34th VIRTUAL ESPKU CONFERENCE

October 30th, 2020
November 1st, 2020

THE PROGRAMME & ABSTRACT BOOK

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Announcement

The 35th ESPKU Annual Conference

Given normal circumstances, the 35th ESPKU Annual Conference will take place as a social event in Madrid (Spain) in 2021, hosted by our member FEDERACIÓN ESPAÑOLA DE ENFERMEDADES METABÓLICAS HEREDITARIAS.

Please follow our announcements on www.espku.org.

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Welcome

Eric Lange

President of ESPKU

Welcome to our first virtual ESPKU Conference! Technically this is our 34th Annual ESPKU Conference, and we did not want to break the sequence!

There is no need to explain why we are having it, but simply to say that we felt it necessary to offer important perspectives on PKU today.

There are two programmes – for the Professionals only on the Friday and for all on the Sunday (our "Common Programme" at our usual Conference).
In the "Common Programme" we have five excellent topics for your attention from five equally well known and respected speakers. The Professionals programme is tightly packed with nine interesting topics and will appeal to Professionals everywhere.

Many of us have become more proficient at online meetings over the last six months. The ESPKU also has adapted, for example our Spring Delegates virtual meeting went smoothly and was very well received.

Not having our usual conference means not visiting sponsors stands, not meeting other people with PKU from other countries, not learning from other PKU advocates and so on. This we shall all miss in 2020, but please note that we fully intend to re-commence as usual in 2021 – if the situation allows.

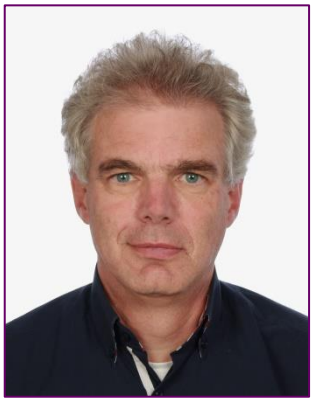
On behalf of the ESPKU Board I wish you a safe and Merry Christmas and Happy New Year.

Eric Lange
President ESPKU

"Ask not what PKU can do for you—ask what you can do for PKU!"

Francjan J. van Spronsen

Chairman of the ESPKU Scientific Advisory Committee



Dear friends, colleagues, patients, families and other interested in PKU,

It is very obvious that COVID has changed the world around us as well as the program of the ESPKU. It is a pity we cannot share our experiences with each other this year as easy as other years, but at the same time this year program may help us to build a new ESPKU using the virtual environment also in annual meetings to come along with a (hopefully) live program.

As usually, we will have a common program as well as a meeting for professionals only. In both meetings we look forward to the future with its present developments. The common program will be put as much as possible on-line. There have been several requests to also publish the data of the lectures 'for professionals only' on-line. Unfortunately, that is not possible. Let me explain why. If data of a study are already available someway on internet, they cannot be published in scientific journals anymore. If data are not published in (peer reviewed) scientific journals we cannot use the data for the further development of evidence based guidelines, and by that we will not be able to raise the bar of the care for PKU patients around the world.

Of course, professionals of every country are welcome and to give a summary of what they heard/saw to the patients they care for or live in their country.

With this all we wish you a very nice meeting without that many problems of the COVID.

Best regards

On behalf of the Scientific Advisory Committee
Francjan van Spronsen

The Professional's Programme

Friday, October 30th, 2020

Access for Professionals ONLY

	Chair: Prof. Dr. Maria Gizewska
14:00 p.m. CET	**Research in PKU: What should be our focus?** Francjan van Spronsen
14:30 p.m. CET	**GMP: Results of a 3-year longitudinal study examining body composition, satiety, amino acid absorption** Anne Daly
	Chair: Prof. Dr. Francjan J. van Spronsen
14:50 p.m. CET	**Comparing cognitive performance of early treated young adults with PKU and older controls** Lucie Thomas
15:00 p.m. CET	**Cross sectional study to characterize protein intake, metabolic control and cognitive development in Chilean Phenylketonuria cohort, 2020** Maria Jesús Leal-Witt
	Chair: Dr. Kirsten Ahring
15:10 p.m. CET	**Long term follow-up in patients with Hyperphenylalaninemia and mild Phenylketonuria – nutritional status and cognitive outcomes** Ana Sofia Freitas and Julio Rocha
15:20 p.m. CET	**Special low protein foods: An essential component in a low phenylalanine diet** Anne Daly
	Chair: Prof. Dr. Anita MacDonald
15:30 p.m. CET	**Issues with eating out safely with PKU and the attitude of restaurant staff** Grace Poole
15:40 p.m. CET	**Low protein food, its provision and supervision in school: How safe is it for children with PKU** Hannah Jones
15:50 p.m. CET	**Long term outcome in late diagnosed PKU patients – a single centre experience** Nour Elkhateeb
16:00 p.m. CET	**Final words** Session chairs

The Open Programme

Sunday, November 1st, 2020
Public Access

12:00 p.m. CET	**Introduction** Eric Lange, President of ESPKU Prof. Dr. Francjan J. van Spronsen, Chair of the ESPKU Scientific Advisory Committee **Presentation of the Sheila Jones Award 2020** Eric Lange, President of ESPKU
12:20 p.m. CET	Chair: Eric Lange **European Dietetic Guidelines** Prof. Dr. Anita MacDonald Moderator for Q & A session: Prof. Dr. Francjan J. van Spronsen
12:40 p.m. CET	Chair: Prof. Dr. Maria Gizewska **Demographics in Phenylketonuria** Prof. Dr. Nenad Blau
13:10 p.m. CET	Prof. Dr. Maria Gizewska to close the session and introduce **Afternoon Tea Break**
13:40 p.m. CET	Chair: Prof. Dr. Maria Gizewska **Growing old with Phenylketonuria** Prof. Dr. Harvey Levy Moderator for Q & A session: Prof. Dr. Maria Gizewska
14:10 p.m. CET	Chair: Dr. Kirsten Ahring **Taking care of mental health needs when aging with Phenylketonuria** Prof. Dr. Susan Waisbren Moderator for Q & A session: Dr. Kirsten Ahring
14.40 p.m. CET	Chair: Prof. Dr. Francjan J. van Spronsen **Pegvaliase and Gene Therapy for Phenylketonuria** Prof. Dr. Jerry Vockely Moderator for Q & A session: Prof. Dr. Francjan J. van Spronsen
15:10 p.m. CET	**Closing Remarks** Prof. Dr. Francjan J. van Spronsen and Eric Lange

The Abstracts and Speakers Biographies

The Professional's Programme,
in the order of appearance

Francjan J. van Spronsen

Groningen (the Netherlands)

Francjan J. van Spronsen is leading the Division of Inherited Metabolic Diseases as Professor in Pediatrics at the Beatrix Children's Hospital, University Medical Center of Groningen/University of Groningen in Groningen, the Netherlands. He currently treats patients with metabolic diseases from birth into adulthood.

