

# PKU: Closing the Gaps in Care

*An ESPKU benchmark report  
on the management  
of phenylketonuria within  
EU healthcare economies*



## Introduction

*The ESPKU is publishing this PKU: Closing the Gaps in Care report with one clear objective – to give PKU patients and their families a greater voice. The ESPKU envisages to initiate discussions and actions to enable a fairer deal for all PKU patients no matter where they live.*

*The research and this report do not amount to scientific review of the management of PKU in Europe. The research on which this report is based has provided a useful insight into some of the issues affecting people with PKU and their families and gives an indication of some of the discrepancies in PKU care between some European countries.*

Phenylketonuria (PKU) is caused by a deficiency of phenylalanine hydroxylase, the enzyme converting the amino acid phenylalanine (Phe) into tyrosine. This causes the level of Phe in the blood to rise. Cases vary from mild to severe, with severe cases having very high blood Phe concentrations. A severe case, left untreated, will result in profound and irreversible mental disability.<sup>1</sup> An abnormally high blood level of Phe is known as hyperphenylalaninaemia (HPA). This may be caused either by PKU or by a deficiency in one of the enzymes synthesizing or recycling the co-factor tetrahydrobiopterin (BH4), which stimulates the above called enzyme phenylalanine hydroxylase. Almost all European countries carry out neonatal screening programmes that identify HPA cases at birth. Cases with HPA are referred to special clinics to identify whether the child has PKU or BH4 deficiency. Once identified, a child with PKU is placed on a low Phe diet which, if initiated soon after birth, will prevent most of the neurological complications. In practice, a low Phe diet consists of a diet low in natural protein combined with a high intake of a protein substitute which has all amino acids but Phe.

Due to the restrictive nature of this diet, however, compliance tends to diminish as the child gets older.<sup>1</sup> Drug treatment can allow some PKU patients to keep their Phe levels under control while on a less restrictive diet. However, data on long term drug treatment compliance on large scale of patient population is further needed.

There is currently no reason why a child born with PKU today should not go on to live a normal, healthy and productive life. Unfortunately, despite the availability of accurate screening techniques, dietary management protocols and effective treatments,\* the European Society of Phenylketonuria and Allied Disorders (ESP KU) is concerned that the management of PKU varies across Europe,<sup>2,3</sup> with inconsistencies of care that could mean some patients are not always receiving optimal care. This may be, in part, connected to the fact that some countries have no national guidelines or inconsistently applied guidelines on how the condition should be managed and perhaps also due to differences between and even within regions of countries in whether or not diagnosis and treatment protocols are standardised.<sup>4</sup> Moreover, reimbursement issues across countries can mean that not all treatment options are available. Therefore, not every patient can receive gold standard treatment, dietary management,<sup>1</sup> or drug treatment with or without dietary management and its testing to determine if a PKU patient may be a drug treatment responder.

In response to this situation, the ESP KU commissioned qualitative research in five European countries to provide insights from healthcare professionals, patients, carers and healthcare purchasers/policy maker on PKU management in their countries with a view to determining what the key issues are and what could be done to improve the management of PKU in Europe so that every European child born with PKU can achieve its full potential with the same chance of growing up to live a healthy and productive life as an unaffected person.

\* Within this report, the term "treatment" is defined as dietary management and/or drug treatment.

## Foreword

**By David Abeln**

President of the European Society of Phenylketonuria and Allied Disorders (ESP KU)

*For thousands of patients and their families throughout Europe, Phenylketonuria (PKU) is a disturbing condition that can affect quality of life significantly. To the casual observer, however, management of PKU can seem a somewhat insignificant healthcare issue. It is, after all, a rare condition, affecting in Europe around one in every 10,000 children born.<sup>1</sup> Its primary treatment is through a modified diet, which (if adhered to) is extremely successful in preventing the devastating brain damage associated with untreated PKU. Recent advances in our understanding of the genetic and metabolic causes of PKU have resulted in effective screening techniques and innovative new treatments. However, due to its low prevalence, PKU is perhaps not always prioritised by European healthcare agendas. Some countries have no national guidelines on how the condition should be managed or guidelines tend to be implemented sporadically. The management of PKU across Europe is, therefore, inconsistent.<sup>2,3</sup> There appears to be little consensus on therapeutic thresholds (when treatment should start), treatment targets or on which medical specialities should be involved in patient care. Dietary treatment, the cornerstone of PKU management, is also different in its implementation.<sup>4</sup> Severe dietary restrictions can limit quality of life and compliance tends to falter as patients enter adulthood. There are also substantial variations in the dietary advice that patients are given, not only between different countries but also between different centres within the same country.<sup>1</sup> The emergence of drug treatment that can relax the strict demands of dietary limitation has been embraced within some specialist PKU centres. Patient advocacy groups, such as the ESP KU and its member organisations have lobbied hard to improve PKU management policies. But too often we have struggled to make our voices heard amid the clamour from equally deserving (but more populous) organisations. We have been encouraged by calls from medical specialists for a more unified approach to PKU care, but often these have been hampered by a lack of baseline data on the condition globally and its care across the European Union. Funding the collection of such data for a 'rare' condition such as PKU is never easy.*



PKU:  
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*There is, however, some hope on the horizon. From 2008 onwards, the ESPKU has been able to harvest the 'ESPKU for professionals', a group of professionals from around the world who discuss each year the latest data on PKU and its treatment in an informal way. Additionally, in 2009, the formation of the European Phenylketonuria Group has provided a valuable forum for specialists and practitioners with an interest in PKU to review the latest research, to discuss how this might be put to practical use in the management of the condition, and to foster medical education. Sponsored by the Serono Symposia International Foundation (SSIF), the group has now held three international symposia to discuss the pathophysiology of PKU, its diagnosis, treatment and recent advances in research. One of the clear messages to emerge from these meetings has been the need for evidence-based international guidelines on PKU.*

*These should seek a consensus on the initiation of treatment, monitoring of therapy and target blood Phe levels. The aim should be to produce optimised treatment protocols for the management of PKU and associated conditions. Another cause for optimism has been the adoption by the Council of the European Union of Recommendations on Rare Diseases. Published in June 2009, these recommendations outline a number of strategies to combat rare diseases such as PKU throughout Europe.<sup>5</sup> This milestone strategy calls on all member states to implement national plans for rare diseases before the end of 2013. These national plans should:*

- Ensure that rare diseases are adequately coded and classified;*
- Enhance research in the field of rare diseases;*
- Identify Centres of Expertise by the end of 2013 and foster participation into European Reference Networks;*
- Support the pooling of expertise at European level;*
- Foster patient empowerment by involving patients and their representatives at all stages of the decision-making process; and*
- Ensure the sustainability of infrastructures developed for rare diseases.*

*Clearly, these developments present the opportunity to bring some much-needed unity in the way that PKU is managed across Europe. It is with this in mind that the ESPKU has produced this report. The first few chapters of report set the scene and give the background to the condition of PKU and its management. At the heart of this report lies a qualitative survey of PKU patients, carers, physicians and health-care providers, carried out in five European countries. As stressed in the introduction, this is not a scientific review of PKU management in Europe; its validity as an initiative to raise awareness of PKU management issues lies in the establishment of confirming, based on first-hand testimony, that PKU has a significant impact on the quality of life of patients and their carers and there are significant differences between countries in the options available to treat the condition. In this context, a group of leading experts in the field have reviewed the medical content of this report and verified its accuracy. The ESPKU recognises that the support of health-care professionals in determining the best outcomes for PKU patients at all levels is vital, and I would like to thank Associate Professor Francjan van Spronsen, Professor Nenad Blau, Dr Anita MacDonald, and Associate Professor Maria Gizewska for their time in reviewing the medical content of this report and their support of the report's call to actions.*

*In presenting this research, we hope to guide healthcare providers and policy makers in their efforts to comply with European Council recommendations and provide a more comprehensive PKU service. I believe the report will also offer valuable support to organisations such as the ESPKU for Professionals and the European Phenylketonuria Group in their efforts to achieve consensus and consistency in the management of PKU throughout Europe.*

