UNMET NEEDS IN PHENYLKETONURIA (PKU): TAKING STOCK, LOOKING AHEAD

Hotel Leopold, Brussels
3 March 2020
Policy Roundtable and Launch of the European Parliament Cross-Party Alliance on PKU

Meeting Report

Welcome and introductions

Co-host Clare Daly MEP welcomed participants, congratulating the organisers for being able to avoid cancelling the meeting, despite the European Parliament's closure at very short notice because of the coronavirus situation. She saw this as a demonstration of the spirit, will and perseverance of the PKU community.
After inviting all participants to briefly introduce themselves, she stated that the mix of different nationalities as well as different specialties and interests represented around the table boded well for future discussions.
Turning to PKU, she underlined the multi-faceted nature of the condition – life-long, with a significant impact on day-to-day living and quality of life.
Ms Daly noted that, very frequently, PKU is presented as a metabolic condition – but there is more to it than that. PKU can have a lasting impact on neurocognitive, emotional, mental health and behavioural aspects as well. Moreover, it affects all dimensions of an individual's life as well as that of their families and carers. This complex impact needs to be better recognised, acknowledged and treated.
By creating the Cross-Party Alliance on PKU, MEPs hope to make a sustained and continued contribution to raising awareness of the condition and of how it could be better managed. 12 MEPs have already committed to becoming full supporters of the Alliance – and the meeting itself is supported by a number of others. Ms Daly congratulated ESPKU for taking the initiative to create the Alliance and for its efforts to coordinate this new and much needed platform.
Turning to the aims of the meeting, Ms Daly expressed her wish for an informed discussion on PKU and its impact, which could help better understand the true nature of the condition and of current unmet needs – something which would in turn shape the agenda and future priorities of the Alliance.

Ms Daly then gave the floor to **Frances Fitzgerald MEP,** who also welcomed the creation of the Alliance, underlining the need for continued action to ensure that unmet needs are better addressed and that patients have access to the therapies and support they need. She offered her full engagement to support its future work.

Victor Negrescu MEP also stated his support for the Alliance and praised the work of the Romanian national PKU patient organisation, which has helped to raise awareness and mobilise policymakers to effect change at the national level.

Keynote Speakers

The opening speaker, **Eric Lange (President, ESPKU)** briefly introduced Phenylketonuria (PKU) as a rare inherited metabolic disorder that affects about one in every 10,000 children born in Europe. If left untreated, PKU results in increased phenylalanine ('Phe') concentrations in the blood and the brain. This can cause severe intellectual disability and epilepsy, as well as neurocognitive, mental health and behavioural problems.
PKU is increasingly recognised by policymakers – in Europe and elsewhere in the world – as a condition which requires special attention. However, sustained efforts are required to anchor it as a public health priority on the EU and national policy agendas. The PKU community sees a pressing need to explore all avenues for policy action to improve the lives of affected individuals across all Member States.
The ESPKU therefore welcomed the opportunity to set up a more permanent platform to drive such policy action, the original idea of which emerged during a Policy Roundtable on PKU held at the European Parliament in July 2018. The Cross-Party Alliance is the direct result of the discussions at that time. Its vision is to 'strive

to ensure that individuals affected by PKU and their families obtain lifelong access to the services, therapeutic solutions and support that they require to best manage the condition and its consequences in their daily lives'. The secretariat of the Alliance will be offered by the ESPKU and shall support and facilitate a broad range of actions, e.g. expanding the Alliance, designing and implementing a work programme, developing policy statements and position papers, formulating amendments to legislative and other proposals and organising (and reporting on) regular meetings of the Alliance.

Some of the themes and issues which will definitely be addressed include:

- Ensuring that new-born screening a consistent reality everywhere across Europe;
- Ensuring access to appropriate diets and therapies;
- Supporting the implementation of good practice guidelines in PKU treatment;
- Ensuring clear protein food labelling;
- Recognising PKU as a lifelong condition requiring a lifelong approach;
- Raising greater awareness of the neurological and mental health implications of living with PKU;
- Facilitating access to all future innovative therapeutic solutions.