Prof. van Spronsen studied medicine in Groningen, after which he did a PhD on phenylketonuria (PKU). At the same time, he became interested in tyrosinemia type I, newborn screening and liver transplantation for metabolic diseases. He obtained his PhD in 1996 and completed his specialization as a general pediatrician in 1997. Afterwards he received his training for metabolic diseases.

His research focus is on the causes and consequences of defects in amino acid metabolism and the relationships between metabolic control, metabolic pathways and neurocognitive outcomes, and the improvement of these abnormalities by treatments from different perspectives as well as improvement and extension of newborn screening for inborn errors of metabolism.

At a national level, he chairs the Advisory Committee on Neonatal Screening with respect to Inherited Metabolic Diseases, and he is a member of the Dutch Committee on Neonatal Screening. At an international level, he chairs the Scientific Advisory Board of the European Society of PKU and Allied Disorders, and is a member of various European and international advisory boards and working groups for various defects in amino acid metabolism.

Prof. van Spronsen has published around 200 articles, of which over 120 on PKU or tyrosinemia type I only. He is in the lead of some 25 European PKU experts who published their first papers on the first European guidelines for PKU and volunteered to do a second edition that eventually may help to develop a world-wide guideline with the professionals of the other continents.

RESEARCH IN PKU: WHAT SHOULD BE OUR FOCUS?

Francjan J van Spronsen
UMC Groningen, The Netherlands

If we compare with 1934, so much has been achieved in PKU. We can diagnose in time by heelprick, we can treat from almost birth onwards by dietary treatment, we have an adequate marker for monitoring of treatment and quality of life measure show that patients are happy with their lifes. So, not that much to be improved…. Or ……. If we think of improvement we usually think of expanding the treatment possibilities, but there is more that needs our attention…

The heelprick is still not in place in all countries and that means that we have to urge the governments of those countries to have or optimize their national plan for newborn screening. In that light we must be aware of the fact that not only PKU patients are helped when they are diagnosed in time, but also patients with other diseases. Where we sometimes need to emphasize the risks and the needs of PKU at itself, here we should identify other patient groups that have the same issues with early diagnosis. Research here is not that necessary, but at the same action is really needed of bodies like the ESPKU.

In some countries the heelprick is organized, but the necessary treatment is far from optimal. Reasons are usually a combination of lack of amino acid supplements, or a lack of optimal amino acid supplements, lack of sufficiently qualified medical professionals including nutritionists/dieticians/ pediatricians and laboratory specialists. Also the laboratory equipment may be not adequate enough. Whereas detection of a PKU patient with newborn screening can (although not optimal) be based on the Guthrie method, monitoring of patients' treatment should be based on quantitative methods like amino acid analyzers or tandem MS. We should not forget that there also is a need for psychologists and social workers either in the core PKU team or just related to that core team. But even if a laboratory has the equipment to produce phe values in a correct way, it needs to be fast. Probably, PKU treatment can be improved by monitoring not only Phe but also tyrosine concentrations and perhaps concentrations of other amino acids. Next, we need home monitoring possibilities comparable to glucose measurements. Here, more research is necessary both to make bloodspot sampling adequate if compared to amino acid analysis in plasma, but also to be able to do blood sampling at home taking not only Phe but also other amino acids like especially tyrosine, leucine, isoleucine and not to forget tryptophan into account to tell about the influx of phenylalanine to the brain. Also, we really need research to have home monitoring of Phe and other amino acids possible.

In Europe we have the possibility to have care in other centres abroad when care in your country is not adequate. For that reason you can ask to be referred to those centres that have the status of centers of expertise. They are officially recognized by the national government and the European colleagues assembled in the European network of reference centers for metabolic diseases. This institute is called the MetabERN. We need close collaboration between ESPKU and MetabERN even knowing that MetabERN as other European Reference Networks have difficulties to develop to adult levels of functioning. We are in need of more research to collect data of large groups of PKU patients that are well characterized and treated from birth to more exactly know their outcome and best

treatment strategy (see later on). To this aim, MetabERN may facilitate collaboration at an European level.

If we call out for monitoring our patients we need to be able to advise on such monitoring. The question is whether we can do that so easily. Do we have enough knowledge about the issues of adult patients when they stopped treatment, the treatment is incomplete, or is complete not knowing whether the treatment strictness maybe is over restrictive. We really need more data from solid research of those patients during various periods of adulthood.

Then about treatment possibilities. Now we have both oral Sapropterin and pegylated phenylalanine ammonia lyase (peg-PAL) for subcutaneous injection we are not yet there for sure. First of all, the Sapropterin does not help every patient and only the patients that are already more lucky than the patients with the more severe enzyme deficiency, and peg-PAL is only available yet for above 16 years of age and has side effects. Even though, especially with peg-PAL it is possible to really get Phe levels within the normal range and even to levels that are regarded too low especially during the vulnerable periods of brain development like in infancy and early childhood. New developments are underway, both nutritionally and medically. Here we see that COVID has negatively influenced most of the research both in phase 1-4 as the preclinical phase. Of course, more research is needed preclinically and clinically and post marketing.

If we will have all those possibilities to treat the next question becomes of course who should receive which treatment at what age. This will become a question of growing importance. So, how can that question be dealt with?

First of all, we would be helped with research that is able to establish a method that -beyond genotyping- can estimate the functional capacity of the enzyme. Such method should -ideally- be independent of age and present treatment. Next we need to think of the question whether each patient need the same severe treatment restrictions.

With this it becomes clear that we need to have much more data about our patients. This needs international cooperation with common registries that fill out the same research and clinical data to answer questions like those on outcome of course in relation to the treatment, the age treatment started and their biological and social background.

ARE THERE ANY DIFFERENCES IN BODY SHAPE IN CHILDREN TAKING GLYCOMACROPEPTIDE OR TRADITIONAL AMINO ACID PROTEIN SUBSTITUTES?