## Foreword

### By Esther de Lange

Member of the European Parliament

*As mother of a son of only 9 months, I remember very well the checks and screenings he had to undergo right after birth in The Netherlands. Too often we take for granted the care we receive in our own country. In my view, it should not make a difference in which EU-country your child is born. Unfortunately, for many diseases, as for PKU, vast differences exist between the Member States of the European Union.*

*In 2009, the Council of the European Union adopted a recommendation on rare diseases, outlining a number of strategies to combat diseases such as PKU throughout the EU. It calls on Member States to implement national plans before the end of 2013. These plans should for example enhance research in this field, support the exchange and pooling of expertise, foster patient empowerment by involving patients and their representatives at all stages of the decision-making process, and ensure the sustainability of infrastructures developed especially for rare diseases.*

*This recommendation was a very welcome signal that more cooperation is needed. I believe that national plans should ideally also include minimum standards of screening, care, support and treatment for newborns and their families. At a European level, the EU should promote a more harmonised approach towards not only how screening is done, but also on the follow-up of screening, to ensure that appropriate support is available for infants and parents. In addition, an improved exchange of information between the Member States should be encouraged.*

*This benchmarking report by the ESPKU clearly demonstrates the differences that exist between the different EU-countries, and the need to work together, so that our children, born wherever in the EU, get the same chances to a dignified and healthy start in life.*

### Medical Review Board

A Medical Review Board was appointed to review the content of this report for medical accuracy. The Board consisted of: Associate Professor Francjan van Spronsen, Beatrix Children's Hospital, University Medical Centre of Groningen, The Netherlands and Chairman of the Scientific Advisory Committee of the ESPKU, Professor Nenad Blau, Division of Clinical Chemistry and Biochemistry, University Children's Hospital Zurich, Switzerland, Dr Anita MacDonald, Consultant, Dietician in Inherited Metabolic Disorders at the Children's Hospital Steelhouse Lane, Birmingham, the UK and Associate Professor Maria Gizewska, Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology Pomeranian Medical University, Szczecin, Poland.

The views expressed in this report are the responsibility of the publisher and authors.

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### Acknowledgment

The ESPKU would like to express their sincere thanks to Associate Professor Francjan van Spronsen, Professor Nenad Blau, Dr Anita McDonald and Associate Professor Maria Gizewska for their invaluable comments on earlier drafts of this report.

We would also like to express our thanks to all the patients, carers, healthcare professionals and policy makers who have been contributing to this report by sharing their professional and personal experiences - without their contributions, this report would not have been possible.

We are also very grateful to Esther de Lange, Member of the European Parliament for her political support with Europe's policy makers, where we realise to have challenges and opportunities ahead.

We would also like to thank Emma Strebe, Medical Affairs Manager from Nutricia, Amsterdam for her support in reviewing this report. We are also grateful to Merck Serono for their continued support in this project.

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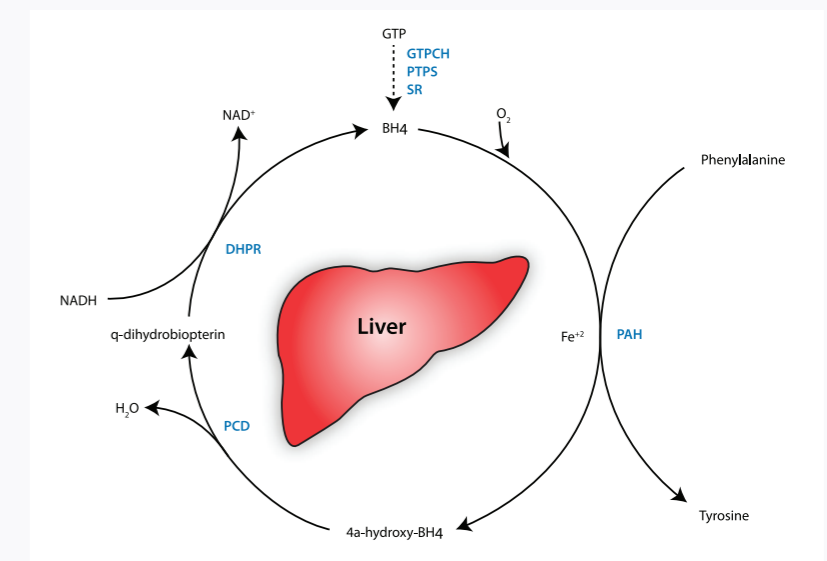


## SETTING THE SCENE

### Setting the Scene

#### What is PKU?

PKU is a genetic disorder caused by a mutation to the gene coding for the enzyme phenylalanine hydroxylase (PAH). PAH is responsible for removing the amino acid phenylalanine (Phe) from the blood (see Figure 1). When it is impaired, blood levels of Phe begin to rise until they reach toxic levels in the brain. Left untreated this can cause devastating damage to brain leading to severe mental disability.<sup>1</sup> PKU is the major cause of hyperphenylalaninaemia (HPA), which means a chronic, abnormal elevation of Phe in the blood. HPA may also be caused by an inborn deficiency in the PAH co-factor tetrahydrobiopterin (BH4). PKU and BH4-deficiency, account for the majority of cases of clinically significant HPA.



**Figure 1<sup>6</sup>**

#### Phenylalanine hydroxylating system

During the hydroxylation of Phenylalanine by Phenylalanine hydroxylase (PAH), and when molecular oxygen ( $O_2$ ) and iron ( $Fe^{+2}$ ) are present, tetrahydrobiopterin (BH4) is oxidised to a 4a-hydroxy-BH4 intermediate, which is subsequently regenerated back to BH4 via quinonoid (q) dihydrobiopterin by the enzymes carbinolamie-4a-dehydratase (PCD) and by the NADH-dependent dihydropteridine reductase (DHPR). BH4 is synthesised from guanosine triphosphate (GTP) by three additional enzymes GTP cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), and sepiapterin reductase (SR). Mutations in genes coding for PCD, DHPR, GTPCH, PTPS, and SR result in BH4 deficiency.

### What is the prevalence of PKU in Europe?

There is a wide variation in the prevalence of PKU throughout Europe. It is at its highest in Turkey, where incidence is estimated at around one case in every 4,000 births.<sup>7</sup> This compares with less than one case per 100,000 in Finland.<sup>8</sup> Overall, the European prevalence is estimated at one case per 10,000 births.<sup>9</sup>

The table below cites the prevalence of PKU (neonatal screening) in the five European countries that were studied in this report.

**Table 1**

Netherlands	1: 18,000 <sup>9</sup>
Poland	1: 8,000 <sup>10</sup>
Spain	1: 20,000 <sup>11</sup>
Sweden	1: 20,000 <sup>12</sup>
UK	1: 10,000 <sup>13</sup>

### What are the symptoms of PKU?

The consequences of elevated blood Phe levels probably decrease with age.<sup>14,15,16</sup>

Untreated PKU in infants and children is associated with:

- Progressive intellectual impairment
- Microcephaly (reduced head circumference)
- Seizures
- Autism
- Motor deficits
- Eczematous rash

If the condition is poorly controlled, studies have shown that high Phe levels can cause problems throughout life,<sup>17,18,19</sup> including:

- Developmental/functional problems<sup>17,18,19</sup>
- Low IQ<sup>18</sup>
- Anxiety<sup>17</sup>
- Reduced emotional wellbeing<sup>19</sup>
- Depression/poor mood<sup>17</sup>
- Low self-esteem<sup>19</sup>
- Poor social functioning<sup>19</sup>
- Poor concentration<sup>18</sup>
- Irritability<sup>19</sup>

More subtle effects of PKU, noted in older children and adolescents, have been linked to a reduced compliance with dietary management. These effects include poor initiation of problem solving, concept formation and reasoning.<sup>20</sup>

### How does PKU affect pregnancy?

Women with PKU need to take particular care to keep their Phe levels under control when planning to start a family; during pregnancy itself as there is a danger for the foetus if levels rise to high. Untreated maternal PKU greatly increases the risk of the infant suffering mental retardation, microcephaly and congenital heart disease. In this study 92 per cent of mothers with blood Phe concentrations of 20mg per dl or higher had at least one mentally disabled child. Breast feeding should not be restricted in mothers with PKU (provided the infant does not have PKU as well).<sup>21</sup>



## How is PKU classified?

In daily practice, the classification on the severity of PKU is challenging. Before the introduction of neonatal screening, patients arrived at the clinic due to their symptoms and the severity of PKU was diagnosed based on the Phe level measured in the blood. The condition in those days was classified as follows:<sup>1</sup>

Phenylalanine concentration	Classification
50-120 µmol/L	Normal
120-600 µmol/L	Mild hyperphenylalanaemia (MHP)
600-900 µmol/L	Mild PKU
900-1200 µmol/L	Moderate PKU
>1200 µmol/L	Classic PKU

Nowadays, the highest possible Phe levels are no longer reached in clinical practice because treatment is initiated well before patients may reach these values.