Eric Lange concluded by thanking the 12 MEPs who have already formally joined the Alliance as "PKU champions" as well as all those who accepted to express their support to the meeting. Clearly, the Alliance has made a good start and ESPKU is looking forward to working with all EU institutions to ensure that unmet needs in PKU are better addressed across Europe.

The next speaker, **Prof. François Maillot (Centre Hospitalier Régional Universitaire (CHRU), Tours, France)** first remarked that PKU can be seen as one of the genuine success stories of the 20th century, and provided an overview of historical achievements over the years – from the discovery of the condition to the development of dietary therapy, generalized new-born screening practices and, most recently, progress in the search for new therapies, all of which have enabled children affected by PKU to increasingly grow up and develop normally. However, Prof. Maillot also underlined that a number of unmet needs still remain to this day.
For instance, there are gaps in good practice in relation to PKU treatment. While European guidelines for PKU diagnosis and treatment have been developed[1]– following the example of the U.S. – support is needed to ensure that these guidelines are adopted in every EU country. As it stands, a 2019 survey covering 22 European metabolic centres in 12 countries found that only 10 of them follow the EU guidelines, with 6 following national guidelines only and 1 following U.S. guidelines.
The guidelines are currently being updated as some new questions have come forward, such as whether all immigrants to Europe should be screened for missed PKU diagnosis, or questions relating to the current status of new-born screening for PKU in Europe. Prof. Maillot announced that the revised guidelines should be published in 2022.
Another unmet need relates to the neurological and mental health impact of PKU, which can be severe, particularly with regard to brain growth and development. Metabolic control during the first 12 years of life is crucial. There is a need to ensure adherence to good practice as stipulated by the guidelines, which state that 'treatment should be started as soon as possible, ideally 'before 10 days of age'.
A further issue relates to the need to address PKU as a lifelong disorder. Currently, in most EU countries, there are major issues in transitioning from paediatric to adult clinics, and in many cases, there are few or simply no specialized adult clinics at all. This means that, all too often, PKU support and accompaniment come to a halt when a person reaches the age of 18. Prof. Maillot argued that it is imperative to follow these adults throughout their lives, in particular because of the wide range of co-morbidities to which they could be exposed (neurological and psychiatric conditions, osteoporosis, obesity, heart disease, etc.) and to design and implement new solutions for more adequate transition regimes.
Similar gaps can be observed across the EU in relation to access to innovation. While new therapeutic options continue to be developed and approved by regulatory authorities, better and more consistent access across EU Member States would be desirable.

Prof. Maillot concluded by offering a "deep dive" perspective on the situation in relation to PKU in France. Overall, the country offers today a good level of coverage by specialized centres. A 3rd national rare disease programme is ongoing (2018-2022), funded by the French Government. In terms of care, PKU patients are followed by competence/reference centres; and a specific centralized system for prescription and delivery of protein-free medical food and amino-acids supplements is in place, which is integrally covered by the national health insurance system.

[1] https://doi.org/10.1186/s13023-017-0685-2

With regard to research, a national group for basic and clinical research on PKU has been set up, supported by French patient association 'Les Feux Follets'[2]. A national cohort study (ECOPHEN)[3] is currently being carried out, involving a 5-year follow up of 187 adults with PKU.

The next speaker, **Manuela Stecher (DIG PKU),** shared her personal story and daily experience with living with PKU. Ms Stecher, now 50 years of age, was the very first person diagnosed with PKU in Germany after the introduction of new-born screening in the country.
Manuela is allowed a maximum of 5 grams of protein per day. Adhering to this strict diet requires a lot of discipline, and a great deal of preparation and checking. Not only is the diet time-consuming – it also turns out to be a permanent source of pressure and stress. About 85% of all foods is off-limits for her, and there is no holiday from the diet for the rest of her life. In addition, with this diet, it is difficult to have a normal social life.

