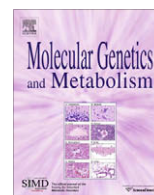




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Management of phenylketonuria in Europe: Survey results from 19 countries

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ABSTRACT

To gain better insight in the most current diagnosis and treatment practices for phenylketonuria (PKU) from a broad group of experts, a European PKU survey was performed. The questionnaire, consisting of 33 questions, was sent to 243 PKU professionals in 165 PKU centers in 23 European countries. The responses were compiled and descriptive analyses were performed. One hundred and one questionnaires were returned by 93/165 centers (56%) from 19/23 European countries (83%). The majority of respondents (77%) managed patients of all age groups and more than 90% of PKU teams included physicians or dietitians/nutritionists. The greatest variability existed especially in the definition of PKU phenotypes, therapeutic blood phenylalanine (Phe) target concentrations, and follow-up practices for PKU patients. The tetrahydrobiopterin (BH4; sapropterin) loading test was performed by 54% of respondents, of which 61% applied a single dose test (20 mg/kg over 24 h). BH4 was reported as a treatment option by 34%. This survey documents differences in diagnostic and treatment practices for PKU patients in European centers. In particular, recommendations for the treatment decision varied greatly between different European countries. There is an urgent need to pool long-term data in PKU registries in order to generate an evidence-based international guideline.

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Introduction

Phenylketonuria (PKU) is an inherited disorder in phenylalanine (Phe) metabolism with an overall incidence in Europe and the USA of 1:10,000–20,000 live births [1]. The implementation of newborn screening to detect PKU has facilitated the early use of dietary treatment, resulting in near normalization of outcomes of individuals with PKU [2]. However, dietary treatment is very restrictive, may be associated with a risk of nutritional deficiencies, compliance is often poor among adolescent and adult patients with PKU [3], and two thirds of pregnant women in the United States do not follow the diet before becoming pregnant [4]. Thus, long-term patient outcome is not always optimal, and published guidelines

for PKU management show considerable variation between PKU centers [5–10]. Recent developments including tetrahydrobiopterin (BH4; sapropterin) treatment [11], large neutral amino acid (LNAA) supplementation [12], phenylalanine ammonia lyase (PAL) enzyme replacement [13], and gene therapy [14] may help to improve the outcome of PKU in the future.

National guidelines for the management of PKU published by several European countries agree that treatment should start as early as possible after birth, and that monitoring of Phe concentrations and clinical parameters should continue throughout life [5–7]. However, these guidelines vary not only between countries worldwide, but also within countries, particularly with respect to recommended plasma Phe concentrations during dietary treatment, the duration of treatment, and the recommended frequency of monitoring blood Phe levels [8,9]. In an effort to gain a greater picture of the most current diagnostic and treatment practices for PKU from a broad group of experts in treatment centers across Europe, a European PKU survey was initiated.

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¹ Appendix.

Methods

Participants

Questionnaires were sent to 243 professionals working in the field of PKU in 165 PKU centers in 23 European countries (Austria, Belgium, Bosnia and Herzegovina, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Serbia, Spain, Sweden, Switzerland, Turkey, and UK). The survey was performed between May and October, 2008.

The questionnaire consisted of a total of 33 closed (answer choices provided) and open (no answer choices provided) questions concerning (a) general information (e.g. number of patients, definition of hyperphenylalaninemia [HPA]/PKU); (b) screening practices (e.g. BH4 loading test); treatment practices and follow-up (e.g. target blood Phe levels); and (c) existing guidelines and protocols.

Data analysis

The responses were compiled in a spreadsheet, open questions were grouped or categorized according to responses received, and tabulated. Due to the nature of the study, only descriptive analyses were performed in the form of sums (reported as percent of total responses) and medians. For analysis purposes, each questionnaire was treated as a single response, even when it was completed by a group of professionals or when centers returned more than one questionnaire completed by different professionals. Thus, the term “response” (or “respondent”) refers to the answers from an individual questionnaire.