## Is PKU screened for?

Almost all European countries screen their newborn babies for PKU (see Table 2).

## SETTING THE SCENE

**Table 2**

Neonatal screening programmes in Europe

Country	Neonatal screening	Method
Austria	Nationwide Program	Tandem mass spectrometry
Belgium	Nationwide Program	Enzymatic assay, tandem mass spectrometry, HPLC**
Bulgaria	Nationwide Program	Bacterial inhibition*, fluorometric assay
Cyprus	Nationwide Program	Fluorometric assay
Czech Republic	Nationwide Program	Bacterial inhibition*, HPLC**, tandem mass spectrometry
Denmark	Nationwide Program	Tandem mass spectrometry
Estonia	Nationwide Program	Fluorometric assay
Finland	No standard screening due to low prevalence of PKU	No standard screening due to low prevalence of PKU
France	Nationwide Program	Fluorometric assay, enzymatic assay
Germany	Nationwide Program	Tandem mass spectrometry
Greece	Nationwide Program	Enzymatic assay
Hungary	Nationwide Program	Bacterial inhibition*
Ireland	Nationwide Program	Bacterial inhibition*
Italy	Nationwide Program	Bacterial inhibition*, fluorometric assay, enzymatic assay, tandem mass spectrometry
Latvia	Nationwide Program	Fluorometric assay
Lithuania	Nationwide Program	Fluorometric assay
Luxembourg	Nationwide Program	Enzymatic assay
Malta	No screening due to low prevalence of PKU	No screening due to low prevalence of PKU
Poland	Nationwide Program	Enzymatic assay, tandem mass spectrometry
Portugal	Nationwide Program	Enzymatic assay
Romania	Nationwide Program	No information yet, screening began in 2010
Slovakia	Nationwide Program	Fluorometric assay
Slovenia	Nationwide Program	Fluorometric assay
Spain	Nationwide Program	Bacterial inhibition*, fluorometric assay, enzymatic assay, tandem mass spectrometry
Sweden	Nationwide Program	Tandem mass spectrometry
The Netherlands	Nationwide Program	Tandem mass spectrometry
UK	Nationwide Program	Fluorometric assay

\* Guthrie Test

\*\* High Performance Liquid Chromatography

Based on Loeber JG. Neonatal Screening in Europe; the situation in 2004<sup>9</sup> and updated by desk research where possible.



A number of screening tests are available including:

*The Guthrie Test* – a simple and reliable test widely used throughout North America and Europe since the 1960s. This test uses a drop of blood from a heel prick taken at the end of the first week of life. However, this test simply gives a positive or negative diagnosis. It does not measure the serum levels of Phe.

*High Performance Liquid Chromatography (HPLC)* – often used instead of the Guthrie test. HPLC gives a quantitative measurement of serum Phe.

*Enzymatic assay* – a number of enzymatic assays for PKU and HPA exist. These use colourimetric analysis of dried blood spot samples to measure the quantity of Phe in the blood.

*Fluorometric assay* – using this assay, it is possible to determine quantitatively the Phe concentration in dried blood spots on filter paper. The test exhibited a linear calibration curve with a good slope as well as sufficient precision and accuracy in the statistical analysis.

## How is PKU managed?

### Dietary management

The primary goal to treat PKU is to maintain blood Phe concentrations within a defined target limit as defined by the physician. Dietary Phe restriction is the cornerstone of PKU treatment and should be initiated immediately in any infant with a positive screening test. Breast or normal infant formula feeds are reduced in volume and must be supplemented with a special phenylalanine-free infant protein substitute. Once weaned the child must avoid protein-rich foods such as meat, fish, eggs, cheese and nuts. Phe-free amino acid supplement formulas, bars, capsules, gels, soups and drinks are available to provide a protein replacement. Studies have

shown that PKU may have an affect on the patient's daily lives because of the strict dietary control, the frequent blood monitoring controls and the hospital visits.<sup>22,23</sup>

Amino acid supplements have to be administered at least three times daily and compliance tends to diminish once the child begins to take control of his or her own food intake.

The cheese whey protein glycomacropeptide may be a more palatable that to some degree may replace amino acid supplements. However, more research is needed to confirm glycomacropeptide as an alternative to amino acids.

Most centres now recommend that dietary restrictions should be continued throughout the patient's life. Compliance with 'diet for life, however, is difficult.<sup>1,24</sup>

### Drug treatment

The enzymatic cofactor BH4 can be a useful treatment that reduces the blood Phe levels in some patients. This allows patients to control their Phe levels and/or to be on less severely restricted diets. A tablet form of BH4, sapropterin dihydrochloride, is licensed in Europe for oral medical treatment for hyperphenylalaninaemia (HPA) in patients with PKU or BH4 deficiency (SmPC available on <http://www.emea.europa.eu>).<sup>25</sup>

In order to identify whether a PKU patient responds to sapropterin dihydrochloride, patients will undergo the so called "oral-response test" before treatment initiation.<sup>26</sup> Blau et al recommend that all patients with PKU should undergo such a responsiveness test. Around 20 to 56 per cent of PKU patients respond to BH4 with the greatest response seen in those with the milder forms of the condition.<sup>27</sup>

When a patient is found to be sapropterin responsive, professionals will undertake a test to initiate and optimize drug treatment. This can be done in more than one way and there is no clear consensus on protocols for treatment initiation. Currently there is the EMA approved protocol<sup>21</sup> and the protocol described by Blau et al.<sup>22</sup> Future studies will have to find out whether the EMA approved protocol is better than Blau et al (2009).

#### **Future therapies**

*Large neutral amino acids* – currently under investigation, large neutral amino acids compete with Phe to cross the blood brain barrier and may help prevent toxic levels being reached within the brain.

*Phenylalanine ammonia lyase (PAL)* – a bacteria-derived enzyme currently undergoing phase II trials for the treatment of PKU. If these trials are successful it is likely to be available in Europe within the next few years.

*Gene therapy* – research is currently underway to design a gene therapy that could correct the genetic mutation that is the root cause of PKU.

#### **How can PKU affect the brain and behaviour?**

Prolonged high blood Phe concentrations are neurotoxic and can lead to the impairment of intelligence and other brain functions (such as attentiveness). Controlling Phe levels is important to protect cognitive function. Left untreated, PKU can result in profound intellectual disability but even in individuals treated early and continuously, there is the possibility of cognitive deficits. One meta-analysis has shown a 1.9 to 4.1 reduction in IQ for every 100  $\mu\text{mol/L}$  increase in mean lifetime over a range of Phe concentration from 394 to 666  $\mu\text{mol/L}$ .<sup>28</sup> Studies have shown that IQ in individuals with PKU is related to factors such as the age at which dietary treatment is implemented and discontinued and also Phe levels

during critical periods of development (from 0 to 12 years of age). Another study showed that even early- and well-treated patients experience hidden disabilities, including subtle deficits in executive functioning, mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years.<sup>20</sup> Thus, the assessment of neurocognitive outcome is an important aspect of routine monitoring management strategies, response to treatment and perhaps the development of treatment guidelines for people with PKU.

