolic centers, parents’ association)	7 (12)						
Dietitian	4 (7)						
In your center, what are the approximate numbers of PKU/HPA patients?							
	Mean (min, max)						
Total patient number (all ages) ( <i>n</i> =55)	195 (11, 2200)						
Number of adult female patients ( <i>n</i> =52)	40 (2, 254)						
Number of adult male patients ( <i>n</i> =52)	31 (0, 210)						

PKU phenylketonuria, HPA hyperphenylalaninemia, Phe phenylalanine

The number of responses per individual question is stated (*n*) as some respondents did not answer the survey in its entirety

nurses, and neuropsychologists. Geneticists, counselors, neurologists, pharmacists, dietetic assistants, and molecular biologists were included in some PKU teams, as described by HCP responses under the open “other” section of the question.

Ninety-one percent of respondents cared for adult patients that had previously been treated at the same center as a teenager or child (Table 2). They also accepted self-referrals from patients, referrals from adult physicians, pediatricians, or dietitians from other centers, social workers, and patients’ associations.

The mean number of adult female and adult male patients with PKU/HPA in a respondent’s center was 40 and 31, respectively, with a mean total patient number (all ages, including children) of 195. The number of patients seen by clinics varied widely (Table 2).

Respondents indicated that 60 % of their adult patients were female, 3 % of which were above childbearing age, which was defined in the survey as  $\geq 45$  years old (Table 3). The majority of adult patients were aged between 18 and 29 years. Most reported adult patients had classical PKU (66 %), 22 % mild PKU, and 12 % HPA.

It was reported that 59 % of patients had a mean blood Phe concentration below or equal to 900  $\mu\text{mol/l}$  and 82 % below or equal to 1200  $\mu\text{mol/l}$  (Fig. 1). There were only 13 responses to the survey question “what is the target range for blood Phe concentrations for your (non-pregnant) adult patients?”. Responses could be divided into four main categories:  $\leq 600$   $\mu\text{mol/l}$  ( $n=5$ ),  $\leq 700$   $\mu\text{mol/l}$  ( $n=2$ ),  $\leq 900$   $\mu\text{mol/l}$  ( $n=2$ ), and  $\leq 1200$   $\mu\text{mol/l}$  ( $n=4$ ).

Over 50 % of respondents had contact with their adult PKU patients 2–5 times/year and 35 %  $\geq 6$  times/year (Table 3). Contact was lost with 15 % of females and 19 % of males.

Seventy-one percent of respondent’s patients were treated with a Phe-restricted diet only; 22 % received no treatment; 4 % received a Phe-restricted diet with BH4/sapropterin (Table 3). Among patients treated with a Phe-restricted diet only, adherence was considered better in adult female than male patients (Fig. 2). No conclusion could be drawn from HCP’s responses regarding adult patient adherence to treatment with BH4 alone or Phe-restricted diet in combination with BH4 because most HCPs responded that these questions were not applicable as none of their adult PKU patients followed these treatments. Multiple reasons were thought to motivate adult patients to pursue their treatment, with improved neurocognitive function considered the most important in both female and male patients (Fig. 3). Twenty-six percent of respondents performed neurocognitive tests in all of their adult patients (Table 3).

## Discussion

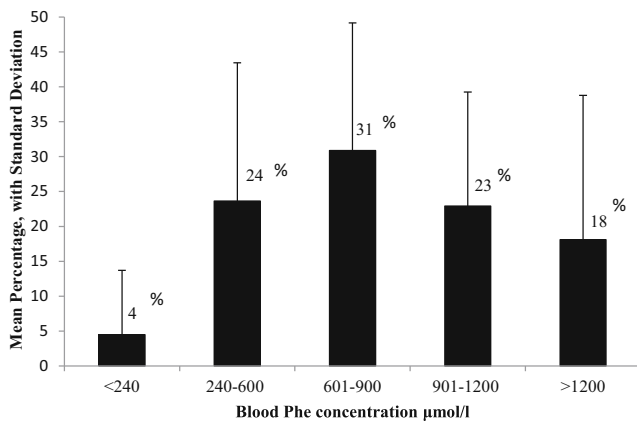
This survey found that most adult patients with PKU were under the age of 30, treated and continued to be followed, with

