EBC RESEARCH PROJECT - THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS IN EUROPE

# BRIDGING GAPS AND ACHIEVING SEAMLESS, COORDINATED CARE

## A JOINT VALUE OF TREATMENT STUDY ON RARE NEUROLOGICAL AND NEUROMETABOLIC DISORDERS IN EUROPE

**#Together4RareDiseases**

Case Study Results and Infographics | Brain Awareness Week 2022

## VALUE OF TREATMENT (VOT) PROJECT

VOT | EBC RESEARCH PROJECT THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS IN EUROPE

EBC European Brain Council

## VOT PROJECT COORDINATOR

The **European Brain Council** (EBC), which coordinates the VOT project, is a non-profit organisation and network bringing together key partners in the brain ecosystem: scientific societies, patient organisations, professional societies and industry partners. Its main mission is to promote brain research with the ultimate goal of improving the lives of the estimated 179 million Europeans living with brain conditions, mental and neurological alike.

## EBC MEMBERS

ean european academy of neurology

ECNP european college of neuropsychopharmacology

EFNA EUROPEAN FEDERATION OF NEUROLOGICAL ASSOCIATIONS

EPA

FENS Federation of European Neuroscience Societies

GAMIAN-EUROPE

THE EUROPEAN ASSOCIATION OF NEUROSURGICAL SOCIETIES

INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

EUROPEAN PAEDIATRIC NEUROLOGY SOCIETY

## OBJECTIVES OF THE VOT PROJECT

Identify treatment gaps (or barriers to care) and causing factors along the care pathway and propose solutions to address them.

Assess health gains and socio-economic impacts resulting from best practice healthcare interventions, in comparison with current care or inadequate treatment.

Converge data evidence to policy recommendations on how to improve the care pathways.

There are three VOT project rounds developed as part of the health economics and outcomes research framework:

VOT 1st ROUND 2015-2017 EARLY INTERVENTION BRIDGING THE EARLY DIAGNOSIS AND TREATMENT GAP

VOT 2nd ROUND 2019-2021 BRIDGING THE GAPS & ACHIEVING SEAMLESS, COORDINATED CARE

VOT TRANSVERSAL TOPICS



**The VOT 2 project (2019-2021),** focusing on rare neurological diseases and neurometabolic disorders, is coming to an end and 2022 will be an important milestone in terms of case study results dissemination. The study looked at early intervention and explored the benefits of coordinated care through the examination of health services, multidisciplinary care patterns (also addressing comorbidity), patient outcomes and costs. Results provide insight on the value of specialist centres for ataxia and dystonia and metabolic care units for phenylketonuria in terms of diagnosis, management of patients with rare conditions. Case studies which combine a care pathway analysis followed by an economic evaluation were conducted with the support of Academic Partners and in collaboration with European Reference Networks experts, applying empirical evidence from different European countries.

## RESEARCH COLLABORATION: ACADEMIC PARTNERS AND ERNs IN VOT2

### ▶ Rare diseases case studies

| UCL | UNIVERSITY OF CAMBRIDGE | SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET | UCD DUBLIN |
|---|---|---|---|
| Ataxia care pathway analysis | Ataxia & Phenylketonuria health economics study | Dystonia care pathway analysis & health economics study | Phenylketonuria care pathway analysis |

Research conducted in closed collaboration with the European Reference Networks (ERN-RND and MetabERN).

They are two of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States.

ERN-RND : neurological diseases

MetabERN : hereditary metabolic disorders

European Reference Network | Neurological Diseases (ERN-RND)

European Reference Network | MetabERN European Reference Network for Hereditary Metabolic Disorders

### ▶ Transversal collaboration with patient associations

ATAXIA

AISA

DYSTONIA EUROPE

E.S.PKU

PKU ASSOCIATION OF IRELAND Empowering PKU

RARE DISEASES INTERNATIONAL

DIG PKU E.V.