Anne Daly, Sharon Evans, Alex Pinto, Catherine Ashmore, Anita MacDonald
Birmingham Children's Hospital, UK

Background: In children with PKU overweight and obesity is a concern. Growth and the development of muscle (lean mass) are dependent on the quality and amount of dietary protein. In PKU 80% of protein comes from protein substitutes that are traditionally based on amino acids without phenylalanine. Recently, protein substitutes made from glycomacropeptide (GMP), a low phenylalanine by-product of cheese production are being used as alternatives.

Objective: A 3-year prospective study comparing glycomacropeptide (GMP) and amino acids (AA) and the effect on body shape in children.

Methods: 48 children completed the study, 13 took GMP only (GMP100), 16 a mixture of GMP and AA (GMP50) and 19 AA only. Median ages: GMP100 group, 9.2 y, GMP 50 group, 7.3y and AA group,11.1y. A DEXA scan at the start and after 3 years (study end) measured: lean mass (g), and % body fat (g). Weight (kg), height (cm) and body mass index (BMI) were recorded 3 monthly.

Results: Adjusting for age, gender and puberty no statistically significant differences were found between the groups for lean mass, % body fat, weight, or height. At 36m median height Z scores were: GMP100, 0.6; GMP50, 0.3; AA, 0.2; median weight Z scores: GMP100, 0.9; GMP50, 1.2; AA, 1.0; median BMI Z scores: GMP100, 0.9; GMP50, 1.3; AA, 1.0. All groups were overweight.

Discussion: Body shape was similar in all three groups, but all three groups were overweight irrespective of protein substitute type. More emphasis should be placed on weight control in children with PKU.

DOES A GLYCOMACROPEPTIDE PROTEIN SUBSTITUTE IN PKU MAKE YOU LESS HUNGRY?

Anne Daly, Sharon Evans, Alex Pinto, Catherine Ashmore, Anita MacDonald
Birmingham Children's Hospital, UK

Background: traditional protein substitutes are made of amino acids (AA) only, but glycomacropeptide (GMP) is a mixture of a polypeptide (natural protein) and AA. GMP may help improve fullness, thereby leading to reduced calorie intake and lower body weight.

Objective: Over 3 years we compared weight and body mass index (BMI) in children taking GMP compared to AA protein substitutes.

Methods: 48 children completed the study, the children were divided into 3 groups: 13 took GMP only (GMP100), 16 took a combination of GMP and AA (GMP50), and 19 AA only. Median ages: GMP100 group, 9.2y, GMP50 group, 7.3y, AA group, 11.1y. Dietary assessments measuring food

intake (carbohydrate, fat and protein) and weight, height and BMI were measured 3 monthly over 3 years.

Results: Adjusting for age and gender no differences were found for energy intake, weight or BMI between the three groups. The number of children who were overweight or obese was also similar between the groups.

Discussion: There was no indication to support the theory that GMP helped improved satiety. We did not find a decreased energy intake or a difference in the number of children who were overweight or obese in the group taking GMP100 or GMP50 compared to the AA group.

DOES THE TYPE OF PROTEIN SUBSTITUTE CHANGE HOW QUICKLY AMINO ACIDS ARE ABSORBED IN THE BODY?

Anne Daly, Sharon Evans, Alex Pinto, Catherine Ashmore, Anita MacDonald
Birmingham Children's Hospital, UK

Background: In a normal diet, amino acids (AA) are slowly digested from food; they are essential for growth and to build muscle. In contrast, in PKU, AAs from protein substitutes need minimal digestion and are quickly released into the body. The fast digestion of AA from protein substitutes may lower their efficiency and availability. It is commonly recommended that extra AAs are given to compensate for this rapid absorption. Glycomacropeptide (GMP) is made up of peptides and AA and there is a suggestion it may be absorbed more slowly similar to normal foods.

Objective: In children with PKU, we compared what happens to blood amino acid levels after taking one of three protein substitutes: traditional AAs, and two formulations of GMP containing different amounts of amino acids (GMP 1 and 2).

Methods: 43 children, median age 9 years (range 5-16 y) were studied, 11 took GMP1, 18 GMP2 and 14 AA. A blood sample was taken fasting and 2 hours after eating breakfast with 20g of protein from protein substitute provided by AA, GMP1 or 2.

Results: Comparing the three groups no differences were found in the total amounts of AAs in the blood either fasting or after 2 hours. Some individual amino acids e.g. tyrosine and leucine were higher after taking GMP2, but this was because the amounts of these amino acids were higher in GMP2 compared to GMP1 and AA. The amino acid levels in the blood 2 hours after consumption appeared to mirror the composition of the protein substitute.

Discussion: GMP made up of a peptide and AA, does not appear to be absorbed differently from protein substitutes made of only AAs.

COMPARING COGNITIVE PERFORMANCE OF EARLY TREATED YOUNG ADULTS WITH PKU AND OLDER CONTROLS

Lucie Thomas, Cristina Romani
Aston University, Birmingham, UK

Background: In people with PKU, following a PKU diet dramatically decreases impairments in brain development and cognition. However, people with PKU tend to relax diet with age. This is the first cohort of early treated adults with PKU (AwPKU) to move beyond middle age, and we do not know yet what the effects of prolonged high levels of Phe on ageing brains will be.

Methods: We compared cognitive performance in young AwPKU and older controls. Behavioural similarities may suggest similarities in pathogenesis and possible interactions with ageing. We tested in 37 young AwPKU, and 56 healthy older controls; 30 healthy young adult controls were tested to establish baselines.

Results: Compared to younger controls, both AwPKU and older controls demonstrated reduced speed of processing, particularly in tasks tapping visuo-spatial attention, but good accuracy. Both groups also demonstrated impairments in complex executive functions and visuo-motor coordination. However, long-term memory and learning were impaired in older controls but spared in AwPKU, while IQ was impaired in AwPKU, but not in older controls.

Discussion: These mixed results point to some different biological mechanisms of impairment, but also to possible common mechanisms which may cause an exacerbation of symptoms with age in AwPKU.

CROSS SECTIONAL STUDY TO CHARACTERIZE PROTEIN INTAKE, METABOLIC CONTROL AND COGNITIVE DEVELOPMENT IN CHILEAN PHENYLKETONURIA COHORT, 2020.