**Table 3** Characteristics of adult patients: demographics, follow-up, treatment, and neurocognitive testing

What is the gender distribution of your adult patient sample? (%)	Mean ( $n=39$ )
Females $>12$ and $<45$ years (child bearing age)	57 %
Females $\geq 45$ years	3 %
Males	40 %
What is the age distribution of your adult patients? (%)	Mean ( $n=44$ )
18–29 years	69 %
30–39 years	23 %
40–49 years	7 %
$\geq 50$ years	1 %
What is the percentage of adult patients with?	Mean ( $n=47$ )
Classical PKU (untreated blood Phe level $>1200$ $\mu\text{mol/l}$ )	66 %
Mild PKU (untreated blood Phe level between 600 and 1200 $\mu\text{mol/l}$ )	22 %
HPA (untreated blood Phe level $<600$ $\mu\text{mol/l}$ )	12 %
What proportion of your adult patients have you lost contact with?	Mean
Adult female patients ( $n=47$ )	15 %
Adult male patients ( $n=45$ )	19 %
On average how frequently do you have contact with your adult patients?	$n$ (%)
More than 10 $\times$ /year	6 (11)
6–10 $\times$ /year	13 (24)
2–5 $\times$ /year	28 (52)
1 $\times$ /year	7 (12)
Less than 1 $\times$ /year	0 (0)
What % of your adult patients are treated with?	Mean ( $n=40$ )
No treatment	22 %
Phe-restricted diet	71 %
Phe-restricted diet in combination with BH4	4 %
BH4 alone	2 %
Other	1 %
Do you perform neurocognitive tests on your adult patients?	$n$ (%)
Yes, for all patients	14 (26)
Yes, for some patients	18 (34)
No	21 (40)

PKU phenylketonuria, HPA hyperphenylalaninemia, Phe phenylalanine  
The number of responses per individual question is stated ( $n$ ) as some respondents did not answer the survey in its entirety

half of HCPs having contact with their adult patients 2–5 times a year. Life-long treatment recommendations appear to be followed by most clinics as patients now reach adulthood; however, maximum target blood Phe concentrations were



**Fig. 1** Adult patient mean blood Phe concentrations. Survey question: what percentage of your adult patients has mean blood Phe concentrations of a) <240  $\mu\text{mol/l}$  (%), b) 240–600  $\mu\text{mol/l}$  (%), c) 601–900  $\mu\text{mol/l}$  (%), d) 901–1200  $\mu\text{mol/l}$  (%), e) >1200  $\mu\text{mol/l}$  (%) ( $n=43$ )

inadequately reported and wide ranging. In contrast, a European study of PKU treatment of all age groups found that standard treatment protocols or follow-up procedures for PKU patients were used more frequently in infants and children than in adults [4]. The uncertainty and variability of HCP's responses in this survey may be a reflection of the current inconsistent treatment target recommendations for the adult patient population. Future guidelines should address this and the follow-up care of all adult patients, both willing and unwilling to be treated [23].

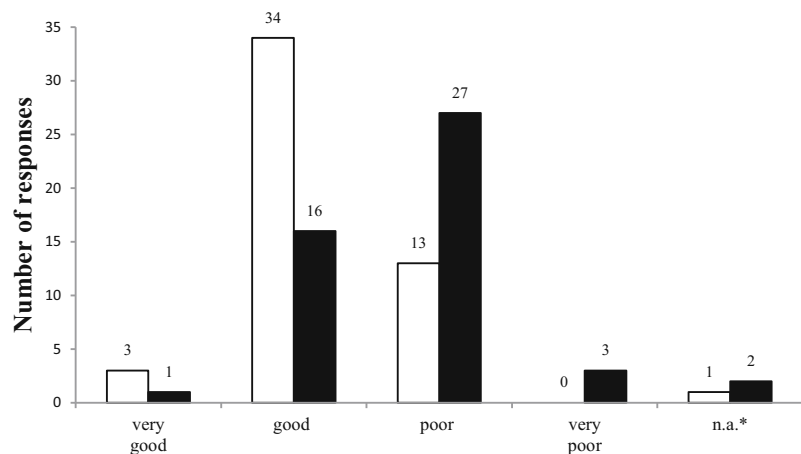
The survey raises many issues worthy of further exploration. For example, improved neurocognitive function is considered the most important motivating factor in both female and male adult patients to adhere to treatment. It would be of interest to know if the patients' responses would correspond to that of HCPs. It is known that high plasma Phe concentrations have a direct negative effect on both sustained attention and on

