Networking Across Borders for Individuals with Organic Acidurias and Urea Cycle Disorders: The E-IMD Consortium

**Stefan Kölker • Dries Dobbelaere • Johannes Häberle •
Peter Burgard • Florian Gleich • Marshall L. Summar •
Steven Hannigan • Samantha Parker •
Anupam Chakrapani • Matthias R. Baumgartner •
on Behalf of the E-IMD Consortium**

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Abstract Background: Patients with organic acidurias (OAD) and urea cycle disorders (UCD) are at increased risk of disability, impaired quality of life and reduced life expectancy. Clinical care in any one centre is constrained by small patient numbers; and furthermore diagnostic and treatment strategies vary between metabolic centres and countries, resulting in significant inequalities and disparity in patient outcome.

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S. Kölker (✉) • P. Burgard • F. Gleich
Division of Inherited Metabolic Diseases, Department of General Pediatrics, University Children's Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany
e-mail: Stefan.Koelker@med.uni-heidelberg.de

D. Dobbelaere
Centre de Référence des Maladies Héritaires du Métabolisme de l'Enfant et de l'Adulte, Hôpital Jeanne de Flandre, Lille, France

J. Häberle • M.R. Baumgartner
Division of Metabolism and Children's Research Centre, University Children's Hospital Zurich, Steinwiesstraße 75, 8032 Zurich, Switzerland

M.L. Summar
Children's National Medical Center, 111 Michigan Avenue, N.W., Washington, DC 20010, USA

S. Hannigan
CLIMB, National Information Centre for Metabolic Diseases, 176 Nantwich Road, Crewe, CW2 6BG, UK

S. Parker
Orphan Europe Sarl, Immeuble "Le Wilson" 70 Avenue du Général de Gaulle, 92058 Paris La Défense, France

A. Chakrapani
Birmingham Children's Hospital NHS Foundation Trust, Steelhouse Lane, Birmingham B4 6NH, UK

Aims/methods: The overall objective of the EU-funded activity 'European registry and network for intoxication type metabolic diseases' (E-IMD) is to collect systematic data to improve the knowledge of these diseases, to develop consensus care guidelines and to provide detailed information materials for families and professionals.

Results: Within three years E-IMD has (1) established a network of 87 partners in 25 countries (2) set up a patient registry of more than 1,000 individuals with OAD and UCD, (3) launched a website (www.e-imd.org) including detailed information materials in 11 languages, (4) developed guidelines for OAD and UCD, (5) organised two teaching courses and various scientific meetings, (6) extended the IT platform clustering with other inherited metabolic diseases (IMD) and (7) strengthened the collaboration with other international scientific consortia.

Conclusions: E-IMD has made important steps towards improving and sharing knowledge on OAD and UCD and harmonisation of diagnostic and therapeutic strategies. Through the establishment of a modular patient registry, clustering with other IMD and stepwise extension of the network, E-IMD has implemented the core components of a European Reference Network for rare diseases.

Abbreviations

EAHC	European Agency for Health and Consumers
E-HOD	European network and registry for homocystinurias and methylation defects
E-IMD	European registry and network for intoxication type metabolic diseases
ERN	European reference network
EUCERD	European Union Committee of Experts on Rare Diseases

GA1	Glutaric aciduria type 1
IMD	Inherited metabolic disease
IVA	Isovaleric aciduria
MMA	Methylmalonic aciduria
MS	Member state
OAD	Organic aciduria
PA	Propionic aciduria
PO	Patient organisation
UCD	Urea cycle disorder
UCDC	Urea cycle disorders consortium

Introduction

Organic acidurias (OAD) and urea cycle disorders (UCD) are rarely inherited metabolic diseases (IMD) with an estimated cumulative incidence of 1 in 35,000 newborns (UCD) or 1 in 14,000–30,000 newborns (OAD), respectively (Kasper et al. 2010; Schulze et al. 2003; Summar et al. 2013; Wilcken et al. 2003). Affected individuals often present with first symptoms in the newborn period or infancy and are at an increased risk of severe disability, impaired quality of life, and reduced life expectancy (Bachmann 2003; Enns et al. 2007; Grünert et al. 2013; Hörster et al. 2007; Kido et al. 2012; Kölker et al. 2006; Nassogne et al. 2005; Pena et al. 2012; Strauss et al. 2003; Summar et al. 2008). Because of their life-threatening character and the permanent risk of metabolic crisis OAD and UCD are also called intoxication type IMD. In some countries these diseases are included in newborn screening programmes, hereby allowing early detection and start of treatment in asymptomatic individuals. This early intervention hopefully leads to improved health outcome, as it has been shown for glutaric aciduria type 1 (GA-1) and isovaleric aciduria (IVA) (Grünert et al. 2012; Heringer et al. 2010; Kölker et al. 2007a).