For the overall objective of the paper, most attention was focused on questions concerning screening and treatment practices and the use of guidelines and protocols; less attention was given to questions pertaining to general background information. Some questions could not be included as the variation between responses was so great or too few responses were received such that no meaningful grouping and interpretation of results could be made.

Results

Of the 165 centers in 23 European countries that were contacted, 93 (56%) centers from 19 countries responded (number of responses received): Austria (1), Bosnia and Herzegovina (1), Croatia (1), Denmark (1), Finland (1), Greece (1), Poland (1), Czech Republic (2), Serbia (2), Switzerland (2), Norway (3), Sweden (3),

Netherlands (4), UK (8), Italy (11), Spain (12), Turkey (13), France (16) and Germany (18). Six centers returned more than one questionnaire so that the total number of questionnaires (responses) received was 101. Sixteen questionnaires were answered by 2–5 professionals from the same center. For the full list of centers that contributed to the survey, see the Appendix. No responses were received from professionals at PKU centers in Belgium, Hungary, Ireland, or Portugal.

Table 1 contains data on PKU patients and the professionals contributing to PKU teams. The majority of respondents diagnosed less than five new patients per year and were involved in the care of a wide age span of patients (including newborns, children and adults). Regarding the respondent's profession, metabolic pediatrician was the most frequently reported (76%). Four percent of respondents reported that the PKU team at their center did not include a physician; 6% reported that their team did not include a dietician or nutritionist. Only 12% reported a full team consisting of physicians, dieticians/nutritionists, specialty nurses, psychologists and clinical biochemists.

The total number of PKU patients followed up per year in the 93 centers was 12,409 (the median number was 71). The total number of PKU patients reported in these centers was 14,837. Thus, 84% of PKU patients in these centers were followed up at least yearly.

Table 2 presents data on diagnostic testing and treatment practices. Genotype analysis was performed as part of routine diagnostic testing by almost half of the respondents, and the BH4 loading test was performed by more than half of the respondents. The majority of those who performed the test used one single dosage over a 24 h time period. Of those who specified the dose, all reported using a dose of 20 mg/kg/day. BH4 responsiveness was defined most frequently as a 30% reduction in blood Phe levels after 24 h. The majority of respondents indicated that they performed a BH4 loading test in infants, and less frequently in older age groups. Approximately one third of respondents reported that they used BH4 in their patient management. Treatment was started at different blood Phe concentrations. Possible answer choices for blood Phe levels at which treatment with a low Phe diet was initiated were: (a) >200 $\mu\text{mol/L}$, (b) >400 $\mu\text{mol/L}$, (c) >600 $\mu\text{mol/L}$, and (d) other, with levels of <600 $\mu\text{mol/L}$ (>200 and >400 $\mu\text{mol/L}$) being the most reported (42%). The most common “other” responses included PKU levels of 300, >360, and >400–600 $\mu\text{mol/L}$ (depending on age of patient). Concerning Phe concentrations during treatment, Phe blood testing was most commonly performed at clinical laboratories without the use of home blood collection (with samples then sent to a clinical laboratory).

Regarding the definition of severities of phenylalanine hydroxylase (PAH) deficiency, more than 70% of respondents classified classical PKU as an untreated Phe concentration >1200 $\mu\text{mol/L}$

Table 1
Summary of PKU patients and medical team profile.

<i>How many PKU patients in your center are newly diagnosed each year?</i>					
0–5	6–10	11–15	16–20	>21	No answer
69.3%	16.8%	5.9%	2.0%	5.0%	1.0%
<i>With which group(s) of PKU patients are you involved?</i>					
Only adults	Only newborns and children		All		No answer
3.0%	18.8%		77.2%		1.0%
<i>Your function^a</i>					
Metabolic Paediatrician	Adult physician	Dietician	Adult and child metabolic physician	Other	No answer
76.2%	1.9%	7.9%	14.9%	9.9%	1.9%
<i>The PKU team at your center includes which of the following?^a</i>					
Physicians	Dieticians/nutritionists	Specialty nurses	Psychologists	Clinical biochemists	Other
96.0%	94.1%	34.7%	65.3%	66.3%	24.8%

^a As more than one answer was given by respondents, the total exceeds 100%.