## Treatment of PKU across Europe

### The issue of inconsistency

There is evidence that PKU care varies considerably across European countries in terms of the diagnosis, initial treatment, management and continuing care. One recent study surveyed 101 PKU professionals in 93 PKU centres in 19 European countries.<sup>2</sup> The responses showed a wide variation and no consensus in the definition of the severity of PKU, the untreated Phe level at which treatment should be initiated, therapeutic targets for blood Phe concentrations and follow-up practices for PKU patients. Only 34 per cent of the respondents reported offering BH4/sapropterin dihydrochloride as a treatment option. Another study obtained information on the routine dietary management of PKU from 10 European centres.<sup>4</sup> This found that the training, roles and responsibilities of dieticians and nutritionists at the centres varied widely. In some centres dieticians were responsible for managing the diet while in others this was carried out by a physician. There were also marked differences in target blood Phe concentrations, the dosages of protein substitutes, systems for allocating daily Phe allowance and the definition of foods that could be eaten without restriction. The wide variation in target blood Phe concentrations for different age groups throughout Europe can be seen in Table 3.<sup>1</sup>

**Table 3:<sup>1</sup>**

Target blood Phenylalanine concentrations (µmol/L) in PKU patients in European countries

	< 2 years	2-6 years	7-9 years	10-12 years	13-15 years	> 16 years
<b>Austria</b>	40-240	40-240	40-240	40-900	40-900	40-1200
<b>Croatia</b>	130-240	130-360	130-360	130-600	130-600	130-960
<b>Denmark</b>	120-300 (<4 years)	120-400 (4-8 years)	120-600 (8-10 years)	120-700	120-900	120-900
<b>France</b>	120-300	120-300	120-300	120-600	120-900	120-1200
<b>Germany</b>	40-240	40-240	40-240	40-900	40-900	40-1200
<b>Hungary</b>	120-360	120-360	120-480	120-480	120-480 (7-14 years)	120-600 (>14 years)
<b>Italy</b>	120-360	120-360	120-360	120-360	120-600	120-600
<b>Netherlands</b>	120-360	120-360	120-360	120-360	120-600	120-600
<b>Poland</b>	120-360	120-360	120-360	120-720	120-720	120-720
<b>Portugal</b>	120-360	120-360	120-360	120-360	120-480	120-480
<b>Spain</b>	<360	<360	<480	<480	<720	<720
<b>Turkey</b>	60-240	60-240	60-240	60-240	60-240	60-240
<b>UK</b>	120-360	120-360	120-480	120-480	120-700	120-700

### Reimbursement policies

One of the reasons for the discrepancies in management protocols is the different ways that European countries organise their reimbursement policies. The ESPKU has identified a huge variation in reimbursement policies across Europe for both dietary and drug treatment of PKU (see Table 4).

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TREATMENT OF PKU ACROSS EUROPE

**Table 4**  
Reimbursement situation

Country	Amino Acid supplements/protein substitutes*	If yes, how?	Low protein food	If yes, how?	BH4/sapropterin dihydrochloride	Comments
Austria	Yes	Health insurance	No		Yes	
Croatia	Yes	Government	Yes	10 kg flour per month, 80% of this is paid by the government	No	Additional flour is not covered
Denmark	Yes	Social Healthcare	Yes	subsidised by the local community	Yes	
Germany	Yes	State Insurance companies but not always for private insurances	No		Yes	PKU patients are entitled to a tax deduction
Italy	Yes	National Health System	Yes	National Health System	Yes	
Lithuania	Yes	Prepayment of a fixed amount by the government	Yes	Prepayment of a fixed amount by the government	No	
Norway	Yes	National Health System	Yes	National Health System, patients are reimbursed up to a fixed amount per month	Yes	
Poland	Yes	National Health System	No		Under decision	
Russia	Yes	National Health System	No		No	
Spain	Yes	National Health System	No		Yes	Low protein food only reimbursed in some regions
Sweden	Yes	State	Yes	State, only until 16 years	No	Reimbursement of low protein food only until 16 years; BH4/sapropterin needs to be approved by county council. If county council agrees, a large amount of the cost is reimbursed
Switzerland	Yes	Health insurance	Yes	Health insurance (depends on company), only until 20 years	Under decision	
The Netherlands	Yes	Health insurance	No		Yes	PKU patients are entitled to tax deduction
UK	Yes	National Health Service (NHS)	Yes	National Health Service (NHS)	No	BH4/sapropterin dihydrochloride available, but not reimbursed (only for BH4 deficiency)

\* Some countries do only reimburse amino acids/protein substitutes up to a certain age.

**Guidelines**

The only European countries to have published guidelines on the management of PKU are France, Germany, the UK, and Poland published in 2005, 1999, 1993 and 2001, respectively.<sup>29,30,31,32</sup> These guidelines contain several areas of disagreement – for instance each state different Phe levels as when to start a low Phe diet. Also the target ranges of Phe concentrations vary, as does the extent to which the diet may be relaxed as the child grows older. It is also notable that all guidelines were produced before the licensing of drug treatment as an additional option to treat PKU.



## Pan-European Survey of PKU Policy, Practice and Personal Experience

### Structure and scope

A qualitative survey based on a series of stakeholder interviews from five EU member states – The Netherlands, Poland, Spain, Sweden and United Kingdom – together with literature review and desk research is the basis of the ESPKU's *Closing the Gaps in Care* report. The survey sought insight to the following issues:

- Social impact of PKU
- Applied treatment and care
- PKU health policy agenda

The undertaken survey provides a snapshot of PKU policy, practice and personal experience in five countries. The overall objective of the research was to understand respondents' feelings and thoughts about PKU itself, as well as its treatment and management in clinical practice. The core objectives were:

- To gain insight into how PKU affects the lives of patients and their carers;
- To gain insight into the experience of PKU patients and their carers of diagnosis and management of PKU with particular reference to any concerns;
- To gain insight into what barriers exist for PKU patients and their carers to optimal outcomes from their perspective.

### Methodology

The survey was conducted on behalf of the ESPKU from beginning of July until mid-August 2011. The findings are based on a series of qualitative phone interviews with physicians, patients, carers and representatives from healthcare authorities.

*Structured interviews* – a series of structured, 60-90-minute phone interviews were carried out with healthcare professionals who had experience of treating PKU patients (n=12), patients (n=11) and carers (n=11). The profile of the individuals interviewed and the selection criteria are detailed in Annex 1. Qualitative research was chosen in order to get more in depth answers and personal insights. The sample of people affected by PKU included children, teenagers and young adults to reflect the range lifestyle issues that can occur; the patients interviewed also had a range of treatment experience, including dietary only management and dietary management with drug treatment experience.

The patients interviewed from the same country were mostly treated at different hospitals and regions within the country; likewise, the healthcare professionals interviewed per country also practised at different hospitals. Interviewers used a pre-prepared discussion guide covering issues such as: the physical, emotional and social aspect of PKU, diagnosis, treatment and management as well as topics around access to treatment and cost. All interviews were done in the local language and each interviewee was asked the same set of questions. A separate series of interviews was also conducted with representatives from health authorities and healthcare purchasers (n=9) on the visibility of PKU as a rare disease. The discussion guides are made available on the website of the ESPKU ([www.espku.org](http://www.espku.org)).

*Desk research* – the information about PKU comes from a range of sources, including disease awareness websites, patient advocacy group websites and published scientific literature.

*Expert review* – the final report was submitted to an expert panel of scientific medical advisers for review of the accuracy of the medical content (see Annex 2).

*Feedback* – recognising that this Benchmark report only states a snapshot of the PKU landscape in these five countries and new developments in PKU are carried out, the ESPKU welcomes feedback on this report. Please send any feedback on this report to [info@espku.org](mailto:info@espku.org).

## Results

The interviews, in transcript form, were analysed for common themes and issues. This was enabled by the fact that all interviewees were asked the same questions so answers were grouped accordingly. References to these themes and issues were selected to enable listing of the universal themes and to provide a resource for highlighting the theme or issue by way of a direct quote from the interview.

