ADDRESSING THE HIGH BURDEN AND SIGNIFICANT UNMET NEEDS IN PHENYLKETONURIA (PKU)

WEDNESDAY 11 JULY 2018

POLICY ROUNDTABLE AT THE EUROPEAN PARLIAMENT, BRUSSELS

Meeting Report

This Policy Roundtable, organised by the European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU), was hosted by MEPs Deirdre Clune (Ireland, EPP) and Nessa Childers (Ireland, S&D).

EXECUTIVE SUMMARY

Objectives

- to have an informed discussion on phenylketonuria (PKU) and its impact;
- to support understanding of the true nature of the condition;
- to identify the unmet needs in the area of PKU;
- to gather expert opinions on what can still be done to advance the interests of people living with PKU;
- to generate political momentum.

Potential areas of action, arising from the meeting

- The need to ensure new born screening across the EU (setting up and actual implementation) bearing in mind existing initiatives in this field (seeking further advice from Commission officials);
- The need to ensure EU food labelling laws are adapted and appropriate; labels should provide clear and complete information;
- The need to ensure appropriate HTA criteria and appropriate end points
- More attention to the process of transition of care between child and adult care and access to services;
- Ensure dissemination and implementation of PKU treatment guidelines (via MetabERN);
- The possibility of a MetabERN-coordinated ´twinning' project where advanced countries work with less advanced countries to train and learn to put appropriate measures in place e.g. newborn screening.

Roundtable Discussion

Deirdre Clune MEP opened the meeting, underlining her interest in PKU as a condition that merits more attention. According to Ms. Clune, the most striking feature of the condition is its multi-faceted, complex and lifelong nature, with so many consequences for day-to-day living.

Technically, it is a metabolic condition, but PKU can have a lasting impact on all other areas of health and daily living, including neurocognitive, emotional and behavioural aspects. It affects all dimensions of an individual's life and this impact needs to be better recognised, acknowledged and treated.

Ms. Clune then briefly underlined the aims of the meeting. She also warmly invited all participants to have their photograph taken while holding a placard with a supportive message relating to PKU at the end of the meeting.

Nessa Childers MEP also congratulated ESPKU for taking the initiative to put the spotlight on PKU. Meetings such as these can really be helpful to create more visibility and to generate action, both by stakeholders as well as by policymakers. Ms. Childers reminded participants that, throughout her career, she devoted much time and energy to mental health and brain-related disorders, offering support to patients, health professionals and other stakeholders. She also stated that, as a psychotherapist by training, it has always struck her that so many conditions which are not generally presented as brain disorders also turn out to be related to neurocognitive and behavioural aspects – and that these aspects also need to be addressed if patient outcomes and quality of life are to be improved.

She then gave the floor to **Eric Lange (President, ESPKU)** who warmly thanked both MEPs for their willingness and support to host the event, and proceeded to briefly introduce PKU and its impact. He described PKU as an inborn error of metabolism, where the enzyme PAH (phenylalanine hydroxylase) is not working properly or at all, and the amino acid phenylalanine ('Phe') cannot be broken down. When not broken down, blood phenylalanine levels can be toxic. This toxicity gets into the brain and hinders brain growth, which in turn results in low IQ outcomes, impaired executive functioning and mental retardation.

The treatment of the condition has traditionally consisted of an artificial diet, where protein intake is highly restricted. Affected individuals cannot eat meat, fish or dairy products. The widespread use of aspartame in soft drinks (as a consequence of the introduction of sugar taxes) is also a problem. There are pharmacological therapies available as well; however, while

these have already benefitted many of those affected by PKU, further innovation would be desirable.

He stressed that while there are many remaining gaps in care, the most important one in his view relates to newborn screening. In today's Western world, newborns are generally screened for PKU. However, across Europe, gaps in this practice can still be observed, despite the fact that policies and measures have been put in place. Therefore, Mr. Lange called for 'audits' at the national level to ensure that every baby born in Europe is actually screened for PKU and that every hospital has robust screening programmes in place.

Deirdre Clune MEP then gave the floor to **Prof. Francjan van Spronsen (Groningen University, Netherlands)** who underlined the fact that successful treatment for PKU has existed for over 65 years, consisting mainly of early screening and an adapted diet, and that it has contributed considerably to a better management of the condition in affected individuals.