Patients with rare diseases like intoxication type IMD have become a healthcare priority in developed countries where other causes of infant mortality such as infectious diseases are now treatable (Commission of the European Communities 2008). OAD and UCD patients are scattered across countries and as a result medical expertise for each of these diseases is a scarce resource. Fragmented disease knowledge means that care is not optimal, and there are significant differences in the infrastructure, expertise, diagnostic procedures, time to diagnosis, strategies and outcome. In analogy to other rare diseases it can be expected that this diversity has a negative impact on health outcome and on socio-economics (Brimley et al. 2013; Linertová et al. 2012; López-Bastida et al. 2008; López-Bastida et al. 2009).

The overall aim of the European registry and network for intoxication type metabolic diseases (E-IMD) is to promote health for individuals affected with OAD or UCD by pooling of expertise and networking and by reducing avoidable inequity. E-IMD has two specific objectives: (1) to establish a European patient registry describing the disease course, epidemiology, diagnostic and therapeutic strategies for OAD and UCD and (2) to provide European evidence-based consensus care protocols for patients with OAD and UCD serving as a template for the development of guidelines and patient brochures. This paper describes the establishment of E-IMD, major achievements within the first three years of the project and important obstacles that the consortium learnt to deal with.

Methods and Results

The Network

E-IMD partners have already successfully collaborated for several years in various projects on OAD and UCD. In 2010, a strategic decision was made to formalise cooperation by establishing E-IMD. E-IMD has been partly funded from 1 January 2011 to 30 April 2014 by the European Union [via the European Agency for Health and Consumers (EAHC); agreement no. 2010 12 01], in the framework of the Health Programme 2008–2013. It is coordinated by the University Hospital Heidelberg and started with 28 project partners (coordinator, 12 associated and 15 collaborating partners) from 15 European countries. Associated partners received on average 60% EU co-funding from the grant whilst collaborating partners participated on a voluntary basis. The network has developed beyond expectations and now includes 87 partners from 25 countries on four continents (Fig. 1). Sixteen patient organisations (PO), four industrial partners and 67 clinical partners form the network. Representatives of the adult metabolic and dieticians' groups of the Society for the Study of Inborn Errors of Metabolism, the Urea Cycle Disorders Consortium (UCDC) and the Japanese Consortium for Urea Cycle Disorders are E-IMD partners. Applications for memberships of clinical partners have been evaluated by the steering committee based on the following criteria: (1) clinical and scientific expertise in intoxication type metabolic diseases, (2) metabolic service provided by an interdisciplinary team of experts and (3) capacity and relevant infrastructure to contribute to E-IMD.

The E-IMD advisory board including all network partners is the principal decision-making and arbitration body for the network and registry. The steering group comprising the lead of each work package and a representative of collaborating partners has the overall responsibility

Fig. 1 Crossing borders for patients with rare OAD and UCD. The E-IMD network so far includes 87 partners from 25 countries on four continents. Note that the coloured areas do not reflect the exact geographical coverage of E-IMD

to ensure satisfactory progress of the work and promptly deal with problems. It assists the network director in the implementation of the integrative management of the network. All E-IMD partners have signed a consortium agreement which specifies and defines the organisation, management, responsibilities and tasks of the network.