Table 2

Summary of diagnostic and treatment practices.

<i>Do you routinely perform genotype analysis in all of your PKU patients?</i>						
Yes	No					No answer
43.6%	49.5%					6.9%
<i>Do you currently use BH4 in your patient management?</i>						
Yes	No					No answer
33.7%	63.4%					3.0%
<i>Do you routinely perform the BH4 loading test?</i>						
Yes	No					No answer
53.5%	44.6%					2.0%
<i>If you routinely perform the BH4 loading test, please specify the time period and dose division</i>						
Over 8 h, 1 dose	Over 8 h, no dose division specified	Over 12 h, 2 doses	Over 24 h, 1 dose	Over 24 h, 2 doses	Over 24 h, no dose division specified	Over 48 h, 1 dose
5.6%	3.7%	1.9%	61.1%	3.7%	20.4%	3.7%
<i>How do you define BH4 responsiveness?</i>						
30% Phe reduction after 8 h	30% Phe reduction after 24 h	30% Phe reduction, other	50% Phe reduction after 24 h	50% Phe reduction, other	Other	
12.1%	34.5%	17.2%	12.1%	5.2%	19.0%	
<i>For which age groups do you perform the BH4 loading test?^a</i>						
Adults	Children		Infants		No answer	
22.7%	29.7%		52.4%		31.6%	
<i>At which blood Phe levels do you treat patients with a low Phe diet? Consistently elevated blood Phe levels of (in $\mu\text{mol/L}$)^a</i>						
>200	>400	>600	Other		No Answer	
4.9%	36.6%	27.7%	23.7%		9.9%	
<i>Where do you collect samples for routine dietary control of Phe?</i>						
Clinic laboratory	Home		Both		No answer	
44.6%	33.7%		19.8%		2.0%	

^a As more than one answer was given by respondents, the total exceeds 100%.

(Fig. 1A). Definitions reported for moderate and mild PKU as well as mild HPA varied considerably between respondents (Fig. 1B), with large numbers not answering this question. The most frequently reported treatment option was a combination of treatments that almost always included classical dietary treatment (98%) (data not shown). Only 48% reported classical dietary treatment as being the sole treatment option in their center (data not shown). Dietary treatment in combination with BH4 was reported as treatment options by 33% of respondents, and a combination of dietary treatment, BH4, and LNAA by 12% (data not shown). Five percent reported dietary treatment in combination with LNAA as treatment options (data not shown).

Data on patient follow-up and on the use of PKU guidelines and patient registries is shown in Table 3. Standard treatment protocols or follow-up procedures for PKU patients were used in infants and children more frequently than in adults. More than half of respondents reported having a local or national PKU registry, while almost all reported to be interested in participating in a European PKU registry.

The majority of respondents were aware of published guidelines or protocols that are useful in the screening and treatment of PKU patients. More than half of the respondents reported using the guidelines or protocols from their own centers for screening and treatment of patients, and 78% reported a need for a joint European guideline.

Discussion

The most important finding of the European PKU Survey is that there is a great discrepancy regarding the screening, treatment, follow-up and organization of PKU in European centers. This is in line with previous studies on guidelines and day-to-day practice [8,9], and stresses the need for European guidelines [10].

Results of the survey showed that PKU treatment is provided most frequently by metabolic pediatricians, and that the team at PKU centers nearly always includes physicians or dietitians/nutritionists. Surprisingly, only 12% of respondents reported a full team at their center consisting of physicians, dietitians/nutritionist, specialty nurses, psychologists and clinical biochemists. This may suggest a need for additional expertise and/or staff at PKU centers. The majority of respondents (77%) reported being involved in the care of PKU patients of all age groups; 3% reported that they were only involved with adults. Interestingly, nearly the same percentage (76%) of respondents reported their function as metabolic pediatrician. This result may be due to an inconsistency in the self-perceived role or actual title within an institution and the actual function of the physician. It may also indicate that there is a shortage of specialists for adult PKU patients, that adult patients are less likely to be followed up by a physician, trained in metabolic diseases, who treats adults. It is also possible that physicians who treat adults were not reached through the questionnaire. Furthermore, the category of specialty nurses may not be well defined in some centers; thus their reporting may not reflect the actual adequacy of the clinical team.