A person affected by PKU is allowed minimal amounts of natural protein per day – some 5 grams, i.e. the equivalent of less than one glass of milk. Normal nutrition is not possible. Individuals affected by PKU generally have lower IQs, problems with normal brain functioning, and they may also appear a little different from those not affected by the condition. However, it should be possible to better treat PKU to ensure that those affected can lead normal lives. Pharmacological treatments exist, which do not benefit yet 100% of patients. But it is good news that new treatments are being researched and developed.

Prof. van Spronsen then turned to the PKU treatment guidelines, which were developed some years ago. It was a major journey to move from national to European guidelines. However, some countries are still not implementing these as it is sometimes felt that national guidelines suffice. Quite obviously, however, European guidelines have the power to be much more effective by ensuring similarity and consistency in practices and in outcomes across countries. Unfortunately, there is today no dedicated body or institution that can harbour guidelines once they have been developed and adopted by the community concerned. This is something the European Parliament and Commission could take up as they have also been behind the development of new initiatives and actions plans in support of rare diseases and, most recently, of the European Reference Networks (ERNs). MetabERN, the European Reference Network dedicated to rare metabolic disorders, could possibly play a role in this situation and help ensure that the debate around European vs national guidelines moves towards a positive solution. Clearly, it is better to work together and to strive towards the same goals, than to work alone.

Nessa Childers MEP then gave the floor to **Prof. Anita MacDonald (Birmingham Children's Hospital, Honorary Professor in Dietetics at Plymouth University, UK)** who underlined that 80 % of children affected by PKU can only tolerate less than 10 grams of protein per day – about the amount of protein in one glass of milk. In PKU, whole proteins cannot be metabolised, so they are replaced by Phe-free L-amino acid supplements (cups containing this supplement where distributed to participants). Low protein foods such as bread and pasta are allowed.

At the EU level, several initiatives have been taken in relation to foods for medical purposes. In 2017, the European Commission issued a Notice on the classification of Foods for Special Medical Purposes (FSMPs), i.e. foods that are 'specially processed or formulated', under medical supervision, for individuals with an inability to metabolise specific nutrients. In 2015, the European Food Safety Authority (EFSA)'s Panel on Dietetic Products, Nutrition and Allergies recommended an information file for each FSMP. EU legislation influences the nutritional composition of FSMPs. However, these laws only go so far; there is a lack of harmonised guidance on protein substitutes, in terms of protein and amino acid profile, of age-specific guidelines, of the upper Phe amount permitted and of the definition of efficacy. The same lack of guidance applies to low-protein special foods, in relation to upper Phe content and energy, fat and carbohydrate composition. In addition, food business operators have too much autonomy when designing the nutritional composition of FSMPs for PKU.

Another issue relates to the fact that protein food labelling is not a priority. The EU regulates for gluten, allergens, lactose, weight control foods, infant formula and baby food but not for people on low-protein diets. Food protein labelling is often misleading and should ensure accurate protein content identification. Prof. MacDonald provided several examples of the misleading nature of food labelling which can lead to poor metabolic control in PKU patients, and noted this as an issue to address as a matter of urgency.

Another problem relates to non-EU foods. The EU is the world's largest multi-nation trading bloc. There are many US food products on the market but harmonisation of protein labelling does not always occur, particularly with regard to protein content, whilst non-EU foods should comply with EU protein labelling rules.

Prof. MacDonald also focused on the specific case of aspartame. Sugar taxes apply in an increasing number of countries and this is leading to a higher use of aspartame in drinks. As aspartame contains Phe, all manufacturers should declare the amount of Phe in aspartame-containing foods/drinks. Its presence should also be emphasised in bold on food labels. In addition, there should be clear identification of aspartame in commercial outlets and vending machines. In conclusion, Prof. MacDonald underlined her take-home messages, i.e. the need to harmonise the nutritional composition of FSMPs for PKU, to improve protein labelling and to conduct more work on aspartame labelling.

Nessa Childers MEP then announced **Agata Bak (Spanish Federation of Hereditary Metabolic Disorders-FEEMH, Spain)** who talked about her personal experience with PKU. Agata Bak is only allowed 7 grams of protein a day and does not eat meat, fish, cereals, or dairy products. Her diet mainly consists of vegetables, fruit and low-protein products. Agata Bak underlined that PKU patients could consider themselves lucky: a diagnosis can be obtained, and diets help stop symptoms from appearing. Patients can pursue our life goals and have a reasonable quality of life. However, this is not the full story.

Yes, a diet can be followed – but it is not easy. Not all patients have access to low-protein foods. Adherence to treatment can be a health problem as such: some patients spend 19 hours per week or more to manage their diet. Some people in Spain need to drive for 2 hours to get the low-protein foods they need. Parents often give up their jobs to attend to the needs of their children affected by PKU.