The research identified a number of universal themes and issues relating to PKU management and its impact on individuals and their families that applied in each country. There were also themes and issues particular to the countries surveyed.

This section of the report **summarises the universal themes and issues, the perceptions and experience** of healthcare professionals, patients and their carers and representatives of health authorities and healthcare purchasers for each country to provide a **snapshot of today's practice, policy and personal experience**.

### Positive themes common to each country

- PKU can be diagnosed at an early stage;
- PKU can be successfully treated;
- PKU patients benefit and need multidisciplinary support, which is widely available;
- Living with PKU does not necessarily mean an affected person will be less successful or happy;

- PKU can give you the drive to live life to the full;
- Medical options allow patients to live with less food restrictions;
- PKU can give you a uniqueness and living with PKU can make you stronger;
- Parents feel it is their duty to encourage their children to take responsibility for PKU from an early age.

*“PKU is an unpleasant illness but one that can be treated well”,* paediatrician from The Netherlands

*“We are able to provide patients with intensive treatment, with the possibility of self-management and enough support from our side by means of education, information and personal support to give people affected with PKU a good perspective,”* Swedish paediatrician

*“I remember when people with PKU suffered much mental disability. Nowadays, treatment options allow children with PKU to have normal expectations for the future,”* paediatrician from The Netherlands

*“I wish every PKU patient could try medical options because you can potentially live life without food restrictions,”* PKU patient from The Netherlands

*“Though PKU may be seen as a handicap, such as wearing glasses for poor eyesight, it doesn't have to be as you can still fulfil your dreams. I have not experienced any limitations because of PKU,”* Swedish PKU patient

### Issues common to each country

Research could identify a list of common issues to each country affecting the disease management as well as the social and personal impact of PKU to the individual.

- General satisfaction with PKU treatment options but where medical options are unavailable, concern that patients are not being offered all the options that could potentially improve their condition and quality of life;
- Variation in Phe level targets for age groups within countries and across countries;
- Standardisation of diagnosis and treatment guidance and practice would be beneficial;
- Not all PKU patients have access to the same treatment options and setting to develop their full potential;
- PKU treatment is not reimbursed equally across Europe; Variation in reimbursement policies for drug and dietary treatment, including amino acid supplements and low protein foods within and across countries;
- Patients would benefit from more resources devoted to developing more specialist centres;
- Life-long financial, medical and social support to help PKU patients should be provided consistently;
- Compliance with diet is a major issue as patients grow older; Patients have difficulties transitioning from child to adult because they have more responsibility for managing their diet and medication; Carers worry about the impact of PKU and following a strict diet when their children go through adolescence and about losing control;
- Patients report a dislike of following a strict diet, particularly a dislike of taste of protein supplements;

- Parents worry about the impact of PKU on pregnancy for their children when they grow up;
- Concentration can be affected by PKU;
- PKU has a huge impact on quality of life;
- Negative impact on social life but this can be managed; Parents worry that their children may feel left out when they reach adolescence because they are perceived as different;
- Family relationships can be put under strain due to the restrictions PKU places upon patients;
- Monthly cost of low Phe food (bread/pasta/rice) was around 100 Euros across the countries, which represents a two-to-eight fold increase in comparison with the price of regular bread/pasta/rice, etc;
- If lobbying for rare disease plans, including PKU, was a national priority PKU patients may benefit by widening treatment options.

*"I do not like that I have to follow a strict diet,"*

PKU patient from The Netherlands

*"My son thinks it is a real shame that he has to eat differently from his peers. The fact that he eats a different cake at a birthday is more difficult for him than liking or disliking the cake,"* Mother of a PKU patient from the Netherlands

*"At a certain age, you can be very sensitive at school if you have something that deviates from the norm and you can get teased,"* Swedish PKU patient

*"My relationship with my wife has suffered without a doubt because of PKU,"* UK carer

*"The low protein foods are very, very expensive and not easy to get hold of,"* Spanish carer of PKU patient



## Country snapshots

*“His ability to concentrate is affected in two ways: either he has eaten the wrong goods and his Phe levels are high and that has affected him or he has starved himself and he is hungry,”* UK carer of PKU patient

*“There are huge physical and psychological burdens for parents at the beginning of the illness, the feeling of responsibility, lack of support, little access to information,”* Polish carer

*“Varied reimbursement policies put some patients, depending on where they live, at an advantage over others,”* Swedish healthcare professional

*“A national programme for ultra rare diseases based on standards and patients receiving all the care they need would be beneficial,”* Polish paediatrician

*“There are large differences in Europe as to what Phe levels to manage patients to,”* Swedish paediatrician

*“Standardisation of treatment and diagnosis is possible and would be beneficial,”* Spanish healthcare professional

*“Patients and their families have to think about diet on a daily basis and children have to take regular supplements that they often find unpalatable,”* UK paediatrician

*“Patients have the right to only limited benefits and social care is available only to the very poorest; this is a key issue in Poland,”* Polish paediatrician

### The Netherlands

Two male patients, aged 17 and 36, were interviewed from The Netherlands. Both were diagnosed at birth; one patient’s PKU is managed with diet alone while the other patient is also receiving medical treatment. These patients had a very positive attitude to their condition, accepting PKU and the restrictions on diet it can place as a way of life. One patient felt his lifestyle and aspirations were not affected by PKU whilst the other patient said PKU influenced his daily life very much in terms of food and relationships, though not substantially such that his “dreams were limited”. Two carers, one with a nine-year-old son with PKU and one with a seven-year-old son with PKU, were interviewed. Both carers reported that though their sons had come to terms with the need for dietary restrictions, they did not like them, particularly when they affected restaurant visits and holidays. One of the carers was very concerned that being on a strict diet disadvantaged her son in terms of making and maintaining friends and she was worried about how he might cope with this during adolescence. **“I am afraid of watching him ruin himself,”** she said. Both carers reported issues in finding the right way of explaining PKU to others, particularly other parents in relation to play dates and school trips. They also said their lives were very affected by their sons’ condition as they spent a great deal of time buying food and planning meals.

**“I want my son to be seen as a normal child and be treated normally but I have to make it clear that he has to eat his own food,”** mother of seven-year-old son with PKU.

Three paediatricians working in university hospitals and two policy advisors to Dutch ministries were interviewed. The following issues and themes emerged:



PKU:  
Closing the Gaps in Care

- A well-organised screening programme for PKU exists based on tandem mass spectrometry; standard screening procedure for newborns between 72 and 168 hours after time of birth;
- Standard guidelines for PKU screening and diagnosis, treatment and national protocols exist;
- High degree of satisfaction with treatment plans and options;
- Paediatricians and dieticians are involved in taking care of PKU patient during childhood. When patients reach adulthood, patients are sometimes transferred to an internist or remain to be treated in paediatric clinics. Occasionally, psychologists may be involved. A package of support is offered to the patient and their family during transition to adulthood, including extended clinic hours, combined meetings involving the paediatrician and internist;
- The primary treatment goal is to manage Phe levels, set individually and determined by age (0-12 years <360, > 12 years 120-600);
- The secondary treatment goal is to strive for normal development, e.g. growth, neurocognitive and psychosocial development;
- Frequency of monitoring depends on the age of the patient. Home blood testing is promoted by all centres except for one;
- Treatment options consist of low Phe food, amino acid supplements/protein substitutes and drug treatment; BH4 responsiveness testing is routinely used to determine if a PKU patient may respond to drug treatment;
- BH4/ sapropterin is reimbursed by health insurance;
- Low Phe food is not covered by health insurance but patients are entitled to a tax deduction;
- Amino acid supplements/protein substitutes are reimbursed;
- Though as rare disease, including PKU, are not affecting a large number of people compared to other diseases, they are not a top priority on the government's strategic agenda;

PAN-EUROPEAN SURVEY OF PKU POLICY,  
PRACTICE AND PERSONAL EXPERIENCE

- There are moves to improve the quality of service for patients affected by rare diseases in The Netherlands; various policy papers have highlighted the need for a particular focus on rare diseases and there is acceptance that rare diseases need to be treated in specialist centres.