The Patient Registry

The E-IMD patient registry is a web-based, password-protected registry (<https://www.eimd-registry.org>) launched on the web in August 2011. It contains comprehensive information on patients with confirmed diagnosis of OAD, i.e. glutaric aciduria type 1 (GA1; OMIM #231670), methylmalonic aciduria (MMA; OMIM #251000, #251100, #251110, #277400, #277410), propionic aciduria (PA; OMIM #606054), IVA (OMIM #243500) and UCD, i.e. inherited deficiency of *N*-acetylglutamate synthase (OMIM #237310), carbamylphosphate synthetase 1 (OMIM #237300), ornithine transcarbamylase (also including heterozygous female carriers; OMIM #311250), argininosuccinate synthetase (OMIM #215700), argininosuccinate lyase (OMIM #207900) and arginase 1 (OMIM #207800), as well as hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (OMIM #238970). Written informed consent is obtained from all study patients before enrolment and baseline visit. The study was approved by the local ethics committee of the coordinating centre (i.e. University

Hospital Heidelberg, application no. S-525/2010) on 31 January 2011 and then approved by the ethics committees of clinical partners contributing to the registry ($n = 44$). As of 30 April 2014, 1,009 patients with a confirmed diagnosis of OAD and UCD have been registered. The registry collects prospective data and contains detailed information on 949 baseline, 1,076 regular (annual), 437 emergency and 17 fatal disease course visits, averaging 2.5 visits per patient. A detailed description of the clinical phenotype will be published separately (Kölker et al. 2015a, b).

Forty clinical partners (of the 44 partners with ethical approval) from 20 countries – 17 European countries [15 EU member states (MS), Switzerland and Republic of Serbia], India, Japan and the USA – have so far contributed to the registry. The maximal population size of EU MS covered by clinical E-IMD partners was 453,288,893 citizens, i.e. 89.6% of the population in 28 EU MS according to Eurostat 2013 (<http://epp.eurostat.ec.europa.eu>). However, since recruitment to E-IMD varies between countries, estimated prevalences of OAD and UCD are likely to be underestimated. For instance, the minimum prevalence of patients with OAD and UCD was 2.10 per million citizens, with a range of 0.15 (Romania) to 8.39 (Denmark) (Table 1). This may skew the results, but with continued registration of patients, this current drawback will diminish.

This variable frequency of UCD and OAD patients is unlikely to reflect true epidemiological differences,

Table 1 Minimum cumulative prevalence of patients with OAD and UCD in Europe

Country	Patients $N_{(pat)}$	Population $N_{(pop)}$	Prevalence $N_{(pat)} \times N_{(pop)}^{-1} \times 10^6$ ^a
Austria	22	8,451,860	2.60
Belgium	22	11,161,642	1.97
Croatia	22	4,262,140	5.16
Czech Republic	29	10,516,125	2.76
Denmark	47	5,602,628	8.39
France	189	65,578,819	2.88
Germany	160	80,523,746	1.99
Greece	8	11,062,508	0.72
Italy	65	59,685,227	1.09
Netherlands	44	16,779,575	2.62
Poland	36	38,533,299	0.93
Portugal	34	10,487,289	3.24
Romania	3	20,020,074	0.15
Republic of Serbia	6	7,181,505	0.84
Spain	145	46,727,890	3.10
Switzerland	24	8,039,060	2.99
UK	129	63,896,071	2.02
Total	985	468,509,458	2.10
Total (EU MS)	955	453,288,893	2.11

EU MS member states of the European Union, *pat* patients, *pop* population

^a Population size in 2013 according to EUROSTAT. Patients from non-European countries ($n = 24$) are not listed

but merely shows the effect of a number of modulatory factors including the number and capacity of E-IMD partners in different countries as well as the rapidity and success of the activation process in individual centres. The activation process is the time interval from becoming a member of the E-IMD consortium and registering the first patient. The process time has been highly variable reflecting national and local differences and ranged from 2 to 20 months.

An important source of variability has been the ethical review process which includes translation into national languages, adaptation of the application to national and local requirements and submission to the board. The regulations governing this process are highly variable in different countries and local centres. Noteworthy, associated partners who have received EU co-funding have achieved ethical approval and started registering patients earlier than collaborating partners who contributed to the project on a voluntary basis (Fig. 2). Furthermore, the 12 associated clinical partners have registered more patients (74% of total) than 28 collaborating partners (26%). Despite the shortcomings arising from the project funding

mechanism, the process of recruiting and registering patients was almost linear with approximately 26 patients with OAD and UCD being newly registered during each month between February 2011 (first patient recruited) and April 2014 (end of the EU funding period). Meanwhile, the follow-up visits outnumber the baseline visits showing that the registry is now increasingly used for systematic follow-up of registered patients (Fig. 3).