mood in adult patients with PKU [21]. An area of important research would be a comparison of the different treatment options vs. no treatment on the neurocognitive capabilities of the adult PKU population. Also, uniform assessment methods for neurocognitive testing are recommended for adults with PKU. The following instruments are suggested ( $\geq 18$  years): BRIEF-A, Behavior Rating Inventory of Executive Function Adult Version; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory (Second Edition) [25].

The majority of responding HCPs indicated that most of their patients do not receive BH4 treatment. It was not explored why this treatment was rarely used, but adult PKU patient treatment options should be investigated further. BH4 treatment may not be available in certain countries or HCPs, or adult patients themselves may have reasons for choosing a Phe-restricted diet-only treatment.

Although this survey found that while the majority of adult patients were in follow-up care, nearly a fifth of adult males and over a tenth of adult females were lost to follow-up. A specific question regarding the percentage of neonates identified with PKU who are followed consistently as adults would have been beneficial. Pregnancy and thus maternal PKU issues is considered a motivation for female patients to maintain treatment and is a possible explanation for higher female adult patient retention. Failure to support female PKU patients both prior to and during a pregnancy is likely to result in significant and permanent disabilities in their offspring [17]. Although the loss of follow-up of adult males may not be critical, the impact of neuropsychological problems and nutritional deficiencies in untreated adult patients is still to be determined. The gender discrepancy and overall loss of patients are important issues in adult PKU management that need to be addressed; however, comparisons of gender and health inequality should always be considered within the context of general population health [2].

**Fig. 2** Adherence of adult patients treated with a Phe-restricted diet alone. Survey question: overall, how would you rank the adherence to treatment of your adult patients who are treated with a Phe-restricted diet alone? (female  $n=51$ , male  $n=49$ ). \*n.a.: not applicable, no patients are treated with this regimen

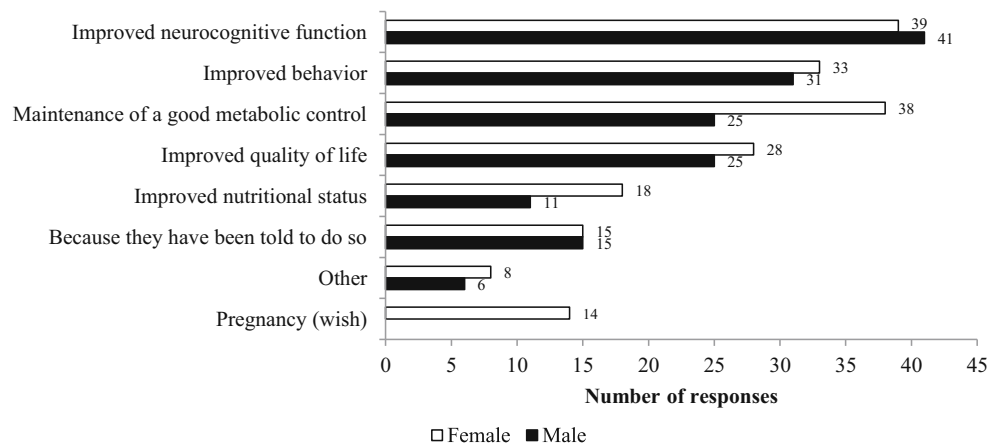


Ranking by HCP of adherence of adult patients treated with a Phe-restricted diet alone

□ Female ■ Male



**Fig. 3** Treatment motivation. Survey question: what are the main reasons motivating your adult male and female patients to pursue their treatment? (multiple answers possible, female question,  $n=50$ ; male question,  $n=49$ )



The high percentage of respondents managing adult patients in pediatric centers is remarkable considering life-long treatment has been recommended since 2001 [16]. It is possible that adult-oriented care may be under-developed, as adult-inherited metabolic disorders is a relatively new specialty [19]. Smaller centers may not have access to a rare metabolic disorders adult care unit to refer their patients to. Patient-centered adult care may be limited to academic clinics and universities, as PKU is a disorder that requires specialist knowledge of both dietary and medical treatment. There are few adult specialists (medical doctors/dietitians) trained in inherited metabolic diseases (IMD) [4]. It is important, therefore, that any optimal care recommendations for adults should also consider PKU clinics that may be unable to establish adult treatment centers.