María Jesús Leal-Witt, María Florencia Salazar, Felipe Peñaloza, Juan Francisco Cabello, Carolina Arias, Pilar Peredo, Gabriela Castro, Alicia De la Parra, Verónica Cornejo
Institute of technology and nutrition of food (INTA), University of Chile

Background: Since 1992 Chile has a Newborn Screening Program (NSP) for Phenylketonuria (PKU) and Congenital Hypothyroidism. After 28 year, the incidence is 1:18,916 newborn. The government subsidize the Phenylalanine(Phe)-free formula (PheFF).

Objective: The aim of this study is to update our Chilean cohort data in metabolic follow up.

Methods: Cross sectional study of the Chilean PKU cohort. Obtained data since January 2019 to July 2020. The diagnosis was confirmed by tandem mass spectrometry and measured Phe levels during follow up by fluorometric methods. In 4yo intellectual quotient (FSIQ) by Wechsler Intelligence Scale. Statistics analyzer: Microsoft Excel 16.34 and JMP®14.2.0.

Results: 271 subjects have been diagnosed by NSP until 2020, with an average age of diagnosis of 17±8 days and average of Phe: 1119.1±543.1 uM/L and Tyrosine:71.1±51.5 uM/L. Regarding protein intake (n=187), each age group complies requirement and 79% (±15.8) of this intake is from the PheFF. Just 15% have a low height for age (<18yo). In average (n=212) until 14y maintain their Phe levels between recommended range (2y:120-360uM/L), but since 15yo the average increase to 480±285.6 uM/L. In relation with cognitive development (n=192), 63% of subjects 4y have normal FSIQ with an average for age group in range (80-120 score). We observed a negative association (p=0.0083; IC 95%: -0.32, -0.05) between IQ score and average of Phe levels.

Discussion: Compared with the European and United States protocols, our cohort has a metabolic control closer to that recommended and, most of them have a normal IQ. Early diagnosis is important, but the key for preventing the intellectual disability, is the follow up and nutritional education for life long.

LONG TERM FOLLOW-UP IN PATIENTS WITH HYPERPHENYLALANINEMIA AND MILD PHENYLKETONURIA – NUTRITIONAL STATUS AND COGNITIVE OUTCOMES

Júlio César Rocha, Ana Sofia Freitas, Manuela Ferreira de Almeida, Carla Carmona, Joana Correia, Anabela Bandeira, Esmeralda Martins, Sara Rocha, Arlindo Guimas, Rosa Ribeiro, Nuno Borges, Anita MacDonald

Nutrition & Metabolism, Nova Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa; Centro de Genética Médica, Centro Hospitalar Universitário do Porto (CHUP), Porto, Portugal; Centro de Referência na área de Doenças Hereditárias do Metabolismo, Centro Hospitalar Universitário do Porto - CHUP, Porto, Portugal. Birmingham Children's Hospital, Birmingham, UK.

Background: The primary goals of phenylketonuria (PKU) treatment are to attain normal neurocognitive development and growth by decreasing blood phenylalanine (Phe). Patients with hyperphenylalaninemia and mild PKU may not achieve optimal nutritional status and cognitive outcomes. Our aim was to evaluate nutritional status, cognitive outcomes and metabolic control in early treated patients with hyperphenylalaninemia or mild phenylketonuria and to compare these outcomes with classical PKU patients.

Methods: A study was conducted in 63 early treated patients on treatment, divided into two groups: 29 patients with hyperphenylalaninemia and mild PKU (Mild Group) and 34 classical PKU patients (Classical Group), according to blood Phe at newborn screening. Age, gender, blood Phe control, genotype, treatment strategy, anthropometry, body composition, biochemical markers, dietary intakes, cognitive outcomes, sociodemographic and psychosocial characterization were collected.
Results: Blood Phe control was significantly better in the Mild Group, with lower median blood [Phe] in Mild Group vs. Classical Group (3,75 [3,02-4,75] vs. 8,00 [6,20-10,80] mg/dL; p<0,001). A higher Phe intake (4586 [3654-5375] vs. 1153 [777-1528] mg/day; p<0,001) and a lower protein equivalent from protein substitutes intakes (0,00 [0,00-0,00] vs. 0,85 [0,73-0,98] g/kg/day; p<0,001) were seen in the Mild Group. Adult height (m) was significantly higher in Mild Group (1,69 ± 0,09 vs. 1,62 ± 0,09; p=0,032). In Mild Group significantly lower levels of uric acid, prealbumin and folic acid, and

significantly higher levels of urea, calcium and phosphorus were found. No significant differences related to the mean IQ (101,8 ± 17,2 vs 91,9 ± 17,9; p=0,134), dropout from school/college or need for additional psychological support for an anxiety/disorder or depression were found.

Discussion: Anthropometry, body composition, biochemical markers and IQ data showed that some patients from Mild Group were outside the target range for the analysed variables, even though with a trend for a higher mean IQ. Long term follow-up is needed irrespective of disease severity.

SPECIAL LOW PROTEIN FOODS: AN ESSENTIAL COMPONENT IN A LOW PHENYLALANINE DIET

Anne Daly, Sharon Evans, Alex Pinto, Catherine Ashmore, Anita MacDonald
Birmingham Children's Hospital, UK

Background: Special low protein foods (SLPF) are manufactured according to European regulations; and are formulated to help meet the energy needs of patients unable to eat a normal diet. There is little information about how much energy SLPFs supply in a low protein diet, or which SLPFs are eaten regularly by children.

Objective: Over 3 years we examined the dietary intake (energy, carbohydrate, fat and protein) of both SLPFs and regular foods in children with PKU treated by diet only.

Methods: 48 children, mean age 9 years (SD±3) were studied. Every 3 months the type and amount of food and drink consumed over 3 days was recorded, and the frequency of all foods and drinks taken over 7 days assessed using a food frequency questionnaire.

Results: The mean total energy intake from SLPFs was 33% (SD± 8), regular foods 42% (SD± 13), and protein substitutes 21% (SD± 5). SLPFs contributed the following mean macronutrient intake: 40% carbohydrate, 51% starch, 21% sugar and 38% fat. Total fibre intake provided 83% of the recommended amount, with 50% coming from SLPFs. The most popular SLPFs were bread, pasta and milk. Intake of sweets (including SLPF biscuits and cakes) was very low. Children ate 3 portions of fruit and vegetables a day, which was below the ideal ‘5 a day’. Older children 12 years or over had more irregular meals compared to younger children.