Dissemination

Dissemination is an integral part of the E-IMD strategy with targeted distribution of disease information and intervention materials, such as protocols and guidelines. E-IMD developed a website (www.e-imd.org) as the main dissemination vehicle for the network. At present, the website provides information for patients and their family (translated into 11 languages) and for healthcare professionals, newsletters and contact addresses. The number of visitors has been increased to approximately 250 visitors per day and is still increasing. The patient information is the most frequently visited part of the website. In addition, the number of cases can be viewed in real-time mode in the public domain of the patient registry (<https://www.eimd-registry.org>).

E-IMD has actively sought to publish its achievements in peer-reviewed journals focusing on epidemiology, clinical phenotyping, therapy and guideline development Baumgartner et al. 2014; Boy et al. 2013; Chapman et al. 2012; Häberle et al. 2012; Kölker et al. 2011; Pena et al. 2012; Rüegger et al. 2014; Summar et al. 2013). Four E-IMD advisory board meetings have been held during annual SSIEM and ICIEM symposia between 2011 and 2014. Since 2013, joint meetings with the E-HOD (www.e-hod.org) and UCDC consortia have been organised.

Finally, E-IMD has partnered with the Recordati Rare Diseases Fondation d'entreprise (<http://www.rrdacademy.org>) to organise three training courses for young doctors in the field of IMD.

Guideline Development

Guidelines are systematically developed statements assisting practitioner and patient decisions in appropriate health-care for specific clinical circumstances. The Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk>) methodology was employed to develop these guidelines.

European consensus guidelines for UCD (Häberle et al. 2012), GA1 (Kölker et al. 2011), and MMA/PA (Baumgartner et al. 2014) have been published under the umbrella of E-IMD. Those for IVA are still under development. Short guideline versions are available online via the E-IMD website. Based on the available

Fig. 2 Milestones of the activation process in associated and collaborating partners. The time required for receiving ethics approval was adjusted to the date when the coordinating partner had received

ethics approval and to the individual dates of signing the consortium agreement (for collaborating partners who have joined the consortium after the kick-off meeting)

Fig. 3 Timeline of recruiting and registering patients. Lines indicate cumulative frequencies of registered patients, baseline visits and regular follow-up visits during the funding period. Dotted lines

indicate the cut-off date for the interim analysis (22 October 2013) and the end of the EU funding period (30 April 2014)

evidence from literature, the statements for OAD and UCD are mostly graded level C or D. The process of guideline development lasted over several years and can be considered as outstanding in the field of metabolic medicine.

Importantly, the use of GA1 guideline recommendations, when evaluated after some years, was shown to improve the neurological outcome and to support normal growth (Boy et al. 2013; Heringer et al. 2010).

Along this, it is anticipated that the achieved publication and dissemination of consensus evidence-based guidelines will further improve care of patients with OAD and UCD.

Evaluation

The evaluation of the project is led by the steering group with strong patient representation. Its overall aim is to appreciate how E-IMD achieved its main goal of building knowledge and whether diagnosis and care improved in the different European countries. The following sources of information and indicators have been used: (1) a survey sent out via national PO, (2) analysis of the use of the E-IMD website and (3) analysis of the patient registry for completeness of geographical coverage, quality and completeness of records and time to diagnosis.

The evaluation highlighted that there is a need to develop care pathways for OAD and UCD patients and to resolve the difficult issue of transition of adolescents into adult care. From the patient perspective there is also a need to develop the PO community for IMD through the establishment of a helpline and online community. E-IMD has been the catalyser in the funding and launching of the European Metabolic Disease Alliance (www.eumda.org).

The website is the principal means of public communication. E-IMD comes up on the first page of Google search engine using the key words ‘organic aciduria’ or ‘urea cycle disorder’; however, it was still difficult to get traffic to the website.

The registry contains data on 1,009 individuals with an OAD or UCD. There must be a concerted effort amongst partners to complete patient records and follow up this unique cohort. Further data is needed in the registry to better understand the outcome of patients diagnosed through newborn screening compared to those diagnosed after the onset of symptoms.

Discussion

In the last three years, E-IMD has started the first collaborative initiative on UCD patients in Europe and the largest initiative for OAD patients worldwide. E-IMD has fostered international collaboration with the American UCDC consortium (Seminara et al. 2010) and the newly established Japanese UCDC. The E-IMD network has developed beyond expectations and now includes 87 partners in 25 countries. The specific objectives of this EU-funded activity are to improve the knowledge base, to develop European consensus guidelines and to foster networking for patients with OAD and UCD in Europe. These goals have all been achieved despite important obstacles and hurdles.