Ms Stecher underlined the lifelong nature of PKU, which she characterised as an invisible disease – something which makes it more complicated and difficult to raise awareness of the impact of the condition.
New-born screening is essential to avoid any form of mental retardation as, if left unmanaged, PKU can lead to profound and irreversible intellectual and physical disability.
In Ms Stecher's own experience, elevated 'Phe' levels are known to cause headaches, irritability, lack of drive, lack of energy, fatigue, anxiety, concentration problems, depressive moods – in other words: elevated 'Phe' levels endanger the mental health of the affected individuals. And, while essential, finding a balance between good dietary management and quality of life remains a daily struggle.

In support of Prof. Maillot's observations, Ms Stecher noted that in Germany there is unfortunately not enough capacity nor specialised knowledge for the care of adult patients: even as an adult, still today, she continues to have to go to a children's hospital to seek medical advice and treatment. The scope for metabolic support has changed over her lifetime: as a child, a lot of support was at hand, but as an adult Ms Stecher confessed to feeling often forgotten. PKU support groups such as DIG PKU in Germany and ESPKU at the European level have stepped up to the task and increasingly offer support to members of the community, helping create many friendships with other fellow individuals affected by PKU in Europe and worldwide.

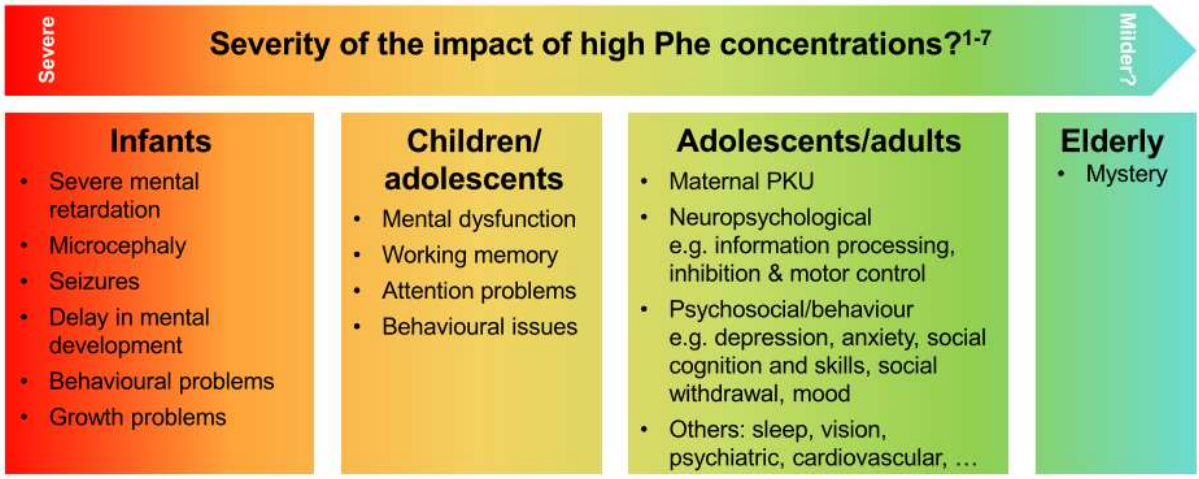
Another profound uncertainty discussed by Ms Stecher relates to questions about what her life will be like in old age. How can a successful transition into old age take place if even the transition from child to adulthood has not been successful? She also voiced questions with respect to the long-term health impact of the strict PKU diet and any possible effects on the mental health of an elderly patient – many questions which remain to this day without clear answers nor a sufficient evidence base.

In her closing remarks, Ms Stecher underlined that, however successful the dietary treatment of PKU has been to this day, it should not obscure the fact that this metabolic disorder still represents a daunting challenge for affected individuals. She expressed her hope that, in the future, acceptance of the PKU diet as a medically required nutritional therapy will be a given, and that PKU will be recognised for good as a life-long condition with a series of strong mental health impacts.