### Sweden

Two Swedish women with PKU, both 31 years of age, were interviewed as well as two carers, a father of a three-year-old with PKU and a mother who has two sons with PKU. There was a strong theme common to each interview of the need for there to be a greater understanding of PKU and its impact on individuals and their families by society at large. ***“It is very important that they have an understanding that I need to go and eat at certain times, even if I am in a meeting or something like that.”*** The patients interviewed felt satisfied screening services were available but that it was unfair medical options were not universally available.

***“You are frustrated that there are better ways to treat PKU that we are not getting today.”*** Indeed, the patients and carers interviewed communicated a great deal of frustration with PKU services in their country: the lack of universal availability of medical options and the too few PKU specialists. ***“Sweden feels like a developing country when it comes to PKU,”*** according to one of the patients interviewed.

Two paediatricians who treat patients once they become adults in the same clinic were interviewed. Two officers of the Swedish National Board of Health and Welfare (NBHW) were also interviewed. The following issues and themes emerged:

- Standard newborn screening in place based on tandem mass spectrophotometry;
- Paediatrician, dietician and nursing staff are involved in the care of PKU patients throughout their lives;
- The goal of treatment is target Phe levels to maintain normal cognitive development and function, and levels vary according to age of the patient; different practitioners also use different target Phe levels for particular age groups;
- Varied reimbursement policies relating to dietary products and medical options across the country;
- Reimbursement of low Phe food and protein supplements depends on age of patient and which part of Sweden patients reside in; low Phe products are reimbursed until the patient is 16 years old;
- Given availability and reimbursement of drug treatment is regional, BH4 testing is also only available in some parts of Sweden; there is lack of consensus on its use;
- Sapropterin is reimbursed in some parts of Sweden, limiting the availability of treatments to patients;
- There is no specific policy focus on PKU at present. Sweden has a decentralised healthcare system, with county councils holding responsibility for healthcare. The issue of rare diseases and ensuring the adequate provision of services for people affected by them is however moving up the political agenda in Sweden, mainly in response to European calls for rare diseases national plans.
- The NBHW is carrying out work to set up a national function for rare diseases, which will be a centre of expertise but this is in the early stages of discussion. As more attention is focused on rare diseases, this could benefit PKU patients – though the policymakers interviewed think that PKU is managed well in Sweden.

## Spain

A 27-year-old woman with PKU, a 19-year-old woman and a 24-year-old man with PKU were interviewed. All are very active advocates for PKU and have enjoyed the contact they have had with PKU patients through their advocacy and campaigning work. None felt that PKU had had a large detrimental effect on their lives but each identified issues that complicated their lives, such as having to travel to buy low protein food, which is expensive, and that PKU services in Spain are not unified. Three carers were also interviewed. One mother of a young boy with PKU has to travel far to take her son to his check-ups and said she would value specialists being closer to where she lives or that social services knew more about PKU so she could go there. She complained that PKU food is expensive and not very accessible. A mother of a nine-year-old boy with PKU also reported the expense and inaccessibility of low protein food as a key issue for her. The third interviewee, a mother of a seven-year-old daughter with PKU said needing to follow a restricted diet was the largest burden of PKU on the family. ***“I would like a medication that enables you to eat more foods that are not normally restricted.”***

Three paediatricians working in hospitals/PKU units and two policy advisers to Spanish health institutions were interviewed. The following issues and themes emerged:

- The Guthrie test is used in some parts of Spain; in others, mass spectrometry is used for newborn screening;
- The primary goal of treatment is to maintaining target Phe levels but there are different opinions on the target levels;
- Guidelines for diagnosis and treatment are not standardised at national level but there are standard protocols at regional level;
- Standardised monitoring procedures are in place, with frequency of monitoring depending on the age of the patient;

PKU:  
Closing the Gaps in Care

- A multidisciplinary team of neurologist, psychologist, dietician, geneticist, biochemist supports paediatricians;
- Patients are managed by the same key doctor from birth through to adulthood;
- Under-staffing may affect PKU care – more staff and specialist units are needed;
- Treatment options consist of low protein diet, protein supplements/ amino acids and BH4/sapropterin; BH4 testing is not standardised, it is done in some hospitals; varies region by region;
- BH4/ sapropterin is reimbursed by health insurance;
- Low protein foods are partly reimbursed by insurance in some regions, not reimbursed in others;
- Reimbursement of non-medicinal products is an issue in Spain and this affects PKU patients.
- There is greater awareness of rare diseases amongst the general public in Spain due to patient organisation campaigns, parliamentary debates and the setting up of specialist centres;
- A national strategy on rare diseases began in 2007, which will include a focus on PKU.

### United Kingdom

Two patients and two carers from the United Kingdom (UK) were interviewed. One patient received drug treatment as he participated in a clinical trial and said his social life had been affected negatively once the trial ended as he had to return to a restricted diet. The patients reported they felt lucky to live in the UK because low Phe foods and protein supplements were available on prescription and were thus available at a significant discount for adults and free for children. Indeed both patients were very positive about the care and support they received in the UK. ***“I have been really lucky with the doctors and nurses that I have had treating me. I have been extremely lucky and well supported.”***

### PAN-EUROPEAN SURVEY OF PKU POLICY, PRACTICE AND PERSONAL EXPERIENCE

The two carers said that parents of newly diagnosed children could benefit from more information but also agreed with the adult patients that care in the UK was of a high standard. ***“It is quite difficult to cope with at first when your child is diagnosed with PKU but you do get round it and there is a lot of support in the UK,”*** carer of daughter with PKU. One carer, however, reported that raising a PKU child had placed a huge strain on his marriage and that his son rebelled against the strict diet during his adolescence to the point of malnourishment. ***“As they develop, there’s a point at which each child begins to find it difficult. My son’s coping strategy was to say ‘ok, I just won’t eat’, which didn’t do him any good and he ended up being malnourished.”***

In response, the father self-funded drug treatment for 18 months but had to stop because this became unaffordable. This carer has challenged the National Health Service in the UK to fund drug treatment.

Two doctors, one who treats adult patients and one who treats children and young people, were interviewed. Two policy makers, a doctor in charge of rare diseases screening and a commissioner of services, were also interviewed to provide feedback from the UK perspective on policies affecting PKU patients:

- All newborn babies are screened for PKU via the Guthrie test within eight days following birth; screening for PKU at birth is fully implemented and is run very successfully;
- Standard protocols for diagnosis exist, set by the National Newborn Screening Service; management standards are in place for children and for pregnant patients, for adults it is less standardised;
- PKU is considered to be well managed in the UK; PKU care is fragmented; some are managed in PKU centers, others not; The UK is well served with centres of excellence for metabolic diseases; with centres of excellence for metabolic diseases;



- PKU patients are managed by a metabolic disease consultant and a dietician, with the dietician having the main role in terms of patient management. Specialist nurses, psychologists and primary care physicians are also involved. Children are under the care of a paediatrician until the age of 16-18 years; adult services and paediatric services work closely together to ensure a smooth transition for patients;
- Primary treatment goal is to provide a good quality of life for patients and enable patients to achieve their goals;
- Treatment goals vary depending on the age of a patient, standard Phe targets set by a Medical Research Council Working Group so are applied nationally (young children below 360 micromoles per litre, relaxed up to 480);
- PKU is typically managed by following a low Phe diet and by taking nutritional supplements and there is good access to these. Sapropterin is available (only reimbursed for BH4 deficiency);
- Low Phe foods and supplements are available on prescription (free of charge to children); however, adults have to pay a prescription payment for each prescription;
- Sapropterin and its reimbursement is a contentious issue at the moment, in the UK with the policy makers interviewed claiming that most metabolic clinicians will not prescribe drug treatment;
- Policy makers feel that no more emphasis needs to be put on PKU in the UK as screening is very successful and management is adequate;
- Policy makers feel that there could be better communication between their European counterparts over rare diseases policy;
- Policy makers feel that dietary management alone is the best approach to PKU;
- The Department of Health is drawing up a plan for rare diseases in response to European Council recommendations.