EURORDIS RARE DISEASES EUROPE

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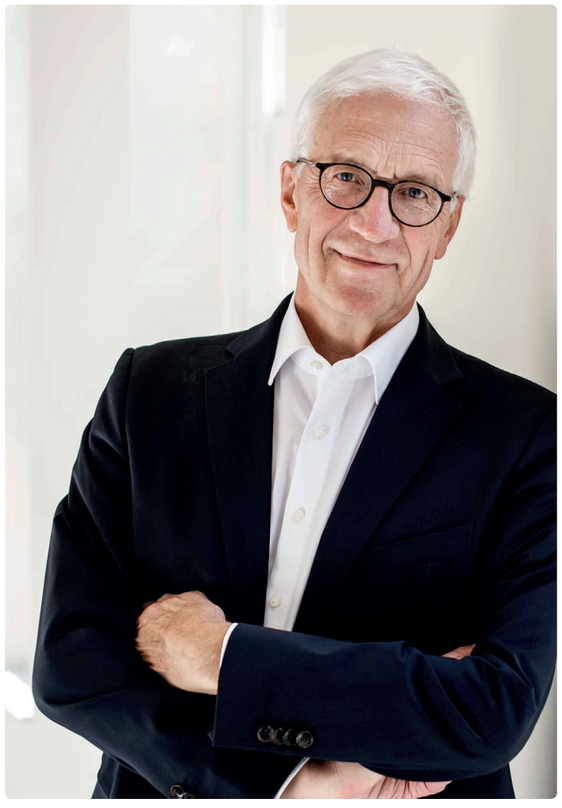


**“Our preferred scenario “greater investment in preventive and medical care across the life course” is defined by the innovation driven by patient’s unmet needs and the value of treatment. Access to optimal, timely care across Europe is essential. Together, this emphasizes the ambition for more patient-empowering research policy and an integrated, multidisciplinary approach to rare diseases looking at payment systems, new treatment paradigms and healthcare digitisation as an innovative boost.”**

***Professor Wolfgang Oertel**,*
*President, European Brain Council.*



# Foreword

**Unprecedented innovation in technology and medical processes is rapidly revolutionising human life.** Current health systems, however, have not been able to adapt quickly enough to maximise the value to patients. This is particularly true for rare brain diseases and particularly challenging for policy makers.

**Value-based healthcare is gaining traction in Europe as the desired solution or path forward in improving health systems**. The approach towards seamless care models critically intertwines wider patient and societal outcomes with efficient spending of resources. Reinforcing this should lead to both a more sustainable framework for payers and better care for patients. Moreover, COVID-19 presents an opportunity to reset fragmented healthcare systems so that they are integrated, driven by people and communities and resilient in the face of future systemic shock.

**The European Brain Council (EBC) initiated in 2019 a research project on the Value of Treatment (VOT) for Rare Brain Diseases, Bridging Gaps and Achieving Seamless, Coordinated Care.** The research project – which prioritises brain health and efficient care pathways for people living with a rare disease – includes 3 case studies related to rare neurological diseases (Ataxia, Dystonia) and neurometabolic disorders (Phenylketonuria). On 14 March 2022, EBC launches a call to action with case study results and infographics during the 2022 Brain Awareness Week. Results will be further published in the European Journal of Neurology and presented at scientific congresses. This project aims to uncover the many facets of the policy challenges facing Ataxia, Dystonia and Phenylketonuria. Analysing these diseases jointly make it more impactful for public health. Case studies were analysed in collaboration with EBC’s scientific societies and patient organisations in line with the research framework. The project assesses the treatment gaps and the costs of inadequate treatment. Our findings recommend early intervention and the promotion of a comprehensive healthcare approach (as opposed to fragmentation in separate medical “silos”), address combined research and public health policy gaps and opportunities at the EU level, and translate the findings into policy recommendations.