There are choices to make: do you stick rigorously to the diet, or can you be slightly more relaxed? Giving up on the diet causes mental health problems, like depression and other disorders which make it more difficult to come back on treatment. With respect to the neurodegenerative aspects, even if there are pharmacological treatments, we do not know the consequences in the longer term. Psychological support is required but sadly, often lacking.

In short, living with PKU is an everyday struggle. Some aspects may seem small, but they count for patients, such as the smell of the Phe-free L-amino acid supplements. And in schools, how to deal with the food in the canteen, school outings and holidays? Ms. Bak underlined her concerns about the future and stated that, while PKU patients are lucky in some ways, unmet needs remain. A holistic approach, comprising physical as well as psychological elements, is required to better address and manage the condition.

Panel Response

The first panellist was **Prof. Serap Sivri (Hacettepe University, Turkey)** who stated that PKU is the one of the most prevalent inherited metabolic diseases in Turkey. This includes a high number of late-diagnosed cases, probably due to the relatively recent availability of screening and treatment. Newborn screening started as a pilot in 1983 and, today, a full screening programme (up to 97,5% coverage) is in place. The estimated prevalence of PKU is 17/100,000, with an estimated prevalence of PAH deficiency around 73/100,000.

Almost all individuals with untreated classical PKU experience severe intellectual disability. Mental retardation and neurological findings (e.g. autistic features, microcephaly, tremor and motor delay) are common. Considering the detrimental effect of high blood Phe levels on brain

development and function, strategies to lower Phe levels should be initiated as early as possible and maintained throughout life.

Although the goal is to maintain blood Phe levels as close as possible to the target range, the threshold above which Phe levels in the blood become neurotoxic is currently not well defined. Prof. Sivri shared the findings of a recent study (currently being peer-reviewed) addressing the real picture for milder cases of PKU. This involved 41 children between 6 and 16 years of age with untreated mild HPA. It was found that the mean IQ scores of those affected by PKU are significantly lower than for the non-PKU control group. These children showed difficulties relating to attention and learning processes as well as relating to executive functioning.
They also seem to have more difficulties in learning and attention than healthy controls. Children with higher blood Phe have more attention problems than children with lower levels. Healthy children were more successful in performing cognitive tests and mental scales.

The second panellist, **Antoni Montserrat Moliner (European Commission, DG Santé)** reminded participants that a European framework for newborn screening is currently not in place. However, both the 2008 Communication and the 2009 Council Recommendation on Rare Diseases state that the Commission should adopt a framework on newborn screening.

While most of the other points contained in these documents have met with implementation and success, this is not the case as far as newborn screening is concerned. A call for tender, with the purpose of analysing the situation across all Member States, was issued in 2012. As a result, a detailed report was prepared and then discussed at the European Union Committee of Experts on Rare Diseases (EUCERD). It was found that only 6 of the 26 Member States at that time did support the idea of a European framework on newborn screening, whereas the 20 others did not. This rejection was mainly grounded in a resistance to putting in place European guidelines as opposed to national ones.

Turning to current options at the EU level today to ensure more consistent newborn screening across the EU, Mr. Montserrat listed a number of relevant developments and opportunities, all of which ESPKU should be looking at:

- While EUCERD has ceased to exist, the Commission has put in place a new structure, the Steering Group on Health Promotion and Prevention. This now acts as the main public health committee of the EU and one of its explicit missions is rare diseases. As prevention is currently one of the Commission's main priorities, the debate on newborn screening is highly relevant.

- EUnetHTA is another important agent in this discussion as there are political discussions towards putting in place a framework for carrying out Europe-wide HTAs. However, it needs to be borne in mind that the Commission is not in a position to oblige Member States to put in place guidelines impacting on the delivery of healthcare services nationally.

- New and important agents for change are the European Reference Networks (ERNs), specifically the ERN on rare metabolic diseases, MetabERN. The possibilities of this European network should be carefully looked at.

The third panellist, **Enrique Terol (European Commission, DG Santé)** reminded participants of the prevailing concept of "subsidiarity" in the field of health, i.e. that healthcare systems remain first and foremost the competence of the Member States. While there are some aspects in relation to health that can be regulated (e.g. blood, tissues and organs safety issues, medicaments and medical devices or communicable disorders), all aspects relating to the development and implementation of healthcare services and healthcare delivery remain beyond the remit of the European Commission.