The total number of PKU patients reported was greater than the total reported to be followed up annually, suggesting that not all patients are followed up at least once a year. These findings may indicate that there is a need for improved follow-up procedures or that patients are lost in follow-up, which is in accordance with other studies [9]. Regarding newly-diagnosed patients, only 30% of respondents reported that more than 5 patients were newly diagnosed at their center each year.

Most respondents defined classical PKU at an untreated level of Phe >1200 $\mu\text{mol/L}$. However, the definitions reported for moderate and mild PKU and mild HPA varied considerably not only between countries, but also between centers within one country. This

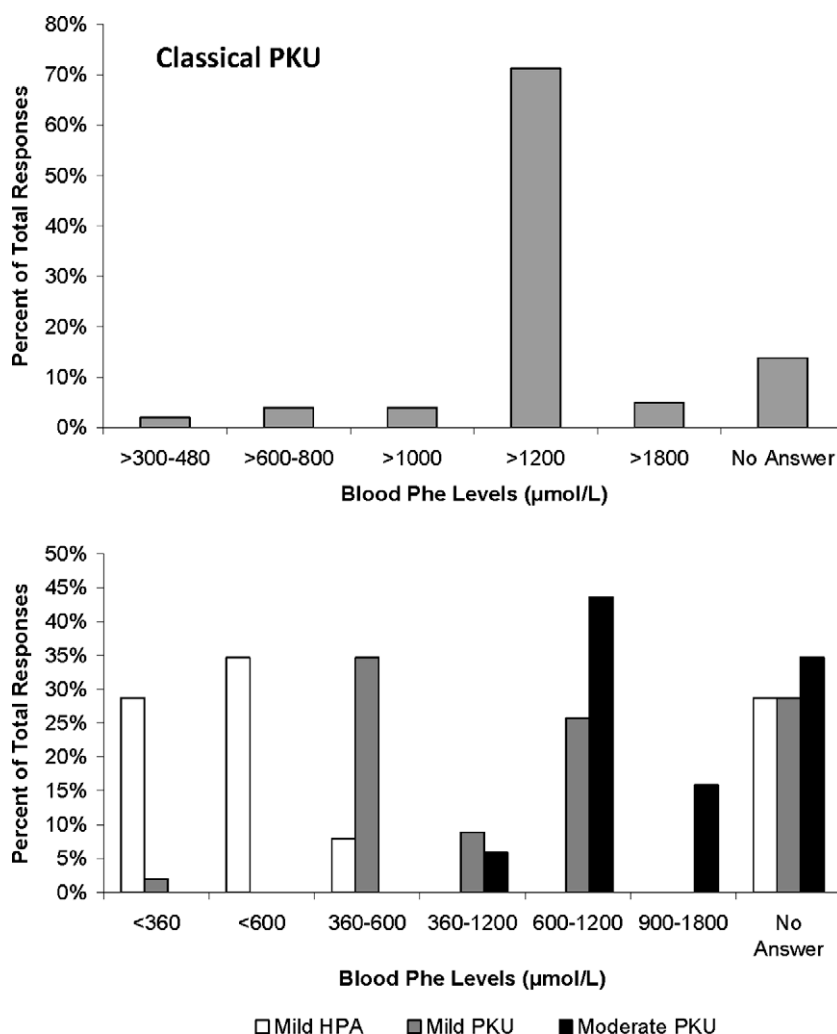


Fig. 1. Definition of PKU and HPA according to untreated blood Phe levels in European PKU centers. (A) Classical PKU; (B) Mild HPA, mild and moderate PKU.