Discussion: SLPFs are important, providing energy and giving variety in a limited diet. They should be recognised as an essential part of treatment and available without financial burden to all patients.

ISSUES WITH EATING OUT SAFELY WITH PKU AND THE ATTITUDE OF RESTAURANT STAFF

Grace Poole, Alex Pinto, Sharon Evans, Catherine Ashmore, Suzanne Ford, Anita MacDonald
Birmingham City University and Birmingham Children's Hospital, UK

Background: In PKU, stringent dietary management is challenging and social exclusion is common. Patients report that eating out at restaurants and cafes is a negative experience and is often avoided.

Objective: This study aimed to further investigate the experiences of people with PKU when dining out and explore the knowledge and attitudes of restaurants when catering for PKU.

Methods: Individuals with PKU were invited to complete an online questionnaire, hosted on the National Society for PKU (NSPKU) website, about their experiences when eating out in restaurants. Chain restaurateurs (n=27) were also asked to complete an online questionnaire.

Results: Interim analysis of responses from patients with PKU (n=43, 38%) or caregivers/parents (n=71, 62%) are given. No restaurants chose to respond or participate (n=0/27). 63% (n=72/114) rated their experience in restaurants as less than satisfactory. Most respondents (n=79/114; 69%) ranked restaurant employees' knowledge of the PKU diet as very poor, with 68/114 (60%) stating restaurant staff were unhelpful or only sometimes helpful. 54% (n=62/114) had 'bad' experiences in restaurants; with refusal to prepare alternative foods (53/114, 46%), not being permitted to bring in low protein foods (52/114, 46%), and refusal to prepare special low protein foods (50/114, 44%). 44% (50/114) reported feeling anxious when eating out and 25% were disappointed or frustrated afterwards.

Discussion: People with PKU on dietary management commonly experience discrimination in restaurants, with chain restaurateurs failing to support their dietary needs. It is important that restaurant staff all receive training about low protein diets and are more flexible, enabling people with PKU to enjoy a safe meal and to socialise with others.

LOW PROTEIN FOOD, ITS PROVISION AND SUPERVISION IN SCHOOL: HOW SAFE IS IT FOR CHILDREN WITH PKU?

Hannah Jones, Alex Pinto, Sharon Evans, Catherine Ashmore, Suzanne Ford, Anita MacDonald
Birmingham City University and Birmingham Children's Hospital, UK

Background: Children with phenylketonuria (PKU) need to be accepted and join in everyday school activities, including eating school lunch with their peers. In the UK, it is expected that school catering services make reasonable adjustments to cater for children on special diets.

Aim: To explore the experiences of caregivers of children with PKU regarding provision of food at school.

Methods: An online questionnaire, hosted on the NSPKU website was completed by parents of preschool and school aged children with PKU.

Results: There were 159 responses from parents. 94% of children (n=g149/159) attended state school and 6% (n=10/159) private school with 14% (n=22/159) at preschool, 50% (n=80/159) primary school and 36% (n=57/159) secondary school. 62% (n=98/159) said their child did not have school dinners due to lack of understanding of PKU, inadequate skills and capacity of catering staff, child's fear of appearing different to peers, bad past experience, school refusal to provide for PKU, limited food choice, and inadequate supervision. Of the children receiving school lunches, 39% (24/61) said the catering team had not received PKU training from a health professional. Children were commonly unsupervised at mealtime (43%, n=66/154) or snack time (48%, n=74/155). Of those supervised, 38% (33/88) of lunchtime supervisors had limited or no PKU knowledge. 33% (n=53/159) of children had eaten non permitted foods whilst at school with 38% (n=60/159) reporting no strategies in place to avoid incidents.

Discussion: There were significant issues in safe school food provision for children with PKU. Some parents experienced discrimination and rejection when requesting a suitable low phenylalanine diet for their child.

LONG TERM OUTCOME IN LATE DIAGNOSED PKU PATIENTS – A SINGLE CENTRE EXPERIENCE

Nour Elkhateeb, Chong Y Tan, Patrick Deegan, Elizabeth Caller, Elizabeth Morris, Lisa Gaff, Sarah Donald, Sarah Hogg
Cambridge University Hospitals, UK

Background: Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine metabolism. If left untreated, it results in increased phenylalanine (PHE) concentrations in blood and brain leading to severe intellectual disability, epilepsy and behavioral problems. In Europe, the mean prevalence is approximately 1:10,000 newborns. Since the newborn screening (NBS) and subsequent early treatment were introduced in the UK in 1969, classical manifestations of PKU were rarely seen. However, late diagnosed PKU patients born prior to NBS continue to have a wide range of morbidities late in life despite initiation of diet later in life.

Objective: We aim to describe the spectrum of morbidities, despite being on diet, in late diagnosed PKU. We outline the challenges they face including medical, psychological and social challenges in order to highlight their needs the level of support required.

Methods: We retrospectively recorded the clinical, biochemical and radiologic data of late diagnosed PKU patients in our center.

Results: Six patients were included. 5 females and 1 male. All of them were born in 1970 or before. Age at diagnosis and initiation of diet ranged between 3 months and 51 years. All 6 patients continue on proper PKU diet, with most recent mean PHE level of 754 umol/L (range 489 – 1644 umol/L). All

patients had learning disability and a majority had neuropsychiatric manifestations (learning disability in 6/6, depression in 2/6, bipolar disorder in 1/6 and psychosis in 1/6). Only 1/6 patient remain independent, with 3/6 have a care package at home and 2/6 remain in a care home full time. One patient continued on antiepileptics for epilepsy. 2/6 are obese and 2/6 are overweight. 3/6 show short stature. Osteoporosis developed in 2/6, osteoarthritis in 2/6 and renal calculi in 2/6.

Discussion: Patients who were born prior nationwide screening were not diagnosed until later in life when irreversible brain damage develops. They face many challenges and health problems which requires support and care. Many of these patients do not achieve independence in their lives despite initiation of special diet and continue to have social, psychological and other health issues requiring lifelong treatment and care. Despite the miraculous success of the NBS screening and early initiation of PKU diet in mitigating the poor long-term outcomes of PKU, the needs of late diagnosed PKU patients should always be recognized and addressed.