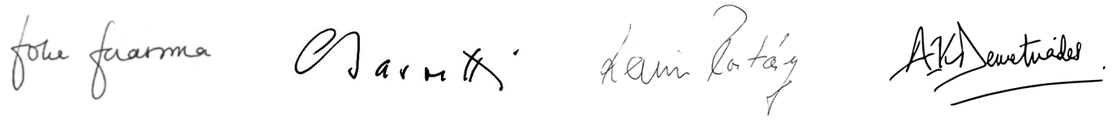
**With this new study, EBC is not only looking at the socio-economic impact and value of optimal healthcare interventions** but is also emphasising how timely care pathways are likely to need greater integration and how better collaboration can be achieved in the future for the benefit of those living with a rare disease. We address patients’ biopsychosocial needs and concerns, and pinpoint common denominators linking studies of Ataxia, Dystonia and Phenylketonuria. We highlight the value of specialist centres and the key role of multidisciplinary care teams as a solution to improve patient quality of life and as beneficial to society and health systems in the long term. Research links early intervention to measurable health gains, reduced complications and disability, improved survival rate, better use of resources. However, effective implementation of early diagnosis and treatment varies widely across health systems and many European countries are still lagging behind, with wide clinical practice variations even within countries (health inequalities). Rare diseases can be both life-limiting and life-threatening, and disproportionately affect children, with serious implications for families dealing with prolonged impairment. Patients and their families continue to have difficulties getting a diagnosis and accessing appropriate health services. This is particularly blatant for rare neurological diseases and neurometabolic disorders. VOT is addressing the obstacles to optimal care pathways while providing innovative solutions.

**The release of the study results is timely. The rare disease community, with a leading number of scientific societies representatives, patients, parliamentarians and member states, is calling the European Commission to increase cooperation on rare diseases while addressing unmet needs by 2030.** With rare diseases part of the priority agenda of the French Presidency of the Council of the European Union (January-June 2022), the focus is on seamless cross-border data sharing to underpin research into diagnosis, treatment, and care. With 30 million patients in the bloc and treatments available for only 5% of the diseases, the issue has been on the EU agenda for years. In 2009, the Member States adopted policy recommendations initiating new efforts, while the European Commission has invested €1.8 billion in research in the last 14 years. Science, Economics, and policy need to better coalesce to inform investment decisions. It follows that these three dimensions must be addressed in concert for innovation to flourish in rare and pediatric-onset diseases. Stakeholders must share a 'moonshot' mindset to foster scientific breakthroughs, abate existing barriers (including regulatory and pricing & reimbursement hurdles), and develop well-calibrated incentives. Change in the rare disease and pediatric spaces should be geared towards agile collaboration frameworks that allow meaningful partnerships towards the shared goal of reducing unmet needs. This is the aim of current discussions under several strategies, including the EU Pharmaceutical Strategy, the Disability Strategy or the Data Strategy, for a new legislation to be adopted by the end of the year.

**The reality of rare diseases is increasingly situated at the network level.** Early 2022, 620 new healthcare units joined the European Reference Networks (ERNs) in 24 EU Member States. In 2017, when the ERNs were established, nearly 900 healthcare units had joined. The European Commission prepares to build the European Health Data Space (EHDS) to promote better exchange and access of data. Another avenue for encouraging translation of academic research is through a new Horizon Europe partnership between the European Commission, Member States and the rare diseases community. This will build on the European Joint Programme for Rare Diseases that coordinated funding and supported research at EU level. The new partnership, expected to launch around 2023, will aim to transform the links between clinical care and research and to create the ecosystem truly required to make Europe a leader in rare diseases research. The ultimate goal for the EU is a new action plan for jointly tackling the burden of rare diseases that would set out objectives and policy recommendations for its member states. Following the momentum at the global level, the United Nations adopted on 16 December 2021, the first-ever Resolution for Persons Living with a Rare Disease and their Families, this marked a significant step towards greater equity for patients.

**Together we are stronger. We don't have all the solutions at once, but these are promising,** and the research will be pursued based on a common approach. Through building up evidence, EBC is providing the necessary policy recommendations and a call for action to address the treatment gap and its consequences. We would like to take the opportunity to thank all EBC members and partners for being part of this challenging journey.