The only relevant piece of legislation addressing healthcare is the 2011 EU Cross-Border Healthcare Directive, which governs the rights of patients to receive care outside of their home country. This includes a chapter on cooperation and refers to the ERNs, eHealth and a European HTA framework. The ERNs are predominantly a voluntary exercise; however, a number of rules do apply. The ERNs function in a top-down as well as in a bottom-up way. They focus on disseminating best practices, and function as networks that help generate knowledge and advice. ERNs are not only about training and guidelines; they take a holistic approach to foster a new model of healthcare system cooperation between Member States. PKU can be part of this cooperation in complex cases when Member States lack the relevant knowledge. In that regard, MetabERN is addressing a broad range of rare and complex metabolic disorders, and is equipped as a large network of more than 60 centres to share and support real-world evidence development and to address new research questions.

Mr. Terol indicated being aware of the PKU guidelines as developed by the PKU community, and commended the authors for their excellent work. However, there is to this day no EU agency in a position or with the authority to endorse these guidelines and actively support their implementation. The ERNs provide a common framework and common methodology on how to generate and identify the evidence which would be more difficult to gather without the ERNs.

MetabERN could well be in a position to develop or endorse guidelines that can be used by all of us. These guidelines should also be recognised as the gold standard and should be seen as

'bottom up'. If the Member States keep being supportive and approving of the ERNs, this could create an opening to more easily accept and enforce at the national level guidelines developed or approved by the ERNs. This is an approach which could be explored.

The final panellist, **Kate Hall (International Society for Neonatal Screening)** told the audience about a recent visit to Romania. She expressed her shock upon meeting young PKU patients born in the 21st century who are brain damaged due to late diagnosis of their disorder.

Due to the slow, patchy introduction of newborn screening for PKU in countries like Romania, many individuals remain who have never been screened as newborns. For many institutionalised patients, being able to access a PKU diet could help with reduction in drug treatment and numbers of staff needed to look after these individuals, hence generating a cost saving to society which needs to be quantified. Ms. Hall also pointed out serious deficiencies in the number of paediatricians trained in inborn errors of metabolism, as well as the fact that there are currently no expert clinicians from Romania on board MetabERN. A similar lack of paediatric dietitians and more broadly of dietetic training for healthcare professionals in the country has also been noted. Dietitians are for the most part private practitioners in Romania and often most parents cannot afford to consult them
There is a significant financial loss to the economy of any nation when young people are brain-damaged and unable to work.

Outside Romania, newborn screening for PKU is unavailable in several countries in Europe (e.g. Montenegro, Albania and Azerbaijan). It has been introduced slowly and imperfectly in other countries like Romania. There are also many individuals born before the dates at which newborn screening was introduced, and those may be identified late, if at all – thus missing the opportunity to receive treatment.

Absence of timely "safety checks" for babies who may have missed newborn screening appears to be fairly prevalent in South-eastern Europe, where lists of babies screened vs those of babies born may be compared annually (which is already too late) and often without any concrete follow-up to identify the omitted babies and to take corrective action. In some countries, no cross-checks are even performed. The opportunity to correct this exists in Romania, by improving the use of the Medilog birth recording software available in all maternity homes, which all 5 screening laboratories in the country have access to.

Printed information leaflets for prospective parents are not available in some countries such as Romania, and parents are therefore not empowered to check whether their baby has been offered newborn screening or whether the test result is available. This is another opportunity.

Ms. Hall ended her comments with a question, i.e. to know whether it would be possible for European experts to assist with training Romanian staff (both medical and dietetic) on PKU?

Audience Debate

In the debate that followed, a number of participants took the floor:

Prof. Maurizio Scarpa (Coordinator, European Reference Network for Hereditary Metabolic Diseases, MetabERN) welcomed the Roundtable as it will help raise awareness. MetabERN is a natural European counterpart and partner for PKU patients' organisations. MetabERN involves today around 69 hospitals and 1,700 health care professionals in 18 EU countries. It is following 43,000 patients of which about 5,000 are affected by PKU. Much information is currently being generated and there is a true PKU community within the ERN. Furthermore, as conditions should never be comprehended in silos, MetabERN strives to collaborate with other ERNs too (e.g. in the area of rare neurological disorders).

MetabERN should be seen as the first real example of critical mass, consisting of a network of European centres of excellence which, in collaboration with patient organisations, are devoted to finding the best way to diagnose, treat and manage patients with rare diseases. MetabERN aims to have a tangible impact on all aspects concerning rare metabolic diseases, and Prof. Scarpa deemed newborn screening a major issue indeed.