The Abstracts and Speakers Biographies

The Open Programme,
in the order of appearance

PRESENTATION OF THE SHEILA JONES AWARD 2020

Eric Lange
President of ESPKU

In 2018, the ESPKU launched the Sheila Jones Award to recognise Sheila Jones and her family's contribution to the PKU community. After numbers of scientific or industrial awards, this award is the first ever distinction particularly for patient advocates.

The award is named after Sheila Jones, the first ever successfully dietary treated Patient with Phenylketonuria. In 1951 - 1954, her mother persisted in urging Professor Bickel and colleagues at the Birmingham Children's Hospital to develop a therapy for retarded Sheila. Since then, her persistence made the significant difference between a life with disabilities and a normal life for countless patients.

This award should not only remember the legacy of Sheila Jones, it should be a public recognition for outstanding projects or services of voluntary patient representatives, whose work is often not sufficiently appreciated. It should motivate individuals to volunteer in their patients association. It will prove: With patience, dedication and perseverance, patients can make a difference.

Every year, a panel of judges at Birmingham Children's Hospital, where Sheila was treated, reviews all applications and proposals and selects a worthy award winner.

Anita MacDonald

Birmingham, United Kingdom

Dr. Anita MacDonald OBE is Consultant Dietitian in Inherited Metabolic Disorders at Birmingham Children's Hospital, and an Honorary Professor in Dietetics at Plymouth University, UK. Although she semi-retired almost 5 years ago, she is even more involved in PKU work, concentrating solely on this group as well as doing some voluntary work for the National Society for PKU (NSPKU).

Her involvement in inherited metabolic disorders (IMD) has spanned almost all her working life (>40 years).

Dr. MacDonald obtained her PhD in phenylketonuria (PKU) in 1999. She has directly cared for over 400 patients with PKU. She has always been involved in PKU research, supervises 4 PhD students, 6 Master students and lectures worldwide on PKU. She has around 400 publications – many are research publications on PKU.

She is a member of the European PKU Guidelines group (which is aiming to standardise PKU care across Europe), is a member of ESPKU Scientific Advisory Committee, member of the UK NSPKU Medical Advisory Panel and many other working groups on metabolic disorders.

There is still no time for painting or watching the world go by!

PKU DIETARY HANDBOOK TO ACCOMPANY PKU GUIDELINES

Anita MacDonald

Birmingham Children's Hospital, UK, on behalf of the European PKU Guideline's Group

The European PKU Guideline's group not only develop recommendations for management, but they have a responsibility to support the PKU community with the provision of practical information to help with guideline implementation. The PKU dietary handbook is a practical resource that should help health professionals deliver PKU dietary management according to the statements issued by the PKU European Guidelines (2017). Although new therapies are being developed, most patients with classical PKU are still dependent on diet treatment, so it is important that there is pragmatic and consistent information given to people across Europe. Generally, there are still many countries with limited numbers of dietitians trained in PKU management, and in some countries, it is the patient support groups who provide considerable practical support who are dependent on evidence-based resources. We hope the guidelines will assist professionals and PKU patient support groups give evidence based dietary information and support to patients with PKU.

Nenad Blau

Zürich, Switzerland

Nenad Blau is a Senior Consultant in Biochemical Genetics and Professor Emeritus in Biochemistry and Metabolic Diseases at the University Children's Hospital of Zürich, Switzerland.

Prof. Blau completed his PhD in Biochemistry at the University of Zürich. Previously, he was the Head of the Laboratory for Tetrahydrobiopterin and Neurotransmitter Diseases at the University Children's Hospital in Zürich, Switzerland. His research group discovered several inborn errors of metabolism, including guanosine triphosphate (GTP) cyclohydrolase deficiency, pterin-carbinolamine dehydratase deficiency, and sepiapterin reductase deficiency. He established and curates the phenylalanine hydroxylase (PAH) locus-specific database, BIOPKU database of phenylketonuria (PKU) genotypes, database of tetrahydrobiopterin (BH4) deficiencies and the PNDdb database of mutations causing pediatric neurotransmitter disorders (www.biopku.org). He is chairing the Executive Editorial Board of the IEMbase, an online knowledgebase and diagnostic tool for inborn errors of metabolism (www.iembase.org).

His current research focuses on epidemiology, population genetics, genotype-phenotype correlation, and genotypic phenotype prediction in PKU and other inherited metabolic diseases.

Prof. Blau is an honorary member of the Italian Society for Pediatrics. In 2001, he received the Horst¬ Bickel-Award for his research in the field of tetrahydrobiopterin (BH4) and PKU, in 2005 the Gowland Hopkins Award, and in 2011 the Asbjørn Følling Award for PKU research.

Prof. Blau is author of more than 400 research publications and 10 books, including the standard textbooks Physician's Guide to the Laboratory Diagnosis, Treatment and Follow-up of Inherited Metabolic Diseases, and Laboratory Guide to the Methods in Biochemical Genetics.

DEMOGRAPHICS IN PKU

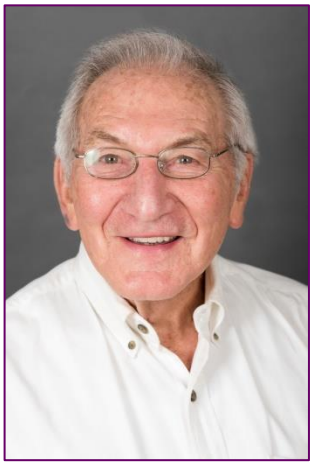
Nenad Blau
University Children's Hospital Zürich, Switzerland

Phenylketonuria (PKU) is caused by more than 1180 variants in the phenylalanine hydroxylase (PAH) gene. It is the most common autosomal recessive disorder in amino acids metabolism, with an estimated global prevalence of ~1:15'000 live births (from 1:850 in Karachay-Cherkess Republic, Russia to 1:227'273 in Thailand). Genotype and metabolic phenotype analysis from more than 16'000 PKU patients from all over the world revealed differences in diseases severity, with the phenotype distribution of 62% classic PKU, 22% mild PKU and 16% mild hyperphenylalaninemia (HPA). There is a gradient in both mutations and phenotype severity across Europe, from the classic PKU in eastern countries to mild HPA in the southern part of Europe. Worldwide, the frequency of classic PKU is

highest in Australia with >80% and lowest in Europe (average of all EU countries ~60%). The mutations p.R408W, IVS10-11G>A and p.R261Q are most common and responsible for the two common genotypes R408W/R408W and IVS10-11G>A/IVS10-11G>A. Most patients are compound heterozygotes (75%) and more than 50% of different genotypes occur in a single patient only. A genotype-based phenotype and BH4 responsiveness can be predicted with a high accuracy.