*by **Ms Joke Jaarsma** (President, European Federation of Neurological Associations), **Professor Claudio Bassetti** (President, European Academy of Neurology), **Professor Kevin Rostasy** (President, European Paediatric Neurology Society), **Professor Andreas Demetriades** (President, European Association of Neurosurgical Societies).*





# Acknowledgements

Due to their small prevalence rates and often complex care pathways, rare diseases continue to present policy and health systems challenges globally. Given the related gaps in understanding around best practice to address challenges related to rare diseases, EBC conducted research to highlight the burden, unmet needs and opportunities related to these diseases. Key rare disease experts and stakeholders were engaged to illuminate challenges, and to stimulate discussion on opportunities or addressing rare brain diseases. Our sincere thanks go to several people for both their time and contributions to this work.

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All output is non-promotional and not specific to any particular treatment or therapy.

# Case study results

In this section, we present a summary of each case study, briefly setting out the context, the treatment gaps identified and the proposed recommendations to tackle them, while highlighting the potential socio-economic impact of their implementation. The results of the case studies will be submitted to a peer review journal (The European Journal of Neurology). All the documents related to the project and to the individual case studies are available online:
Value of Treatment: 2nd Round – European Brain Council (EBC)

VOT
**The value of treatment for persons living with Ataxia**

VOT
**The value of treatment for persons living with Dystonia**

VOT
**The value of treatment for persons living with Phenylketonuria**



UCL VOT by EBC European Brain Council

# Unmet needs in the management of the ataxias

**Julie Vallortigara[1], Julie Greenfield[2], Barry Hunt[2], Deborah Hoffman[3], Carola Reinhard[4], Holm Graessner[4], Antonio Federico[5], Steve Morris[6], Vinciane Quoidbach[7], Paola Giunti[1]**

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# Background

The ataxias are a group of complex chronic rare neurological disorders affecting motor functions. Patients with ataxia experience lack of balance and coordination, slurred speech, impaired eye movements among other symptoms. Gait and balance problems often progress to the point at which patients become wheelchair-bound, and, in general, the level of disability progresses at the cost of functional independence. Global epidemiological studies on ataxia have estimated an overall ataxia occurrence rate of 26/100,000 in children, and for hereditary cerebellar ataxia an occurrence rate of 2.7 to 3.3 /100,000[1]. Friedreich's ataxia is the most common inherited ataxia, with an estimated prevalence of 3.4 cases per 100,000 individuals[2]. A lack of awareness and understanding of these rare neurological disorders among Healthcare professionals (HCP) makes their management challenging and highlights the importance of specialist clinical services for diagnosis and treatment. Ataxia management warrants a broad and multi-disciplinary approach to suit patients' need. The aim of this project was to understand if the existing specialist ataxia centres could provide an improved coordinated care pathway and better management of these conditions.

# Methods

Three countries with existing Specialist Ataxia Centres (SAC) are covered by this study: UK, Germany and Italy. We count two centres in the UK, nine in Germany and eleven in Italy, all spread out across respective countries. The ataxia case study aims to expand on preliminary evidence for the value of Specialist Ataxia Centres in being able to deliver early coordinated interventions in both the management of patients with the ataxias and in diagnosis. This project explores the patient pathways of individuals with different progressive ataxias in Specialist Ataxia Centres compared with usual care scenario in non – specialist settings. To do so, we ran a survey in the UK, Germany and Italy to collect information from patients about patient's pathway including the diagnosis and the management of their ataxias. In addition to the survey, a targeted literature review was done on the treatment patterns for the hereditary ataxias in Europe. Through these approaches, we have identified unmet patients' needs and treatment gaps for the ataxias. Here we present a summary of converging data, from the patient survey, collected and analysed for the three selected countries.

# Treatment Gaps/Unmet Needs

- **Difficulty in reaching a specific diagnosis:** Diagnosis can be long and complex, involving tests that do not always result in a conclusive diagnosis: between 20-40% of the surveys respondents live with ataxia of unknown cause. This data not only came out of our survey but also was supported by the literature review. (Giunti et al, in preparation).