Joining the meeting, **Barry Andrews MEP** took over the chair, stating his interest in learning more about PKU – a new area for him, but one that reminds him of his earlier work in and commitment to rare diseases like cystic fibrosis, and with many parallels and similar needs and issues.
He welcomed the experience, expertise and knowledge represented by speakers and participants and was particularly struck by the issues related to the (lack of) transition regimes from childhood to adult care and the life-long nature of the condition.

He then handed over to **Prof. Alvaro Hermida Ameijeiras** (Unidad de Diagnóstico y Tratamiento de Enfermedades Metabólicas, Santiago de Compostela, Spain), who spoke about the need for a life-long approach to the complexities of PKU, best illustrated by the slide below which describes the currently documented impacts of elevated Phe concentrations at the various stages of life – while impacts are well known to be at their most severe in childhood and teen years, they are no less significant in adults and, much to Prof. Hermida's concern, they are very probably present but to a large extent unknown or ignored in the elderly.

[2] www.phenylcetonurie.org
[3] https://clinicaltrials.gov/ct2/show/NCT01619722?term=maillot&cond=PKU&cntry=FR&draw=2&rank=2

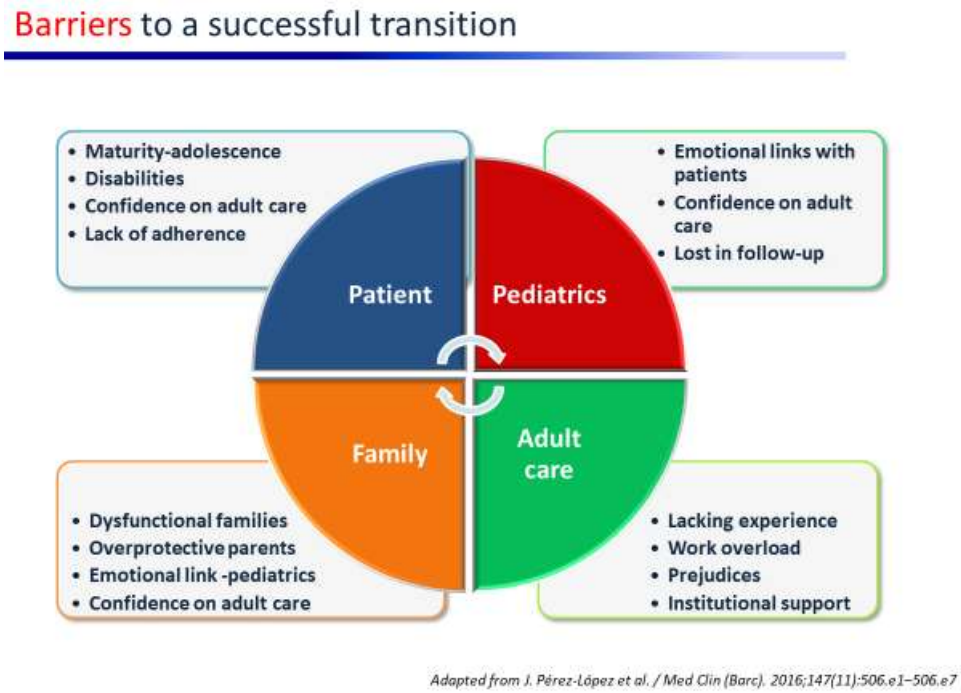


Source: Dr Francjan van Spronsen, SSIEM 2019, Rotterdam

While new-born screening policy frameworks are in place in most countries, variations exist on a massive scale in terms of the number of conditions actually screened or of the time intervals for screening. He noted that, when the screening result is delivered too late for certain reasons, an infant is put at risk of suffering clinically or even dying – which diminishes just as much the value and impact of screening itself.

Prof. Hermida also showed a variety of recent research findings showing the clear links between PKU and intellectual disability, ADHD, mental health (depression), brain atrophy, neurocognitive functioning and brain vulnerability. Physical co-morbidities are also frequent and above the average in the general population, e.g. osteoporosis, high blood pressure, overweight, asthma, chronic ischemic heart disease, etc. Finally, in terms of socio-demographic impact, it is now established as fact that people affected by PKU are more often unmarried and have fewer children than those not affected by the condition.