Harvey L. Levy, MD

Boston, USA



Dr Levy is senior physician in medicine/genetics of Boston Children's Hospital and Professor of Pediatrics at Harvard Medical School. He has been involved in PKU for over 50 years, including newborn screening, diagnosis, therapy, and research. For many years his particular interest was in maternal PKU, which he along with Dr. Roger Lenke brought to worldwide attention in 1980, but Dr. Levy has conducted research and published on many other areas of PKU. Dr Levy trained in metabolism under Dr Mary Efron in 1966-68 at the Massachusetts General Hospital and was appointed to the faculty following completion of his training. In the next 15 years he continued his laboratory association at the Massachusett General Hospital while also serving in the Massachusetts Newborn Screening Program as consultant, then director, and when the program evolved into the New England NBS program, served as Chief of Biomedical Genetics. In 1978 Dr Levy was invited to the Boston Children's Hospital to expand the PKU clinic into a much larger metabolic clinic. He as director of the clinic for many years, then as director of metabolic research. At the Boston Children's Hospital Dr Levy diagnosed, treated and followed many children and adults with PKU while continuing his extensive research in PKU. Dr Levy was one of the Principal Investigators of the international Collaborative Study for the Treatment of Maternal PKU. He has published over 400 articles on metabolic disease, many on PKU. He serves on the editorial board of the International Journal of Neonatal Screening and as an ad hoc reviewer of the many of the leading medical and genetic journals. Dr Levy has been honored with many national and international awards including the 2012 Asbjorn Folling Award from the European Phenylketonuria Group (EPG).

GROWING OLD WITH PKU

Harvey L. Levy, MD

Little did I know when I began my journey in metabolism over 50 years ago that I would still be around when both PKU and my patients would grow older (only one of us has grown "old"). One never knows where life will take you. But here we all are and for the better! Since my first exposure to PKU I learned PKU from not only brilliant physicians and investigators such as Dr. Robert Guthrie and Dr. Robert MacCready but very much from and along with wonderful families and children. From then to the present I have had a primary involvement in the diagnosis, treatment and research of PKU. Later my education continued from two extraordinary associates, Dr. Susan Waisbren, one of the world's foremost psychologists in PKU, and Ms. Fran Rohr, not only a world expert in the dietary treatment of PKU but who becomes a veritable member of every PKU family she encounters. But when we all began this voyage I assure you that none of us could anticipate the changes that have come and are still coming to PKU. So as we grow older with PKU, PKU is growing younger for all of us.

So let me tell you about these recent and still new changes in PKU.

Newborn Screening

When I first encountered newborn screening for PKU it was a bacterial assay called the “Guthrie Test''. It was wonderful, revolutionalized PKU. But it did not measure the blood Phe level very well. A new method known as tandem mass spectrometry is now used that provides a direct measure of Phe and not only provides newborn screening but follow-up testing and even testing for research.

Diet

It is hard to believe that once upon a time many centers considered that the proper course for treatment was to discontinue the diet at 5 years of age. Thanks to landmark research from Poland this was recognized as incorrect and today dietary treatment for life is accepted as critical for optimal outcome in PKU .

Blood Phe Levels

When we began our journey the usually recommended safe level for Phe was 600-720 umol/L. Some even believed that by adolescence the Phe level could safety be allowed to rise to almost 1200 umol/L. Today the safe level is considered no higher than 360 umol/L for life (United States) or until age 12 when the level might safely rise to 600 umol/L (Europe). However, we now know that most individuals with PKU have Phe levels considerably higher than these as they reach adolescence and into their adult years. This is probably due to a waning in dietary compliance plus an increasing metabolic difficulty in keeping Phe levels low as one gets older despite good compliance.

Outcome

Dr. Susan Waisbren is far more knowledgeable about outcome as those with PKU become older so I will leave this to her. Suffice to say that although many with PKU continue to have no difficulties others experience problems in their work and social lives. Much current research is devoted to addressing this area of PKU.

New Non-Dietary Treatments

The most exciting development in PKU today are the new non-dietary treatments that are available or proposed. The first of the available treatments is sapropterin, a cofactor drug that can stimulate the defective enzyme in some people with PKU and allow a degree of dietary freedom, even replace the diet in a few. The second available treatment is an injectable enzyme known as phenylalanine ammonia lyase (PAL) or pegvaliase, which substitutes for the defective phenylalanine hydroxylase (PAH) enzyme and in many if not most adults with PKU can allow a normal diet. And proposed is gene therapy which means that the DNA for a normal PAH enzyme is carried into the liver and may provide sufficient enzyme activity to “cure” PKU in adults. Gene therapy is under investigation in a number of clinical trials.

As those with PKU become older there are challenges but these challenges are now beginning to be met. It is my hope that in the not too distant future all of these challenges will be in the past with only bright futures for all.

Susan Waisbren

Boston, USA

Dr. Waisbren is Professor of Psychology in the Department of Medicine at Harvard Medical School and Boston Children's Hospital, in Boston, Massachusetts. She received her Bachelor's degree from Yale University and her doctorate in Clinical Psychology from the University of California, Berkeley. She conducted her doctoral research in Copenhagen, Denmark in the 1970's. During her 40-year career at Boston Children's Hospital, she provided leadership in psychology and developed multiple innovations for the Metabolism and Genetics Programs. She evaluated and counseled patients from infancy through adulthood and investigated factors related to neuropsychological functioning and emotional well-being. She is one of the few psychologists in the world specializing in PKU and other metabolic disorders. She served as the lead psychologist for the international Maternal PKU Collaborative Study, participated in the development of guidelines for the treatment of PKU and is currently working on several publications related to factors associated with outcomes in PKU and other disorders Early in her career, she recognized the need to study psychosocial in addition to biological factors contributing to adherence to medical recommendations, cognitive development and quality of life. Recently retired from clinical work, Dr. Waisbren continues to mentor younger psychologists and medical fellows and consults on psychological issues related to PKU and other conditions. She is working on a book entitled, The Emerging Science of Neuropsychology in Metabolic Disorders.