The survey indicates that the majority of adult patients (under 30 years of age) in follow-up care are those that have been treated since the life-long treatment recommendation. This may have led to some bias in the survey. It also highlights the possibility that there could be a “lost” generation of patients over 30 years of age that could experience improved quality of life with return to treatment [3, 6]. Further investigation into the reasons for loss of patient follow-up is essential. It is possible that PKU registries may facilitate maintenance of follow-up in adult patients in the future.

The successful transition of patients from pediatric to adult care is also an important consideration [20]. It is known that there can be multiple barriers, such as anxiety and a lack of information for a smooth and timely transfer [18]. Good practices for transition of PKU patients have recently been reviewed and include a written transition policy, opportunities for the young person to meet the adult team, and early transition initiation (~12 years of age) [10]. Suggestions to improve current transition processes also include a joint interdisciplinary consultation with both adult and pediatric physicians present [15]. However, although these approaches may be ideal, organizational and financial restraints may impede the implementation of such practices.

It is unknown whether adult patients are at a disadvantage by continuing their care in a pediatric environment, if their complex neuropsychological and psychosocial needs are being met, and whether, as the adult population continues to age and expand, this model is sustainable. Identifying what adult PKU patients require in terms of quality care needs careful evaluation. Pediatric vs. adult physicians’ views on treatment in adult PKU should be taken into account, as should the structure of established adult-only PKU clinics. Application of the multidimensional World Health Organization Quality of Life questionnaire (WHOQOL-100) may prove to be a useful tool to assess patient management and has recently been used in adult patients with other inherited metabolic diseases (IMDs) [7]. The need for a multi-professional team that not only focuses on physical and/or biochemical aspects of the disease, but also the psycho-social dimensions of life, has been identified in other adult patients with IMD [12].

There are limitations to this survey. Although the questionnaire response rate was satisfactory, the survey was only sent to email addresses of those provided by the EPG group, and therefore does not include information on patients from HCPs who did not receive the survey or of those that did not respond. This may have led to some survey bias. Also, as the survey was not sent to HCPs in some countries (in particular the USA) and because not all countries that were contacted responded the survey does not reflect the practice of these countries as a consequence.

With hindsight, it is clear that some questions could have been more specific in their formulation in this survey, and the survey would have benefitted from a beta-test by non-authors before distribution. As a consequence, some questions may have been misinterpreted by responding HCPs. For example, questions regarding treatment did not distinguish between PKU and HPA patients, and a time range for lost to follow-up and mean blood Phe concentrations (Fig. 1) is lacking. Also, one patient contact was defined as a blood Phe measurement sent by the patient. There is clearly quite a difference between a blood measurement and an actual outpatient appointment in

assessing metabolic control and general patient management. A Phe-restricted diet was also undefined. The stated Phe-level definitions of classical PKU, mild PKU, and HPA were agreed upon after discussion within the author group; however, such definitions are a contentious issue and many PKU-related terms are still awaiting a consensus definition. Restrictions on time and access to hospital databases inhibited some respondent's ability to answer the survey in its entirety, a possible problem for surveys in general in terms of response rate.

This survey evaluated adult PKU patient characteristics and the current clinical practices employed in treating them. The findings have implications not only for adult patients but for all patients and treating HCPs in the pediatric environment, where most adult individuals with PKU are managed. Above all, the survey highlights the need for treatment target recommendations and guidelines, more research into adult PKU patient management, and the need to identify those patients lost to follow-up in order to ensure management for life.

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**Authors' contributions** All authors contributed to the conception, design, analysis and interpretation of the content, manuscript preparation, and revision and have read and approved the final version of the manuscript.

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