Prof Hermida also provided his own perspective on the issue of transition. Recent research has found that non-adherence to clinically recommended Phe concentration levels increased with age, helping to pinpoint the start of the process of non-adherence at somewhere between 13 and 17 years of age – the age of transition from child to adult care. Moreover, the proportion of total patients considered as "lost to follow-up" tends to increase with age.



Turning his attention to low-protein diets, Prof. Hermida noted that a number of psychological factors influence disease perception and adherence to diet in adult PKU patients. In addition to the intrinsic characteristics of amino-acid formulas (e.g. palatability, ease of preparation and use), the most important factor influencing consumption was the increased social pressure (55%).

In addition, whereas amino-acid formulas are generally reimbursed by health systems, other low-protein foods are not, which has the practical consequence that some patients will not necessarily be able to have access to or to procure these foods.
Further therapeutic innovation and new treatments can help and ease the burden of patients. Prof. Hermida underlined that new therapies are needed insofar as they could help address the persisting issues of non-adherence, nutrient imbalances caused by strict low-protein diets, or still problems with diets during pregnancy.

He called on governments and public bodies, payers, clinicians, and industry partners to consider even more patient input when developing and approving new therapies and treatments for PKU – hence giving PKU patients the possibility to indicate what matters most to them, e.g. increasing their protein intake without worsening their symptoms, or the ability to eat any foods they choose regardless of their protein content.

Prof. Hermida concluded that the difficulty in managing PKU increases with age and that management of PKU continues to vary across Europe, with the consequence that some European patients are not always receiving the optimal care to which they should be entitled. Reimbursement issues across countries also play a role in this, as they mean that not all treatment options are available everywhere.

<u>Policymakers' Responses</u>

Antoni Montserrat (European Commission, DG Santé) took the floor and outlined some of the overarching Commission's achievements in the area of rare diseases. The framework for a policy on rare diseases was put in place by the 2008 Communication on Rare Diseases and by the 2009 Council Recommendation on an Action in the Field of Rare Diseases. Thanks to these two foundational initiatives, some meaningful progress has been achieved, e.g. the establishment in 2017 of 24 European Reference Networks (ERNs) including one specialised on rare metabolic disorders, MetabERN[4], which also addresses PKU. The ERNs, which bring together 943 clinical units (plus another 247 associated clinical units) across Europe are based on the idea that it is the knowledge rather than the patients that should travel. Sharing knowledge about rare disorders, including PKU, is key to ensuring progress and good practice sharing.

A second positive development is the fact that cooperation with respect to rare disease registries now exists. The creation of a European Platform on Rare Disease Registration[5], located in the Commission's Joint Research Centre in Ispra, Italy now enables the 753 different rare diseases registries currently in place across Europe (managed by academic and pharmaceutical stakeholders, patient organisations, etc) to work together more seamlessly for the first time ever. In this respect, Mr Montserrat remarked that it could be an aim for ESPKU and the Alliance to push for the establishment of a unified European registry for PKU under this European Platform, something which would help share and disseminate knowledge of the condition even further.

The recent revision of the International Classification of Diseases is another achievement. In the former version, ICD 10, only 559 out of the 6172 rare diseases documented in the Orphanet database had a specific ICD code attributed to them. Mr Montserrat noted that, if a condition does not have an ICD code, the consequence is that it simply does not exist for certain health systems and in the eyes of certain government bodies and agencies. The new classification, ICD 11, which will come into force in most Member States as of 2022, grants a specific code to <u>all</u> different forms of metabolic disorders, incl. PKU, and represents a step forward towards better public recognition of the condition.