Table 3
The use of standard treatment protocols or follow-up procedures, published PKU guidelines and a PKU patient registry.

	Yes	No	Don't know	No answer
Do you have standard treatment protocols or follow-up procedures for following PKU patient groups?				
Adults	52%	23%	–	25%
Infants and children	66%	19%	–	15%
Do you have a local or national PKU patient registry?	56%	42%	–	2%
Would you be interested in participating in a European PKU patient registry?	93%	4%	–	3%
Are you aware of published guidelines or protocols that are useful in screening and treatment of PKU patients?	87%	9%	–	4%
Does your center use its own guidelines or protocols for screening and treatment of patients?	53%	33%	–	14%
In your opinion is there a need for a joint European guideline?	78%	7%	13%	2%

finding may indicate that respondents had difficulty with the definition or interpretation of the question. There appears to be a need for a common definition for classification. This is important as the decision of treatment also depends on the definition of mild HPA and mild PKU.

Phe blood testing was most frequently performed at clinical laboratories, without the use of home blood collection. The majority of respondents routinely performed the BH4 loading test in their patients, particularly in infants.

As would be expected, the treatment option for PKU most commonly used was classical dietary treatment. This may, however, change with the recent approval of the pharmacological form of sapropterin (Kuvan®) by the European Commission in the

European Union in 2008 and with new recommendations for its use, at least for PKU patients who respond to sapropterin oral administration [1]. Depending on the patient's phenotype and genotype as well as on the outcome of the sapropterin oral challenge, they may potentially be able to either fully replace the diet or, more commonly, combine the diet with sapropterin.

One of the most difficult issues regarding the treatment of PKU is the blood Phe concentration at which treatment should begin. The results of this survey indicate a limited consensus, reflecting the lack of knowledge on this issue. Based primarily on the study by Weglage and colleagues [15], the German recommendation is to start treatment only when untreated Phe concentrations reach 600 µmol/L. However, this recommendation may be difficult to

comprehend, as patients with classical PKU already show symptoms when Phe concentrations reach levels above 240 $\mu\text{mol/L}$ [16]. Theoretically, one explanation could include that patients tested by Weglage et al. [15] may just not have presented symptoms because they had relatively normal cerebral Phe concentrations [17,18]. Other possible reasons for a difference in findings between classical PKU and mild HPA may be that the variation in Phe concentrations, rather than the exact Phe concentration, is the most important determinant of mental dysfunction in PKU [19]. Thus, there is a clear need for clinical studies that address this issue.

Standard treatment protocols or follow-up procedures for PKU patients were commonly used by respondents in infants and children, and less so in adults. This could be a reflection of the known damaging effects that PKU has in the early years of life if strict treatment protocols are not followed [20–22]. Psychiatric or psychological difficulties may develop in adults if diet is discontinued or is not well-controlled [23]. When guidelines make recommendations regarding the duration of treatment, they proclaim a reduction of Phe concentrations for life [10]. As the precise mechanism of brain dysfunction in PKU is still under discussion [24,25], it is rather unclear how strict treatment should be during adolescence and adulthood. There is, however, clear evidence of short term effects of high blood Phe concentrations on brain metabolism and neurophysiology [26,27], necessitating long-term studies in patients of those ages.

More than half of the respondents reported having either a local or a national PKU registry, and most reported that they would be interested in participating in a European PKU patient registry. The majority of respondents were aware of published guidelines or protocols that are useful in the screening and treatment of PKU patients. However, surprisingly, only about half of them reported actually using the guidelines or protocols from their center for screening and treatment of patients. This may be one of the explanations for the variation of plasma Phe concentrations between centers using national guidelines [3,28]. Importantly, a great number of centers reported a need for a joint European guideline; the main reason given was to implement common practice of PKU management across Europe. As reported very recently by van Spronsen and Burgard [10], such a guideline should not only address blood Phe targets and frequency of blood sampling for measurement of Phe concentrations, but also discuss nutritional issues, psychosocial care and neuropsychological issues, as well as shared responsibilities of professionals and patients (and care givers). This applies to all age groups. Such guidelines should also address whether patients with all degrees of PAH deficiency need the same target Phe ranges, or if patients with untreated Phe concentrations <600 $\mu\text{mol/L}$ require treatment.