Project Funding Mechanism

A major drawback was the funding mechanism of this project. The activation process time and the number of patients registered differed between associated and collaborating partners. Whereas associated partners received partial EU funding, collaborating partners contributed on a voluntary basis without financial compensation for their working time. Therefore, it can be assumed that the activation process would have been accelerated and the total number of patients would have been significantly increased, if a larger proportion of clinical partners had received project funding. In addition, the shared cost principle and financial mechanism have been a challenge as hospital administrators are often unable to prefinance. In conclusion, the management of this project could have been improved if European regulations had been harmonious on a national level and the financial plan for such projects had been more flexible.

Ethical Review Process

Another source of significant variability in the activation process has been the ethical review. In some countries this is painstakingly long and administrative, whilst in others formal ethical review is not required as the study is regarded as noninterventional audit. It would be of great benefit for rare disease registries to harmonise regulations and to distinguish between noninterventional studies with low or even no risk of potential harm for participating individuals and other types of research, at a European level.

Guidelines for Rare Diseases

Guidelines for OAD and UCD have been developed and published under the umbrella of E-IMD (Baumgartner et al. 2014; Häberle et al. 2012; Kölker et al. 2011). The formal process of guideline development, which was in line with the SIGN methodology, was considered unhelpful by some authors since guidelines for rare diseases often result in low grades of recommendations. It was assumed that such guidelines might be liable to misinterpretation and misuse, not be prescriptive enough and prove to be a hindrance in obtaining funding for treatment (Vockley et al. 2013). However, there are strong refutations to this position:

1. The level of published evidence and grading of a recommendation do not necessarily correlate with its clinical relevance. For instance, although low phenylalanine diet for phenylketonuria has never been tested in a randomised controlled trial, and, therefore, the level of evidence for this intervention has to be formally evaluated as relatively low (Yi and Singh 2008), no

metabolic specialist would doubt that this therapeutic intervention in general is extremely relevant for affected individuals (Blau et al. 2010; Burgard 2000; Camp et al. 2014).

2. The effect size of therapeutic interventions in patients with an IMD is often huge. Therefore, it can be reliably identified by a cohort study with low risk of confounding bias (Kölker et al. 2007b; Heringer et al. 2010). There is no doubt that, if affordable and achievable, randomised controlled trials for rare IMDs should be performed, but this is often not feasible due to low number of patients and would require the interest of the pharmaceutical industry (Enns et al. 2007; Levy et al. 2007; Wraith et al. 2004). However, there are also examples of carefully designed *n* of one trials (Bickel et al. 1953).
3. Low grading helps to identify the gaps in current knowledge thereby setting the scene for further research.
4. Setting standards of practice is important to minimise unnecessary variance or – even worse – trial and error.
5. Identification of alternative approaches is important since these are often required when adverse events occur or a drug is not available in a national health system.
6. Practices based upon expert opinion of single physicians or centres with a long-standing experience do not gain wide appraisal and approval without independent and critical evaluation.

The E-IMD consortium will foster the implementation of the guidelines for OAD and UCD in daily practice and will investigate whether the use of guideline recommendations improves the health outcomes and quality of life of affected individuals. First promising results have already been published for the use of the GA1 guideline on a national level (Heringer et al. 2010) and for the UCD guideline (Häberle and Huemer 2015). To evaluate the effect of newborn screening and adherence to guideline recommendations in rare diseases with a broad clinical spectrum will become challenging, since reliable clinical endpoints and a large number of patients are required for the analysis.

In 2013, after the development of the E-IMD guidelines, the Scottish Intercollegiate Guidelines Network implemented the principles of the GRADE methodology. This change will facilitate the process of recommendation development for rare diseases.