Prof. Scarpa emphasised the need for cooperation and sustainability, as well as the need for all European countries to be represented in the ERNs. This is not currently the case – for instance, Romania is not part of MetabERN, while Poland is there but only with a small hospital. He urged ESPKU and its organisations to collaborate closely with MetabERN and encourage more healthcare professionals and hospitals to get involved. He also announced his willingness to start a close collaboration with ESPKU in order to ensure unmet needs are met.

Vinciane Quoidbach (European Brain Council) briefly introduced her organisation's "Value of Treatment" (VoT) campaign[1], which addresses unmet needs in relation to a variety of brain disorders (9 of which were covered in the first phase of the campaign) and how to measure them. The project is a useful example of comprehensive outcomes research, taking both the

[1] http://www.braincouncil.eu/activities/projects/the-value-of-treatment

patients' as well as clinician's perspective, looking at existing guidelines and the impact of the conditions under study on society. Solutions to better address these conditions are also proposed. The second stage of the VoT campaign is about to take off, and PKU is one of the conditions that could be addressed as there are effective interventions. The impact of early screening on the prevention of brain damage, and a forward-looking consideration of new therapeutic options under development could both be interesting avenues to explore.

Representing the Romanian National Association of PKU Patients (Asociația Aproteica) **President Minodora-Laura Petreuș and Vice President Ion Marinel Petreuș** briefly described the situation with respect to PKU in their country. They pointed out the difficulties with the implementation of the Ministry of Health's national programme, mainly due to underfunding. Funds allocated to diagnosis, dietary treatment and monitoring Phe blood levels are insufficient. Multi-disciplinary teams are incomplete, as dietitians are often lacking. Every year, 30,000 newborns are not properly screened in Romania.

Ms. Petreus – a mother of two PKU children which were also not screened at birth – informed the audience about a national charter signed by many people, and which the association is planning to submit to the Ministry of Health, asking to make newborn screening a standard procedure across all Romanian maternity hospitals in order to prevent the neuro-psycho-motor retardation associated with a late diagnosis of PKU.

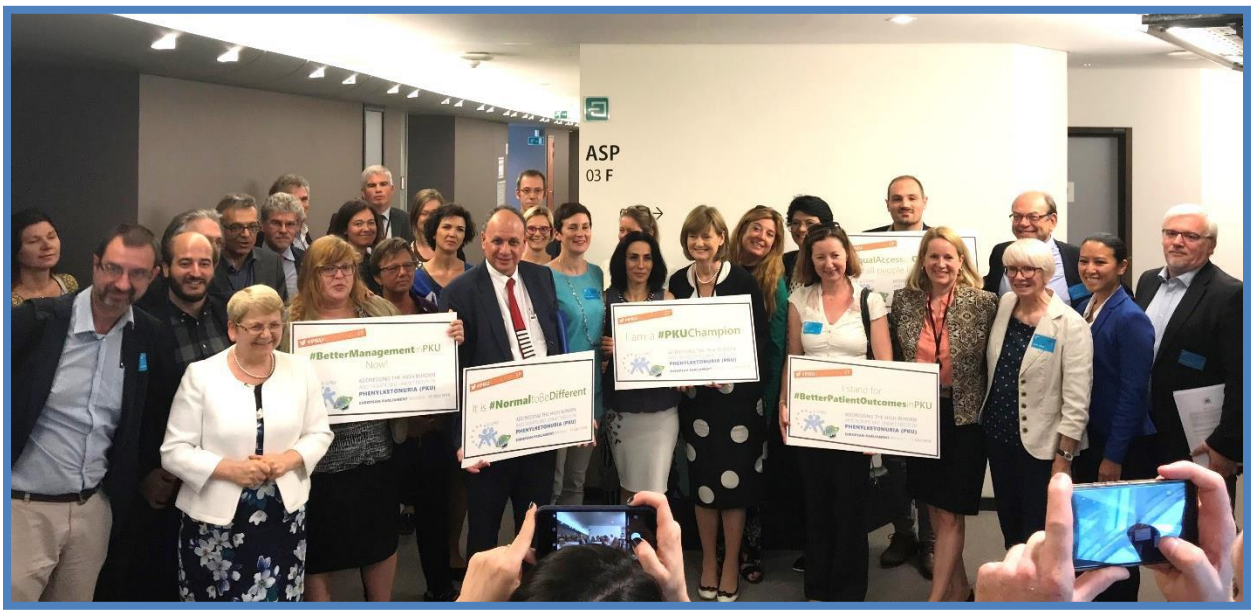
For reference, a few other issues were raised, e.g.:

- While newborn screening may be seen as an investment, it also saves money in the longer term. A robust cost/benefit analysis on newborn screening of PKU should be carried out, taking into account all aspects, including healthcare outcomes and related costs, but also psychological and economic impacts.
- The need to adopt a patient-centred and holistic approach was underlined.
- MetabERN is setting up 'twinning programmes' whereby advanced countries can partner and work with less advanced countries to train local healthcare professionals and equip them to put appropriate measures in place, e.g. in relation to newborn screening. Romania could be a candidate, according to Prof. Scarpa.
- Transition from child to adult care services is a major issue in PKU as it is still today mainly seen as a children's condition.

Concluding Comments

Eric Lange thanked the MEPs, speakers and participants for their contributions and stated that the meeting had well lived up to what it intended to do, i.e. generate concrete proposals for action and collaboration. He invited all participants to the upcoming ESPKU Annual Conference in Italy in November.[2]

Nessa Childers MEP closed the meeting, again underlining her interest in PKU and the need to raise the profile of the condition more broadly. The patients are the ones heard best by policymakers and are in a good position to do so, also by means of social media.



The organisation of this policy roundtable was facilitated by the kind support of BioMarin.

[2] https://www.espku.org/conferences/e-s-pku-conference-2018/

Appendix: Participants List

	Name	Organisation
1.	**Ahring** Kirsten	PKU Clinic, Kennedy Centre, Copenhagen University Hospital, Denmark
2.	**Bak** Agata	Spanish Federation of Hereditary Metabolic Disorders (FEEMH)
3.	**Bihet** Genevieve	Centre Hospitalier Chrétien, Liège
4.	**Boselli** Simone	EURORDIS-Rare Diseases Europe
5.	**Childers** Nessa	MEP
6.	**Clune** Deirdre	MEP
7.	**Costantino** Niko	Cometa ASMME
8.	**Corthouts** Karen	UZ Leuven, Belgium
9.	**De Baere** Lut	Belgian Organisation for Children and Adults with a Metabolic Disorder (BOKS vzw) & MetabERN
10.	**De Meyer** An	UZ Antwerpen, Belgium
11.	**Destrébecq** Fred	European Brain Council
12.	**Donohue** Adrian	BioMarin
13.	**Feillet** Francois	Centre de Référence des Maladies Métaboliques de Nancy, France
14.	**Fresu** Mari	European Psychiatric Association
15.	**Gilroy** Bernadette	PKU Association of Ireland
16.	**Greenop** Kit	RPP Group

17.	**Hall** Kate	International Society for Neonatal Screening
18.	**Hoogland** Emilie	Assistant to Lieve Wierinck MEP
19.	**Jahja** Rianne	UMC Utrecht, The Netherlands
20.	**Ketels** Hilde	Belgian Organisation for Children and Adults with a Metabolic Disorder (BOKS vzw)
21.	**Kool** Ulrike	European Psychiatric Association
22.	**Lange** Eric	ESPKU
23.	**Lalin** Loic	Association Les Feux Follets, France
24.	**Lowell** Kathryn	BioMarin
25.	**MacDonald** Anita	Birmingham Children's Hospital & Plymouth University, United Kingdom
26.	**Maillot** Francois	Centre Hospitalier Régional Universitaire (CHRU) de Tours, France
27.	**Marking** Christine	Marking Public Affairs sprl
28.	**Monavari** Ahmad	National Centre for Inherited Metabolic Disorders, Ireland
29.	**Montserrat** Antoni	European Commission
30.	**Pahne** Norbert	Diätverband e.V., Germany
31.	**Petreus** Ion-Marinel	Asociatia Aproteica a Bolnavilor de Fenilcetonurie, Romania
32.	**Petreus** Laura	Asociatia Aproteica a Bolnavilor de Fenilcetonurie, Romania
33.	**Quoidbach** Vinciane	European Brain Council
34.	**Roux** Jean-Louis	BioMarin

35.	**Scarpa** Maurizio	MetabERN
36.	**Sivri** Serap	Hacettepe University of Ankara, Turkey
37.	**Staicu** Stefan	Permanent Representation of Romania
38.	**Strootker** Anja	Incite-EU
39.	**Terol** Enrique	European Commission, DG SANTE
40.	**Van Spronsen** Francjan	Faculty of Medical Sciences, University of Groningen, The Netherlands
41.	**Willetts** Karen	PKU Association of Ireland