The drawbacks of the present study should be acknowledged. As the questionnaire contained several open questions, it was difficult to determine whether the answers provided to these questions by respondents were a reflection of their actual clinical experience or whether they were what they deemed to be the “most relevant” answer. Furthermore, variability between responses to open questions was often so great that no meaningful groupings or interpretations could be made. In a few centers, more than one questionnaire was completed. Also, some countries with a large PKU population (i.e. Ireland) did not respond to the survey; but this may only have a small impact on the study.

In conclusion, this survey documents that there is a great discrepancy in clinical practice in the management of PKU. Even national PKU guidelines differ to a great extent, such that the variation in clinical practice reflects the variation seen in published guidelines. A broader understanding of clinical outcomes of patients with PKU and optimization of clinical management is needed. There is an emergent need to pool long-term data in an international PKU registry and to establish guidelines through a consensus conference. The following actions are suggested:

1. To have a full PKU treatment team that includes a metabolic physician, a dietician/nutritionist, a clinical biochemist, a psychologist, nurses and a social health worker available in each PKU center.
2. To define if treatment is necessary, and if it is, to start treatment as early as possible. This recommendation influences the timing of obtaining a blood sample from newborns or infants (a heel puncture) until admission to the hospital. This also implies that health care systems will have to take into account the importance of early screening procedures.
3. To have each PKU center offer the possibility of blood sampling at home. This may increase the efficacy of the PKU center, decrease the number of clinical visits and may increase patient compliance.
4. To provide a clinical follow-up to older patients at least once a year, regardless of whether treatment prescriptions are followed.
5. To promote development of standardized definitions for different PKU phenotypes, treatments and follow-up procedures.
6. To inform centers on the status of all new and upcoming therapies and the ever-expanding dietary and pharmacological options or treatment practices for PKU.
7. To provide a unique international platform for all professionals and PKU patients involved.

Conflict of interest

Enad Blau has received grants for educational and scientific work from BioMarin Pharmaceuticals, USA and Merck Serono SA, Switzerland.

Amaya Bélanger-Quintana is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU and the European Nutritionist Expert Panel in PKU. Her laboratory has received research grant funding from BioMarin. She has received honoraria for consulting or lecturing from Mead-Johnson, Cassen, SHS, and Merck Serono.

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François Feillet is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU. He has received honoraria for consulting or lecturing from SHS and Merck Serono.

Marcello Giovannini is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU.

Anita MacDonald is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU. She has received honoraria for consulting or lecturing from SHS International, Nutricia and Merck Serono. She has received research grant funding from Vitaflo International, Nutricia and SHS International.

Friedrich K. Trefz is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU. He has received honoraria for consulting or lecturing from Merck Serono.

Frančjan van Spronsen is a member of and has received honoraria for contributions to the Scientific Advisory Board on PKU. He has received honoraria for consulting or lecturing from SHS and Merck Serono.

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Appendix A. Contributing European PKU centers