Looking Forward: Towards a European Reference Network for Inherited Metabolic Diseases

Despite some significant challenges, E-IMD has succeeded beyond expectations which will ultimately promote health

for individuals with OAD and UCD. However this goal can only be achieved through long-term follow-up, which requires a sustainable funding mechanism. An opportunity for E-IMD could be its establishment as a European Reference Network (ERN) for inherited metabolic diseases. The general concept and implementation of ERNs are defined in Article 12 of the Cross-Border Healthcare Directive (The European Parliament and the Council of the European Union 2011). According to the recommendations of the European Union Committee of Experts on Rare Diseases (EUCERD) on rare disease European Union Committee of Experts on Rare Diseases (2013), which are designed to be complementary to the Cross-Border Healthcare Expert Group on ERNs, a rare disease ERN should cover various core tools and activities, amongst the disease registries, mechanisms for information flow for good practice guidelines, training and education tools and communications infrastructure to ensure visibility. E-IMD has developed these tools and activities.

In addition, E-IMD has proceeded with the concept of disease clustering. Starting with 11 IMD, the modular IT platform has been extended to 26 IMD by inclusion of homocystinurias and methylation defects within the EU-funded project E-HOD (project lead: Prof. Henk Blom, Freiburg, Germany). Since 2013, the IT platform has also been used to gather post-marketing surveillance data for the orphan drug Cystadane™ (betaine anhydrous) which is licensed for adjunctive treatment of homocystinuria caused by deficiencies or defects in cystathionine beta-synthase, 5,10-methylene tetrahydrofolate reductase, and cobalamin cofactor metabolism. The ‘Cystadane Surveillance Protocol’ project has been realised within a public private partnership between the E-HOD consortium and the drug licence holder, Orphan Europe Sarl. This collaboration maps onto the 2011 recommendations of the European Medicines Agency and EUCERD stressing the need to support public private partnerships in the development of registries and collaboration for post-marketing surveillance (European Union Committee of Experts on Rare Diseases 2011). In 2014, the same IT solution will be used for implementing the IMD group of biogenic amine and pterin biosynthesis and recycling disorders (iNTD, project lead: Dr Thomas Opladen, Heidelberg, Germany; funded by Dietmar Hopp Foundation, Germany).

This clearly shows that disease clustering and the development of new applications using the same IT platform and network have many advantages and are a favourable strategy for both sustainment and extension. The strategy for extending the IT platform and the network towards an ERN for inherited metabolic diseases has been elaborated and shall be realised step by step.

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Netherlands: Frits A. Wijburg and Eveline Langereis (Academisch Medisch Centrum, Department of Pediatrics, Amsterdam), Monique Williams (Erasmus Universiteit Rotterdam, Erasmus MC-Sophia Kinderziekenhuis, Rotterdam) and Hanka Meutgeert (Volwassenen en Kinderen met Stofwisselingsziekten [VKS], Zwolle, PO group)

Poland: Jolanta Sykut-Cegielska (Institute of Mother and Child, Screening Department, Warsaw) and Wanda Gradowska (Instytut ‘Pomnik-Centrum Zdrowia Dziecka’, The Children’s Memorial Health Institute, Department of Metabolic Diseases, Endocrinology and Diabetology, Warsaw)

Portugal: Elisa Teles Leao, Susana Soares and Esmeralda Rodrigues (Unidade de Doenças Metabólicas, Serviço de Pediatria, Hospital de S. João, EPE, Porto); Laura Vilarinho (Newborn Screening Unit, Metabolic Genetics Center, National Institute of Health [INSA], Porto); Ana Gaspar (Unidade de Doenças Metabólicas, Serviço de Pediatria Hospital Santa Maria Lisboa, Lisbon); Isabel Tavares de Almeida (Faculdade de Farmácia da Universidade de Lisboa, Lisbon); Vanessa Ferreira (Associação Portuguesa CDG, PO group); Miguel Macedo (Apofen, PO group); and Sérgio Braz Antão (Rarrisimas, PO group)

Republic of Serbia: Adrijan Sarajlija and Maja Djordjevic (Institut za zdravstvenu zaštitu majke i deteta Srbije, Belgrade)

Romania: Paula Avram (Institute for Mother and Child Care ‘Alfred Rusescu’, Bucharest)