Both the 2008 Commission Communication and the 2009 Council Recommendation state that the Commission "should adopt a framework on new-born screening". Unfortunately, this has not happened to date. A detailed report, published in 2012, found that only 6 of the 26 Member States supported the idea of a European framework on new-born screening. This opposition was mainly related to putting in place European guidelines to supersede national ones. In 2018, the exercise was conducted again and, compared to 2012, a certain improvement and progress in screening practices could be observed. However, Member States do continue to appear reluctant to agree on a minimum list of rare conditions to be screened as they feel this should be decided at the national – or even at the regional – level. Even within a single Member State, as in the case of Spain or Italy, the regions that constitute these countries (17 and 20 respectively)do not agree on the diseases to be screened.

If finding scientific and political consensus between Member States in relation to a European new-born screening framework has proved difficult, there is encouraging news. The new EU Health Commissioner, Ms Stella Kyriakides from Cyprus, introduced cancer as the overarching health priority of the new European

[4] https://metab.ern-net.eu/

[5] https://eu-rd-platform.jrc.ec.europa.eu/_en

Commission in a speech delivered on Rare Disease Day 2020. This means that the concept of screening in general is now appearing in the Commission's communications and in the debates in which Ms Kyriakides is taking part. Where the former Commission up to 2019 seemed rather reluctant to compel Member States to address screening practices, the new Commission may be more open to working from the notion that screening for all diseases is useful. It remains to be confirmed, but this new stance may create an opening for advocacy and for the re-introduction of the issue into the public conversation. And this is one thing that could be effectively done via the European Parliament – and, even more specifically, via the Alliance.

Mr Montserrat also advised that having "friends" at the level of the Council – e.g. having the formal support from future EU Presidencies [6]– would also be helpful, especially if one or more of these Presidencies could in their Conclusions refer to the need for better screening of rare diseases (to be enabled via European policy initiatives such as the Horizon Europe Programme, the new Social Fund+, or still the Multi-Annual Financial Framework).
Mr Montserrat added a word of caution, however, to note that a focus on PKU only could be perceived as too limited – in this respect, expanding the scope to screening in general could have better chances of success. A last idea could be to focus on consumer policy rather than on health policy, e.g. when it comes to issues such as food labelling.

Open Floor Debate

In the last part of the roundtable, all participants were invited to comment and take part freely in the conversation.

The **European Brain Council**[7] (represented by Vinciane Quoidbach) shared an update on its "Value of Treatment" campaign, the aims of which are to take a comprehensive look at the various points and milestones along the patient pathway in a variety of brain disorders, in order to analyse and substantiate the positive impacts on health outcomes of providing patients with the best possible therapeutic interventions available today. Ms Quoidbach noted that this campaign now also includes a project dedicated to PKU, to which several roundtable participants have been contributing already, and that this project is currently on track to be finalised by the end of 2020.

Eurocarers, the European network representing informal carers and their organisations (represented by Nadia Kamel) underlined the important role of informal carers in the provision of care, and the need to involve carers more strongly in the care coordination; this will help address the specific barriers in PKU management such as the transition from childhood to adult age.

The crucial need for availability of and access to new-born screening was underlined again by Laura Petreus and Mihaela Talos from the **Romanian Association of PKU Patients - Aproetica**, voiced their opinion that screening should be viewed as a human right.

Prof. Anita MacDonald (Birmingham Children's Hospital, Honorary Professor in Dietetics at Plymouth University, UK) remarked that the need for better labelling of protein in foods is another important matter as current labelling can be misleading and put PKU patients' health at risk.

Prof. François Maillot summarised his perception that, from the entire conversation at the roundtable, access seems to be the key word and the main "stumbling block" – access to screening, access to low-protein foods, access to care, or still access to innovative treatments.

Closing the roundtable, Eric Lange (President, ESPKU) thanked all participants for their time and active contributions and announced on a forward-looking note that the next meeting of the Alliance would tentatively take place in the vicinity of International PKU Day (i.e. late June, exact date to be confirmed shortly).

[6] 2020: Croatia, Germany 2021: Portugal, Slovenia 2022: France, Czech Republic

[7] www.braincouncil.eu