## Poland

A 26-year-old woman and a 21-year-old man were interviewed from Poland. Both patients reported having a lot of emotional problems when they were growing up. ***“I could not accept myself and my PKU.”*** ***“I was embarrassed that I was eating another type of bread than my friends.”*** Both patients are glad that amino acid supplements are reimbursed in Poland but complained that low Phe food is very expensive. Though both patients complimented the doctors and nurses that they dealt with for their support, they complained that there was a lack of social support for PKU patients in Poland. ***“My parents received nursing benefits when I was younger but there are not benefits available to me as an adult.”*** Two carers from Poland were also interviewed. One, a mother of a seven-year-old girl with PKU is a single mother and struggles financially because low Phe food is very expensive. ***“The diet is costly and I do not really have any help from anywhere.”*** She also feels unsupported: ***“There is a need for psychological support from the beginning of the illness.”*** The other carer’s key issue was that he had poor contact with the doctor and met a lot of barriers to getting good information.

Two paediatricians were interviewed, along with a policy maker for the assessment of funding for healthcare services. They provided the following insights:

- All newborn babies are screened; there are eight screening centers, including a central screening laboratory in Institute of Mother and Child in Warsaw. Different screening techniques applied; mostly used screening method is enzymatic assay, in Warsaw screening is performed with tandem mass spectrometry; All positive results (from the whole country, together with differential diagnosis for HPA in local centres) are confirmed also with tandem mass spectrometry in Warsaw.



## Summary & Call-for-Action

- Diagnostic guidelines have been developed and are followed nationally;
- Aim of treatment is for patients to reach target Phe levels to achieve their potential intellectual ability;
- Typical treatment is dietary management and amino acid supplements;
- BH4/sapropterin in patients with BH4 deficiency received a favourable recommendation by the Agency for Health Technology Assessment in Poland (AOTM); reimbursement discussions are underway;
- Adults and children are treated in the same centres; no specific adult treatment centres; usually patients see metabolic expert, dietician and psychologist if needed;
- Only limited number of centres – recently centres had to be closed due to lack of specialists; patients need to travel far to see a specialist;
- Low protein food is very expensive; National Health Fund (NFZ) offers no reimbursement schemes;
- Amino acid supplements are reimbursed but patients need to pay a flat fee;
- Key issues for Polish patients continue to be that PKU is mostly not managed by a multi-disciplinary team, there is a lack of social care, poor access and no reimbursement to low Phe food;
- Some visibility of PKU as a rare disease in Poland, mostly driven by patient associations, health NGOs and media; active patient associations are the only possibility to receive social support;
- There is a dedicated rare disease team in the Ministry of Health currently working on a national rare disease plan.

The research presented in this report presents a snapshot of themes and issues affecting PKU patients in five European countries. It is not a definitive account of the lives and experiences of people living with PKU across Europe but it does indicate that there is a need for improvements in countries in terms of healthcare policies and practice that could improve the quality of life for people affected by PKU across Europe. The patients and carers interviewed at length tell strong stories with connecting themes about the impact of PKU on their lives.

One of the main issues to emerge from the research is confirmation of previous research that shows the availability of treatment options is not equal within a country and across Europe. Low Phe foods and amino acid supplements are not always reimbursed, or only reimbursed until a certain age or are not easy to access and this can cause enormous strain on families if essential items are not affordable or difficult to obtain. Another inconsistency identified by this benchmark report is that drug treatment is available and part of the reimbursement plans in some countries, but not others. Such unfairness should be tackled by a concerted effort to enable PKU patients wherever they live to have access to all the treatment options that could help them live with their condition.

To change this situation, a number of initiatives need to occur. First, health policies need to ensure that PKU receives more visibility and is seen as one of the most common rare diseases in Europe. This should include better information, education and awareness of PKU as well as how patients with PKU can lead happy and productive lives with the right treatment, care and support. PKU patients need to be fairly treated wherever they live in Europe and this will require the commitment of national governments and health institutions to European efforts to help those affected by rare diseases. Second, the healthcare professionals should work to a more harmonised, standard procedure for the diagnosis and management of PKU that is

reflected across Europe. Management guidelines that are written by the European experts in this field and endorsed by their peers then incorporated into national management practice would be a huge step towards helping PKU care become more consistent.

In conclusion to this report, the ESPKU is presenting the following recommendations and current initiatives based on this research. The recommendations are targeted at the European Commission, national health policy-makers and healthcare purchasers, as well as healthcare professionals who can also play a significant influencing role for the following actions:

1. Ensure policymakers are better informed and aware of treatment options, care and support needed for patients with PKU; as the most common rare disease, national governments must prioritise PKU.
2. Ensure equal access for all PKU patients to the same treatment options including dietary and drug treatment across Europe. Establish and foster plans to ensure all treatment options are equally available and accessible. There should be no reason for why a PKU patient in one EU country has different treatment options than a patient living in another EU country.
3. There must be a harmonised approach in the EU on reimbursement policies for all available services and treatments including dietary management with amino acid supplements and low protein foods and drug treatment. PKU is a chronic condition that a patient lives with throughout his or her life. Patients need life-long financial, medical and social support. There is no reason why reimbursement should stop at a certain age.
4. Further standardisation of care on national level and across Europe. Every PKU patient is different and needs personalised care. However, greater consistency in both treatment goals and outcome measures within a country but also across Europe is urgently needed. Consistency will give patients and carers greater certainty of receiving the optimal care and will also help streamline the optimization process of protein/amino acid substitute formulas.

5. Initiation and implementation of measurable compliance programmes to help patients achieve their full potential and a good quality of life. Showcase countries in which patients, carers and healthcare professionals collaborate well and achieve favourable compliance to life-long treatment. Demonstrate which differences good compliance can make on medical, personal and economic level.
6. Initiation and implementation of measurable neurocognitive programmes. Demonstrate which differences good treatment can make on neurocognitive outcome within each stage of a patient's life.
7. Foster the development of tools for easier access to low Phe food within a country and across Europe. With today's technologies, patients should not have to travel far in order to buy medical products.

The ESPKU has taken initial steps towards addressing these essential actions. First, the ESPKU has initiated the development of a European Consensus paper on optimal care of PKU from a patients' perspective across nations. The first draft of this paper together with the *Closing the Gaps in Care* report will be presented and discussed at the 2011 annual ESPKU conference in Warsaw, Poland, among different stakeholders. It is planned to have a final consensus by next year that can be presented to the EPG for further consideration. Second, the ESPKU is planning to launch this report to members of the European Parliament next year to enhance the urgency for making PKU a greater health priority across Europe.

**Annex 1 – Survey sample breakdown**

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8
<b>UK</b>								
Carer 1 (male, adult, dietary treatment experience)	x							
Carer 2 (male, teenager, with drug treatment experience)		x						
Patient 1 (female, adult, dietary treatment experience)			x					
Patient 2 (male, adult, with drug treatment experience)				x				
HCP 1				x				
HCP 2					x			
Policy Maker 1								
Policy Maker 2								
<b>NETHERLANDS</b>								
Carer 1 (male, child, with drug treatment experience)	x							
Carer 2 (male, child, dietary treatment experience)	x							
Patient 1 (male, teenager, with drug treatment experience)	x							
Patient 2 (male, adult, dietary treatment experience)		x						
HCP 1			x					
HCP 2				x				
HCP 3					x			
Policy Maker 1								
Policy Maker 2								

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8
<b>POLAND</b>								
Carer 1 (female, child, dietary treatment experience)	x							
Carer 2 (male, teenager, dietary treatment experience)	x							
Patient 1 (male, adult, dietary treatment experience)	x							
Patient 2 (female, adult, dietary treatment experience)	x							
HCP 1	x							
HCP 2		x						
Policy Maker 1								
<b>SPAIN</b>								
Carer 1 (male, child, dietary treatment experience)	x							
Carer 2 (male, child, dietary treatment experience)		x						
Carer 3 (female, child, with drug treatment experience)			x					
Patient 1 (female, teenager, without Kuvan experience)				x				
Patient 2 (male, adult, with drug treatment experience)					x			
Patient 3 (female, adult, with drug treatment experience)				x				
HCP 1						x		
HCP 2							x	
HCP 3								x
Policy Maker 1								
Policy Maker 2								