TAKING CARE OF MENTAL HEALTH NEEDS WHEN GROWING OLDER WITH PKU

Susan Waisbren, PhD

Boston Children's Hospital, Professor of Psychology, Department of Pediatrics Harvard Medical School

This presentation is about the psychological challenges that adults with PKU may face as they get older. This is important because staying in good health emotionally as well as physically may be especially difficult because of PKU. Psychological challenges include: the knowledge that things that used to be easy to do may now be hard; the loss of close friends or family; and the changes in healthcare providers, jobs, relationships and housing. In addition, there are the decisions about whether or not to try new treatments for PKU or to get back into the clinic and into metabolic control. Metabolic control may have different consequences for adults, most likely in how they are able to interact with others. Anxiety and depression may sometimes be a problem. The good news is that there are many ways to avoid or treat the psychological difficulties and support a good old age for adults with PKU.

Jerry Vockley

Pittsburgh, USA

Jerry Vockley, MD, PhD is a highly respected thought leader in the field of genetic research as a result of his internationally acclaimed work in medical genetics and inborn errors of metabolism. He has published more than 185 scientific articles in peer-reviewed journals. His laboratory has been responsible for identifying and characterizing the molecular basis of multiple new inborn errors of metabolism. The National Institutes of Health has awarded Dr. Vockley continuous funding to support his important work since 1992.

After receiving his bachelor's degree in biology at Carnegie-Mellon University, Dr. Vockley went on to receive his medical degree and doctorate in Genetics from the University of Pennsylvania School of Medicine. He completed his pediatric residency at the University of Colorado Health Science Center, and his postdoctoral fellowship in Human Genetic and Pediatrics at Yale University School of Medicine in New Haven, Connecticut. Before assuming his current position in Pittsburgh, Dr. Vockley was Chair of Medical Genetics in the Mayo Clinic School of Medicine.

Dr. Vockley is board-certified in pediatrics, clinical genetics and biochemical/molecular genetics. He has has received numerous honors for his work. His professional and scientific society memberships include the American Society for Clinical Investigation, Society for Inherited Metabolic Disorders, American Society of Human Genetics, American Academy of Pediatrics, American Association for the Advancement of Science and the Society for the Study of Inborn Errors of Metabolism. He is the past president of the Society for Inherited Metabolic Disorders and the International Congress on Inborn Errors of Metabolism.

PKU: MODERN THERAPIES FOR AN OLD DISEASE

Jerry Vockley, MD, PhD.

Phenylketonuria (PKU) is one of the first described inborn errors of metabolism and the first to be identified at birth through extensive newborn screening programs in many countries worldwide.

While dietary therapy eliminates the devastating neurodevelopmental impairments associated with untreated disease, affected individuals still face a significant burden of illness, especially since phenylalanine (PHE) control almost universally declines with age. Two new pharmacologic therapies, Sapropterin and Palynziq, have provided the first insights into the impact of reducing phenylalanine levels in poorly controlled patients but have practical and functional limits to their use. Next generation therapies for PKU are now currently in development and include gene therapy, mRNA therapy, small molecular chaperonins, and novel enzyme replacement/substitution delivery systems. The spectrum of new treatments and results of current clinical trials will be discussed along with the impact on standard of care for PKU in the future.

Meeting Chair's Biographies

Professor Maria Giżewska, M.D. Ph.D

Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology
Pomeranian Medical University Szczecin, Poland

Professor Maria Giżewska graduated from the Pomeranian Medical University in Szczecin, Poland. She has a specialization in general pediatrics and pediatric metabolism.

From the mid-nineties her researches are focused on early diagnosis and treatment of children, adolescents and adults with different types of inborn errors of metabolism (IEM), including phenylketonuria. She is a consultant on IEM for the Region of West Pomerania, Poland.

In 2009 based on her scientific achievements and publication entitled "Phenylketonuria: selected genetic aspects and squeals of hyperphenylalaninemia" which was a basis of her habilitation thesis, she obtained a title of Associate Professor. In 2015 she received a position of professor at Pomeranian Medical University. Since 2019 she is a full professor of medicine.

Doctor Giżewska is the author of over 100 publications in both Polish and international journals on IEM, general paediatrics, paediatric endocrinology, neurology and genetics. In the last years she was involved in the development of the first European PKU Guidelines.

She was trained in the field of IEM in Denmark, Italy, Qatar and in Saporro, Japan (as a fellow of Japan International Cooperation Agency (JICA). Phenylketonuria and other IEM were the subject of her lectures given in many European countries, USA, Asia, Australia, South America and Meddle East. Since 2011 she closely cooperates with University of Greifswald and recently with Medical University Charitè in Berlin, Germany in the implementation of the UE projects dedicated to create a trans-border, Polish-German newborn screening center.

She is a member of SSIEM, Polish Pediatric Societies, Polish Society of Pediatric Endocrinology and a Board Member of Polish Society of Inborn Errors of Metabolism. Doctor Giżewska is also a vice-chairman of Polish Society of Phenylketonuria and a vice-chairman of Scientific Advisory Committee of European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU).

Kirsten Kiaer Ahring, Ph.D

Copenhagen University Hospital, Denmark

Kirsten Kiaer Ahring Ph.D. is Clinical Dietician / Cand Scient in Human Nutrition at the Copenhagen University Hospital, Denmark. She has 22 years of experience with PKU, including patient counselling, teaching of intern and extern professionals and participating in clinical research projects. She is contact person for late diagnosed PKU patients in Denmark and for the Nordic PKU Maternal Project.

After her Bachelor in Human Nutrtion and Dietetics at the Suhrs University College in Copenhagen in 1990, she worked as a research assistant at The Health Sciences Centre, the Memorial University of New Foundland, St. Johns (Canada) and at the King Faisal Specialist Hospital and Research Centry in Riyadh, Saudi Arabia. In 2010, she completed her Master's degree in Human Nutrition at the University of Copenhagen. In 2019, she obtained an Industrial PhD degree in collaboration between the Copenhagen University Hospital (RH), the Kennedy Centre (KC) and Arlafoodsingredients (AFI), Denmark.

She released more than 30 internationally peer reviewed publications and is a reviewer for various international journals. She gave more than 30 lectures and oral presentations at international conferences. She is an invited member of the European Metabolic Dietitian Group (ENEP).

As a member of the ESPKU Scientific Advisory Committee, since 2005 she co-organises the scientific programmes and chairs scientific sessions at ESPKU conferences.

The European Society for Phenylketonuria and Allied Disorders treated like Phenylketonuria

(ESPKU)

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