Spain: Juan-Luque Moreno (CIBERER, Centro de Investigación Biomédica en Red de Enfermedades Raras); Angeles Garcia-Cazorla, Jaume Campistol, Carlos Ortiz and Elisenda Cortès i Saladelafont (Hospital Sant Joan de Deu, Servicio de Neurologica, Barcelona); Elena Balmaseda and M. Carmen Carrascosa (Complejo Hospitalario Universitario de Albacete, Albacete); Guillem Pintos-Morell (University hospital ‘German Trias i Pujol’, Badalona); Antonia Ribes (Institut Bioquímica Clínica, Corporación Sanitaria Clinic, Barcelona); Eduardo López (Pediatric Neurology Unit Department of Pediatrics, University Hospital Reina Sofia, Cordoba); Immaculada Vives and David Gil Ortega (Hospital Virgen de la Arrixaca de Murcia, El Palmar); Juana Maria de Haro Catellano (Secretaria Técnica del CEI-Granada (HUVN), Edificio Licinio de la Fuente, Granada); Luis

Pena-Quintana (Hospital Universitario Materno-Infantil de Canarias, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria); Magdalena Ugarte and Begona Merinero (Universidad Autónoma de Madrid, Madrid); Consuelo Pedrón-Giner (Hospital Infantil Universitario Niño Jesús, Sección de Gastroenterología y Nutrición, Madrid); Javier Blasco-Alonso (Hospital Materno-Infantil de Málaga, Unidad de Gastroenterología, Hepatología, Nutrición y Metabolopatías, Málaga); Angeles Ruiz Gómez (Hospital Universitario Son Espases, Palma de Mallorca); Maria L. Couce (Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela); Vicente Rubio (Instituto de Biomedicina de Valencia, Valencia); and Sergi Faber (Catalana de Trastorns Metabòlics Hereditaris, PO group)

Sweden: Sofia Nordin (Swedish Orphan Biovitrum AB [SOBI], Stockholm)

Switzerland: Jörn-Oliver Sass (Kinderspital Zürich, Universitäts-Kinderkliniken, Eleonoren-Stiftung, Department of Clinical Chemistry and Biochemistry, Zürich) and Jean-Marc Nuoffer (Universitätsspital Bern, Universitätsklinik für Kinderheilkunde, Bern)

Taiwan: Wu-Liang Hwu, Yin-Hsiu Chien and Ni-Chung Lee (National Taiwan University Hospital, Department of Medical Genetics, Taipei)

Turkey: Mübeccel Demirkol and Gülden Gökçay (Istanbul University, Children's Hospital, Department of Nutrition and Metabolism, Istanbul)

UK: Victoria Riches (Birmingham Children's Hospital NHS Foundation Trust, Birmingham); CLIMB, Children Living with Inherited Metabolic Diseases, National Information Centre for Metabolic Diseases (Crewe); Stephanie Grünwald and Nick Thompson (Great Ormond Street Hospital for Children NHS Trust, London); Robin Lachmann and Elaine Murphy (National Hospital for Neurology and Neurosurgery, Charles Dent Metabolic Unit, London, and representing the SSIEM Adult Metabolic Group); Roshni Vara (Evelina Children's Hospital, St Thomas' Hospital, Department of Inherited Metabolic Disease, London); John Walter and Andrew Morris (Central Manchester and Manchester Children's University Hospital, Willink Biochemical Genetics Unit, Manchester); Bradford Teaching Hospitals NHS Trust, St Luke's Hospital (Bradford); and EMDA, the European Metabolic Disorders Alliance (PO group)

USA: Kimberly Chapman (Children's National Medical Center, Center for Genetic Medicine Research, Washington DC, and representing the Urea Cycle Disorders Consortium) and Jerry Vockley (Children's Hospital of Pittsburgh of UPMC, Pittsburgh)

Synopsis

E-IMD has established an international network, has improved knowledge about organic acidurias and urea cycle disorders and has started harmonising diagnostic and therapeutic strategies. This is the prerequisite for establishing a European Reference Network for inherited metabolic diseases.

Compliance with Ethics Guidelines

Conflict of Interest

Stefan Kölker, Matthias R. Baumgartner, Peter Burgard, Anupam Chakrapani, Dries Dobbelaere, Florian Gleich, Johannes Häberle, Marshall L. Summar, and Steven

Hannigan declare that they have no conflict of interest. Samantha Parker is employed by Orphan Europe Sarl being part of the Recordati Group.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients or their legal guardians for being included in the study.

Details of the Contributions of Individual Authors

Designing, planning and conducting the study: all authors

Statistical analysis: Peter Burgard, Florian Gleich and Stefan Kölker

Manuscript writing: All authors

Animal Rights

This article does not contain any studies with animal subjects performed by any of the authors.

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