- **Challenge in accessing a Specialist Ataxia Centre:** (1) a physical challenge in travelling to a SAC because the SACs are too far away; (2) lack of awareness amongst healthcare professionals about the SAC and lack of clear pathway or referral system to access service, also reported by participants who were never invited to be referred there. Between the cohorts of the three countries, 20-50% participants never attended a SAC. Moreover, there are patients who no longer receive care at SACs because of the travel challenge and the lack of follow up referral.
- **Knowledge and understanding of ataxia:** participants felt there is a lack of understanding of ataxia in primary care services.
- **Clear pathway to access care by a multidisciplinary team:** less than half of the respondents received care from a multidisciplinary team (MDT) and most of them reported a positive feedback about the MDT care being effective. Given this positive feedback the low access to an MDT clinic is a concern.
- **Management of the ataxias:** Patients reported a better overall treatment and care in SACs, with a positive feedback on the understanding how to manage the condition, coordination of referrals and offers to participate in research. Given this positive feedback the low referral to the SACs is a concern.

# Recommendations

- Implement of Whole Genome Sequencing in order to achieve timely genetic diagnosis of the rare ataxias.
- Increase the awareness of Ataxia Specialist Centres in Europe in order to have more timely referrals.
- Implement telemedicine in existing centres to increase the number of patients who can be seen and increase the number of centres when possible.
- Introduce enhanced educational packages related to the ataxias across Primary care services as these services play an important role in the management and care of ataxia patients.
- Develop an increased availability of MDT clinics so that more patients with ataxia can attend. We would also recommend a structural integration and funding of MDT clinic in the care provision by SAC.
- Ensure centres have an interest in translational research so the treatment will be more evidence based for these rare conditions, and they can be sites for clinical trials (recommended by experts' team working in existing SAC).

## Here is what patients say about their visit to a Specialist Ataxia Centre:

*"I truly believe that the ataxia centre helps me to face this stressful situation and to cope with this condition which would be otherwise unbearable."*

*"I feel I get assistance and help and not feel left alone."*

*"Clinicians at the ataxia centre know more than others about the ataxia condition."*

*"Because the clinicians deal solely with ataxia patients, they have more understanding of the disorder. Plus, they are at the forefront of treatment if it becomes available."*

## Here is some patients feedback about how to improve the care for their ataxia:

- Patients wish to see improvement on the information available about the disease and the treatments.
- They want to feel more in control, to get advice on how to cope better, to have better access to therapies.
- They would also like to know more about adaptation to their home, and the local care available to them.
- Overall participants who are not seen in a SAC have expressed more needs for improvements compared with people who are patients in SAC.





# Conclusions

The ataxias are complex rare neurological disorders with no approved therapies, no disease modifying treatments for the majority of the patients. The survey has highlighted a pressing need to implement specialist ataxia centres as patients feel overall the management is better in that setting compared to primary or secondary settings. There are barriers to achieve patient equality in accessing the SACs. Barriers have been identified, being physical distance to centres, lack of awareness of such centres for the ataxias in primary care, and the lack of a clear pathway to refer patients to SACs in order to achieve a coordinated care management and more personalised care pathway. From our experience, the collaboration between Specialist Ataxia Centres and charities relevant to these conditions has been crucial in their success and a tighter collaboration will facilitate the improvement of the access of these patients to these centres. Finally, resources should be deployed to support the existing SACs, responding to the increase demand of patients referred to them and to create new SACs where possible.


# Acknowledgements:

This study is part of the EBC-led Value of Treatment project and supported by Reata Pharmaceuticals and Takeda.


### References:


1. Pilotto F. et Saxena S., Clinical and Translational Neuroscience, July-December 2018, 1-12;
2. Parkinson MH et al, J. Neurochem, 2013 Aug;126 Suppl 1:103-17

## Whole genome sequencing detects the most common inherited neurological diseases

An article published in the Lancet Neurology (March 2022) showed that whole genome sequencing (WGS) can detect common inherited neurological disorders, including some ataxias. Genetic testing can be a slow process, with a number of tests sometimes required to provide a diagnosis. However, this study showed that WGS (a different type of genetic testing) can quickly and accurately detect common neurological conditions. This has the potential to reduce the 'diagnostic odyssey' that a lot of people with rare conditions face.