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8
<b>SWEDEN</b>								
Carer 1 (female, child, dietary treatment experience)	x							
Carer 2 (2 male children, with drug treatment experience)		x						
Patient 1 (female, adult, with drug treatment experience)			x					
Patient 2 (female, adult, with drug treatment experience)				x				
HCP 1					x			
HCP 2		x						
Policy Maker 1								
Policy Maker 2								

## Annex 2 – Medical Review Board

### Associate Professor Francjan van Spronsen

Francjan J van Spronsen received his MD in 1987 and combined research and clinical work for the section of metabolic diseases of the Beatrix Children’s Hospital of the Academic Hospital of Groningen until 1992, when he started his training to become a general paediatrician. He received his PhD in 1996 for his thesis Phenylketonuria: implications of some biochemical and clinical findings. From 1997 till 1999 he was a general paediatrician and supervisor at two clinical units of the Beatrix Hospital in the University Hospital of Groningen and a consultant for neuromuscular diseases. From 1999 onwards, he joined the metabolic section as paediatrician metabolic disease treating patients from 0 to 70 years of age. From 2001 till 2007 he was coordinator of two different studies about medical students, and he now combines clinical experience with management on education of MD students, and chairing of the exam committee for MD students of the University of Groningen. He is a member of various education committees for medical students and paediatricians. At a national level, he is a member of the Dutch organisation for physicians and biochemists working on metabolic diseases, and chairs the Advisory Committee on Neonatal Screening with respect to inherited metabolic diseases, and is a member of the Dutch Committee on Neonatal Screening. At international level he is a member of the Society for the Study of Inborn Errors of Metabolism, he chairs the Scientific Advisory Board of the European Society of PKU and allied disorders, and chairs various European and international advisory boards and working groups on inborn errors of metabolism. His major research topics and peer-reviewed papers are mainly on metabolic and cerebral processes in inherited defects of amino acids (e.g. phenylketonuria, tyrosinaemia type I, urea cycle defects). His working



address is the Beatrix Children's Hospital of the University Medical Centre of Groningen, University of Groningen, The Netherlands.

### **Professor Nenad Blau**

Professor Nenad Blau, PhD, is head of the laboratory for the diagnosis of tetrahydrobiopterin and neurotransmitter disorders at the University Children's Hospital in Zürich, Switzerland (from November 2011 at the University Children's Hospital in Heidelberg, Germany). He is a senior lecturer in biochemistry and metabolic disorders at the University of Zürich and author/senior editor of more than 200 research publications, including the standard books *Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases*, *Physician's Guide to the Treatment and Follow-up of Metabolic Diseases* and *Laboratory Guide to the Methods in Biochemical Genetics*. He is an honorary member of the Italian Society for Pediatrics. He is a curator of several metabolic databases like BIODEF or BIOPKU ([www.biopku.org](http://www.biopku.org)). For his research in the field of tetrahydrobiopterin and phenylketonuria he received in 2001 the Horst-Bickel Award, in 2005 he was honoured by the Gowland Hopkins Award, and in 2011 he received the Asbjorn Folling Award.

### **Dr Anita MacDonald**

Dr Anita MacDonald, Consultant Dietitian in Inherited Metabolic Disorders (IMD) at Birmingham Children's Hospital is an experienced paediatric dietician. She has been working as a clinical dietician for over 30 years, and is a Fellow of the RCPCH. She has worked with some aspect of inherited metabolic disorders almost all her working life and thoroughly enjoys the challenge of evolving new diet therapies, helping develop specialist dietary products and trying to improve dietary treatments. She has always retained an interest in infant feeding and child nutrition. She has extensive research experience and has published over 300 publications, with 100

peer reviewed publications and is a monthly columnist in *Network Health*. She obtained her PhD in Phenylketonuria in 1999. She is actively involved in teaching and training. She has lectured in over 30 different countries, and is responsible for the Inherited Metabolic Disease module for the Paediatric Group of the British Dietetic Association. She is a member of numerous national and International Committees and working groups. She is joining organiser on a MSc module on paediatric IMD dietetics.

### **Associate Professor Maria Gizewska**

Associate Professor Maria Gizewska MD, PhD is the Vice-head of the Department of Endocrinology, Diabetology, Metabolic Diseases and Cardiology of Pomeranian Medical University in Szczecin. From the mid nineties her researches are focused on early diagnosis and treatment of children, adolescents and adults with different types of IEM, including almost 200 patients with Phenylketonuria. Doctor Gizewska is the author of 60 articles in both Polish and international journals on IEM, paediatrics, paediatric endocrinology, neurology and genetics. She wrote about 110 abstracts presented during Polish and international conferences. Phenylketonuria and other IEM were the subject of her lectures given in Denmark, Brazil, Uruguay, Ukraine and China. She is a member of SSIEM, Polish Paediatric Societies, Polish Society of Paediatric Endocrinology, and a Board member of Polish Metabolic Group of Polish Pediatric Society. Doctor Gizewska is a vice-chairman of Polish Society of Phenylketonuria, a vice-chairman of Scientific Advisory Committee of European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPku) and a member of IMD Nutricia Advisory Board.

### Annex 3 – PKU Glossary

#### Amino acid

A type of molecule found inside protein. There are 20 amino acids that are considered standard. Of those, 10 are essential to a healthy diet because the body is unable to produce them. Among the 10 essential amino acids is Phenylalanine.

#### BH4 (Tetrahydrobiopterin)

An enzyme cofactor that works together with Phenylalanine Hydroxylase to convert Phenylalanine to Tyrosine in the liver. Without the action of both Phenylalanine Hydroxylase and Tetrahydrobiopterin, the chemical process cannot take place, resulting in an accumulation of excess phenylalanine.

#### BH4 deficiency

A deficiency of the naturally produced BH4 cofactor, caused by mutation in one or more of the enzymes involved in synthesis or regeneration. BH4 deficiency is not the same disorder as Phenylketonuria (PKU).

#### Cofactor

A molecule that combines with an enzyme in order for that enzyme to function. The cofactor of Phenylalanine (Phe) is Tetrahydrobiopterin (BH4).

#### Dietitian/Nutritionist

A medical expert whose focus is diet and nutrition, and one of the key players in an individual's management of Phenylketonuria (PKU). A metabolic clinic is typically run by a staff of registered dietitians/nutritionists overseen by a few metabolic geneticists and/or physicians. The registered dietitians/nutritionists are responsible for tracking the nutritional needs of PKU patients and recommending dietary changes when appropriate

#### Enzyme

A kind of biological molecule that facilitates certain chemical reactions inside the body. People with Phenylketonuria (PKU) lack a certain enzyme called Phenylalanine Hydroxylase (PAH).

#### Enzymatic cofactor

An enzymatic cofactor is a chemical compound that must be bound to an enzyme in order for that enzyme to become active.

#### PAH (Phenylalanine Hydroxylase)

An enzyme which works together with Tetrahydrobiopterin (BH4) to convert Phenylalanine (Phe) to Tyrosine (Tyr) in the liver. A deficiency in PAH results in high Phenylalanine levels in the blood, which is the biochemical hallmark of Phenylketonuria (PKU).

#### Phenylalanine (Phe) tolerance

The quantity of Phe a patient may consume without a significant increase in her or his target blood Phe levels. Usually expressed as daily intake.

#### Phenylalanine (Phe)

A building block of protein, and one of the 10 essential amino acids. An inability to metabolize excess phenylalanine is the characteristic feature of Phenylketonuria (PKU). When the blood concentration of Phenylalanine exceeds what is considered a healthy level, excess amounts may build up in the brain, causing mental retardation.

#### Protein

A type of molecule produced by the body from Amino acids.

### Tyrosine (Tyr)

An Amino acid. The Phenylalanine Hydroxylase (PAH) enzyme normally converts phenylalanine (Phe) to Tyr.

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