Austria: Children's Hospital, Innsbruck (Karall, D., Scholl-Bürgi, S.). Bosnia and Herzegovina: University Clinical Center, Tuzla (Tahirovic, H., Toromanovic, A.). Croatia: Clinical Medical Center Zagreb, Zagreb (Baric, I., Sarnavka, V.). Czech Republic: Faculty Hospital Brno, Brno (Prochazkova, D.), Charles University and Faculty Hospital Kralovske Vinohrady, Prague (Pazdirkova, R.). Denmark: John F. Kennedy Institutet, Glostrup (Güttler, F.). Finland: University of Turku, Turku (Niinikoski, H.). France: CHU Angers, Angers (Bonnemains, C.), CHU de Besançon, Besançon (Marioli, S.), Hospital des Enfants CHU Bordeaux, Bordeaux (Barat, P.), CHU Hôpital Morvan, Brest (De Parscau, L.), CHU de Clermont Ferrand, Clermont-Ferrand (Meyer, M.), Hôpital de la Mère et de l'Enfant, Limoges (Bedu, A.), Hôpital Edouard Herriot, Lyon (Fouilhous, A.), Hôpital Timone Enfants, Marseille (Chabrol, B.), Hôpital Archet 2, Nice (Wagner, K.), Hospital Trousseau, Paris (Billette de Villemeur, T.), Hopital Necker Enfants-Malades, Paris (De Lonlay-Debeney, P.), Hôpital Robert Debré, Paris (Ogier de Baulny, H.), CHU de Rennes Hôpital Sud, Rennes (Odent, S.), CHU Hôpital Hautepierre, Strasbourg (Eyer, D.), CHU Hôpital Bretonneau, Tours (Labarthe, F.). Germany: Charité University Medical Center, Campus Virchow-Klinikum, Berlin (Hennermann, J.B., Mönch, E.), Carl-Thiem Klinikum Klinik für Kinder- und Jugendmedizin, Cottbus (Stolz, S.), University Children's Hospital, Düsseldorf (Spiekerkötter, U.), Kliniken der Universität Nürnberg-Erlangen, Klinik für Kinder und Jugendliche, Erlangen (Knerr, I.), Universitätsklinikum Freiburg, Freiburg (Schwab, K.O.), Zentrum für Kinderheilkunde und Jugendmedizin Universitätsklinikum Giessen und Marburg, Giessen (Kreuder, J.), University Clinic of Hamburg Eppendorf, Hamburg (Ullrich, K.), Medizinische Hochschule, Hannover (Das, A.M.), Universitätsklinik für Kinder- und Jugendmedizin, Heidelberg (Burgard, P., Konstantopoulou, V., Lindner, M., Müller, E.), Friedrich Schiller Universität Jena Klinik für Kinder und Jugendmedizin, Stoffwechselforschungszentrum Thüringen, Jena (Haase, C.), Klinik und Poliklinik für Kinder und Jugendliche der Universität Leipzig, Leipzig (Beblo, S., Weigel, J.), Children's Hospital, Otto-von-Guericke University Magdeburg, Magdeburg (Plötzch, S.), Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital, München (Muntau, A.), Universität Münster, Kinderklinik, Münster (Weglage, J.), Zentrum für Kinder und Jugendmedizin, Oldenburg (Marquardt, J.), Klinikum am Steinenberg, Klinik für Kinder und Jugendmedizin, Reutlingen (Scheible, D.), Klinik für Kinder- und Jugendmedizin des Klinikums, Schwerin (Clemens, P.). Greece: Aghia Sophia Children's Hospital, Athens (Schulpis, K.H.). Italy: Regional Pediatric Hospital "Giovanni XXIII", Bari (Papadia, F.), Università di Bologna, Bologna (Salardi, S.), Centro Malattie Metaboliche Dipartimento di Pediatria Policlinico, Catania (Meli, C.), AOU Meyer, University of Florence, Florence (Donati, M.A., Procopio, E.), Centro Regionale di riferimento per gli screening neonatali e la diagnosi delle malattie metaboliche – Clinica Pediatrica, Istituto G Gaslini, Genova (Cerone, R.), University of Study of Milan, Department of Paediatrics, Milan (Riva, E., Giovannini, M., Paci S.), Ospedale SS. Annunziata Napoli, Napoli (Carbone, M.T.), University Hospital, Department of Pediatrics, Padova (Burlina, A.), Centro Malattie Metaboliche-Ospedale dei Bambini, Palermo (Iapichino, L.), Ospedale Bambino Gesù, Roma (Cotugno, G.), Università "La Sapienza", Roma (Leuzzi, V.). Netherlands: University Medical Center of Groningen, Groningen (van Spronsen, F.J.), Academic Hospital, Maastricht (Rubio-Gozalbo, E.), Radboud University MC, Nijmegen (de Vries, M.), Erasmus MC/Sophia, Rotterdam (de Klerk, J.B.C.). Norway: Rikshospitalet HF, Center for Rare Disorders, Oslo (Iversen, K., Wiig, I.), Rikshospitalet, Department of Pediatric Research, Oslo (Jørgensen, J.). Poland: Instytut Matki