# Impact of specialist ataxia centres on health service resource utilisation across Europe

**Hudson E[1], Vallortigara J[2], Greenfield J[3], Hunt B[3], Hoffman D[4], Reinhard C[5], Graessner H[5], Federico A[6], Quoidbach V[7], Giunti P[2], Morris S[1]**

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# Background

The ataxias are a group of complex rare neurological disorders, which can have a range of symptoms resulting from the damage to the cerebellum or its connections. The international prevalence of cerebellar ataxia ranges from 0.3 to 3.0 per 100,000[1]. Features of ataxia include dyssynergia, dysmetria, tremor, poor balance, gait instability, dysarthria, and cognitive impairment[2, 3]. Patients with ataxia often have significant needs that require a complex package of health and social care. Given its rarity, accessing suitable care for this condition can be challenging. Specialist Ataxia Centres (SACs), are centres of excellence, where a coordinated service combines diagnosis, treatment, support and research[4]. The SAC incorporate networks of all relevant medical disciplines within the core team as an efficient approach to delivering high quality healthcare. However, it is not known if a patient's attendance at a SAC is associated with reduced utilisation of other health care resources. The aim of this study was to investigate whether patients who attend SACs in three European countries reported differences in their health care utilisation compared with patients who did not attend a SAC.

# Methods

We compared mean resource use per patient affected by ataxia in three European countries (UK, Italy, Germany) over a 12-month period from a health service perspective. Subjects were adults aged 16 years and older with a confirmed diagnosis of ataxia. Data were obtained from a patient level survey distributed by patient organisations and providers. The survey was undertaken in participating countries in 2019 (UK) and 2021 (Italy and Germany). Participants were asked to record the number of health care contacts they had received in the preceding 6-12 months specifically to manage their ataxia, and whether they currently or had ever attended a SAC. We compared average resource use for each contact type over a 12-month period stratifying patients by whether they were currently attending a SAC or had never attended a SAC. We tested for significant differences in mean resource use between the SAC/not SAC groups using unadjusted and adjusted regression analysis, the latter controlling for age, sex, number of symptoms experienced as a result of ataxia, and whether or not the patient had comorbidities.

# Results

After data cleaning we analysed responses from 181 patients from the UK, 96 patients from Italy and 43 patients from Germany who said they were either currently attending a SAC or had never attended a SAC and provided resource use data. The percentage of sample respondents in each country who reported they were currently attending a SAC was 40%, 77% and 77%, respectively. The modal age category in each country was 60-79 years in the UK, and 39-59 years in Italy and Germany. The proportion of respondents who were male was 45%, 49% and 55%, respectively. In the UK the most common contacts for SAC patients were physiotherapy visits (mean 3.1 visits per year) followed by general practitioner visits and other visits (1.9) (*Table 1*). In Italy the most common contacts were physiotherapy visits (14.5) and speech and language therapy visits (6.4). In Germany the most common contacts were physiotherapy visits (27.9) and speech and language therapy visits (11.5). In every country





the SAC group had more specialist centre visits than the non-SAC group, but the differences in the numbers of contacts for the other types of health service use between the SAC and non-SAC groups were mostly non-significant. Exceptions were other clinic visits in the UK (there were higher mean contacts for patients in the SAC group), neurology outpatient visits in Italy (higher mean contacts in the non-SAC group) and speech and language therapy visits in Germany (higher mean contacts for patients in the SAC group). There were notable differences between countries in the volume of contacts – in particular with regards to visits to the physiotherapist, speech and language therapist and occupational health therapist, all of which were lower in the UK.