i Dziecka, Warszawa (Milanowski, A., Nowacka, M.). Serbia: Mother and Child Health Care Institute, Belgrad (Djordjevic, M.), Institut za zdravstvenu zastitu dece i omladine Vojvodine, Institute of Health Care for Children and Young People of Vojvodina, Novi Sad (Laketa, C.). Spain: Complejo Hospitalario Universitario de Albacete Unidad Gastroenterologia y Nutrición Pediátrica, Albacete (Gutiérrez-Junquera, C.), Hospital Materno-Infantil de Badajoz, Badajoz (Márquez-Armenteros, A.), Hospital Sant Joan de Deu, Barcelona (Vilaseca Busca, M. A., Campistol Plana, J.), Complejo Hospitalario Insular Materno-Infantil de Las Palmas, Gran Canarias, (Peña-Quintana, L.), Hospital Ramon y Cajal, Madrid (Bélanger-Quintana, A.), Hospital Universitario Virgen de la Arrixaca, Murcia (Gil-Ortega, D.), Hospital Son Dureta, Palma de Mallorca (Gomez, A.R.), Hospital Virgen del Camino, Pamplona (Valverde, F.S.), Hospital Universitario M. Valdecilla, Santander (Gonzalez-Lamuno, D.), Hospital Clinico Universitario de Santiago, Santiago de Compostela (Couce-Pico, M.L.), Hospital Infantil La Fe, Valencia (Dalmau Serra, J.), Hospital Infantil Universitario Miguel Servet, Unidad de Enfermedades Metabólicas, Zaragoza (Baldellou-Vazquez, A., Garcia-Jimenez, M.C.). Sweden: University of Lund, Lund (Papadopoulou, D.), Karolinska Children's Hospital, Stockholm (Almm, J.), Uppsala University Children's Hospital, Uppsala (Halldin Stenlid, M.). Switzerland: Institute of Clinical Chemistry, Berne (Nuoffer, J.M.), University Children's Hospital, Zurich (Rohrbach, M., Baumgartner, M.). Turkey: Cukurova University, Faculty of Medicine, Adana (Onenli-Mungan, N., Yüksel, B.), Gulhane Military Medical Faculty, Ankara (Aydin, H.), Hacettepe University Children's Hospital, Ankara (Coskun, T., Dursun A., Kalkanoglu, S.H.S., Tokatli A.), Gazi University, Faculty of Medicine, Ankara (Eminoglu, F.T., Hasanoglu, A., Okur, I., Süheyl, E.F., Tumer, L.), Osmangazi University, Faculty of Medicine, Eskisehir (Aydogdu, S.), Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul (Aktuglu-Zeybek, A.C., Cansever, S.), Istanbul University, Istanbul Faculty of Medicine, Children's Hospital, Istanbul (Demirkol, M.), Dokuz Eylul University, Faculty of Medicine, İzmir (Arslan, N., Erdur, B., Ozturk, Y.), Ege University, Faculty of Medicine, Department of Pediatrics, İzmir (Coker, M., Kalkan, U.S.), Kırıkkale University, Faculty of Medicine, Department of Pediatrics, Kırıkkale (Hizel-Bülbül, S.), Cumhuriyet University, Faculty of Medicine, Sivas (Tanzer, F.). UK: Birmingham Children's Hospital, Birmingham (MacDonald, A., Chakrapani, A., Hendriksz, C.J.), Glasgow Royal Infirmary, Glasgow (Galloway, P., Robinson, P., Schwann, B.), Great Ormond Street Hospital for Children, London (Cleary, M.A.), Royal Manchester Children's Hospital, Manchester (Walter, J.).

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