**Table 1. Health care contacts over a one-year period for Non-SAC and SAC patients in three European countries**

| | Patients who reported never attending a SAC | | | | Patients who reported attending a SAC currently | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Health care contacts** | **Obs** | **Mean** | **Std Dev** | **Median** | **Obs** | **Mean** | **Std Dev** | **Median** | **P-value[1]** | **P-value[2]** |
| **United Kingdom** | | | | | | | | | | |
| Specialist centre visits | 109 | 0 | 0 | 0 | 72 | 1 | 0 | 1 | <0.01 | <0.01 |
| General Practitioner visits | 108 | 2.3 | 3.5 | 0 | 58 | 1.9 | 3.3 | 0 | 0.40 | 0.51 |
| Neurologist outpatient visits | 115 | 1.5 | 2.9 | 0 | 59 | 1.3 | 2.6 | 0 | 0.54 | 0.24 |
| Inpatient stays | 110 | 0.3 | 1.0 | 0 | 58 | 0.1 | 0.4 | 0 | 0.20 | 0.17 |
| Accident & Emergency visits | 112 | 0.3 | 1.0 | 0 | 60 | 0.3 | 1.0 | 0 | 0.65 | 0.82 |
| Physiotherapy visits | 109 | 1.6 | 3.2 | 0 | 64 | 3.1 | 4.5 | 0 | 0.01 | 0.11 |
| Speech and Language therapy visits | 113 | 0.7 | 1.8 | 0 | 60 | 0.3 | 0.7 | 0 | 0.06 | 0.23 |
| Occupational Health Therapy visits | 113 | 1.3 | 3.1 | 0 | 63 | 1.5 | 3.0 | 0 | 0.81 | 0.98 |
| Non-neurology outpatient visits | 109 | 0.7 | 2.1 | 0 | 60 | 1.1 | 2.3 | 0 | 0.30 | 0.21 |
| Other visits | 109 | 0 | 0 | 0 | 70 | 1.9 | 2.6 | 1 | <0.01 | <0.01 |
| **Italy** | | | | | | | | | | |
| Specialist centre visits | 22 | 0 | 0 | 0 | 74 | 1.4 | 0.7 | 1 | <0.01 | <0.01 |
| General Practitioner visits | 19 | 1.3 | 2.6 | 0 | 54 | 0.7 | 1.3 | 0 | 0.20 | 0.39 |
| Neurologist outpatient visits | 20 | 2.7 | 5.0 | 1.5 | 55 | 0.4 | 0.7 | 0 | <0.01 | 0.02 |
| Inpatient stays | 19 | 0.3 | 0.6 | 0 | 57 | 0.3 | 0.6 | 0 | 0.91 | 0.51 |
| Accident & Emergency visits | 18 | 0.3 | 0.8 | 0 | 57 | 0.1 | 0.4 | 0 | 0.30 | 0.17 |
| Physiotherapy visits | 21 | 19.0 | 19.6 | 10 | 63 | 14.5 | 19.8 | 2 | 0.37 | 0.40 |
| Speech and Language therapy visits | 19 | 7.8 | 11.6 | 1 | 61 | 6.4 | 12.7 | 1 | 0.67 | 0.78 |
| Occupational Health Therapy visits | 18 | 1.5 | 2.7 | 0 | 50 | 1.3 | 4.1 | 0 | 0.88 | 0.95 |
| Non-neurology outpatient visits | 18 | 1.6 | 4.0 | 0 | 59 | 1.9 | 5.5 | 0 | 0.80 | 0.28 |
| **Germany** | | | | | | | | | | |
| Specialist centre visits | 10 | 0.0 | 0.0 | 0 | 33 | 1.3 | 0.9 | 1 | <0.01 | 0.01 |
| General Practitioner visits | 8 | 5.5 | 10.1 | 2 | 34 | 4.9 | 5.2 | 3.5 | 0.80 | 0.23 |
| Neurologist outpatient visits | 11 | 3.7 | 3.1 | 3 | 30 | 2.5 | 2.9 | 2 | 0.23 | 0.47 |
| Inpatient stays | 10 | 0.0 | 0.0 | 0 | 31 | 0.3 | 0.7 | 0 | 0.24 | 0.24 |
| Accident & Emergency visits | 9 | 0.1 | 0.3 | 0 | 31 | 0.6 | 2.7 | 0 | 0.59 | 0.92 |
| Physiotherapy visits | 11 | 33.7 | 22.8 | 50 | 28 | 27.9 | 23.7 | 40 | 0.49 | 0.92 |
| Speech and Language therapy visits | 10 | 8.9 | 18.5 | 0 | 33 | 11.5 | 17.2 | 1 | 0.69 | 0.02 |
| Occupational Health Therapy visits | 10 | 7.9 | 17.2 | 0 | 30 | 10.4 | 17.7 | 0 | 0.70 | 0.41 |
| Non-neurology outpatient visits | 9 | 1.6 | 2.3 | 1 | 28 | 1.6 | 2.0 | 1 | 0.95 | 0.54 |

1 Test for significant differences in mean contacts between Non-SAC and SAC groups (unadjusted)
2 Test for significant differences in mean contacts between Non-SAC and SAC groups (adjusted for age, sex, and number of symptoms and presence of co-morbidities)

## Conclusions

The ataxias are complex rare neurological disorders with no approved therapies, no disease modifying treatments, and a lack of global guidelines for the management of such conditions often resulting in haphazard and burdensome care delivery. Our findings show that a range of health care professionals are involved in the management of ataxia in Europe. Mean costs per patient will be higher among those attending specialist centres due to the costs of the contacts with the specialists at the SAC; the number of contacts for most other types of health service use were the same, irrespectively or whether or not patients attended a SAC. Our findings also show that differences between countries in some types of health service use. Further research to understand these differences and whether they result in differences in outcomes would be beneficial.

## Acknowledgements:

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# Assessing the value of specialist centres and education for the diagnosis and management of dystonia in Europe

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# Background

Although under-diagnosed, dystonia syndromes (DS) represent the third most common disorder in movement disorder centers. We have reported a lack of specific training in dystonia by general neurologist (GN), family doctors (GP) and health professionals in a study performed by the European Network for the Study of Dystonia[1]. In addition, using on-line questionnaire we have shown a long interval to diagnosis and treatment and consequently pure QoL of dystonia patients in Europe[2]. The sub-analysis was performed in different health care systems, with regards to delivery of services financing and coverage, to investigate the socio-economic impact of structured, accredited postgraduate, or sub-specialising MD training and developed organised centres.

# Methods

The validated on-line questionnaire (available in 24 languages on the Dystonia Europe website) was distributed to dystonia patients. The questionnaire (developed in Croatia, University of Zagreb Medical School) was composed of 30 questions divided into three parts (part I. General questions: as name, age, etc.; part II. Specific questions such as disease duration, type of DS, time to correct diagnosis, who made correct diagnosis, experience with first visit to GP etc.; part III. Availability of therapy, type of therapy, therapy side effects etc.). Data were collected from 2017- 2019. In addition, sub-analysis was performed for four separate health-care systems in Croatia, Italy, Germany and UK, as examples of EU countries on different levels of development with different health care systems with regards to delivery of services, financing and coverage. All variables (whether considered "dependent" or "independent" [terms used although no causality is inferred considering the cross-sectional data]) were categorical: binary (gender), multinominal ordered (e.g., age, time to diagnosis, time to treatment, treatment satisfaction) or not (e.g., type of dystonia [diagnosis]). All outcomes (except for "time-to-treatment" [from diagnosis]) were modeled by fitting generalised linear models. All analyses are limited by the varying amount of missing data. SAS 9.4 for Windows (SAS Inc., Cary, NC) was used.

# Results

A total of 3,210 questionnaire responses were received from EU countries. Sub-analysis was performed on questionnaires received from Croatia (350), Germany (321), Italy (175) and the United Kingdom (741). Women outnumbered men in all countries. In the UK, Germany and Italy only around ¼ of subjects were men (the proportion was by 31% relatively higher in Italy than in the UK). The sample from Croatia comprised only 14.0% of men (i.e, around 40% less, relatively, than the UK) (*Table 1*). In all country samples, most of the subjects were aged 41-50 or 51-60 years. Cervical dystonia was the most common type (48%) followed by generalised dystonia (15%).



Assessing the value of specialist centres and education for the diagnosis and management of **dystonia** in Europe

| TABLE 1 | UK | Germany | Italy | Croatia | Germany/UK | Italy/UK | Croatia/UK |
|---|---|---|---|---|---|---|---|
| N | 751 | 340 | 175 | 379 | | | |
| Men | 171 (22.8) | 86 (25.3) | 52 (29.7) | 53 (14.0) | PR=1.11 (0.89-1.39) | PR=1.31 (1.00-1.70) | PR=0.61 (0.46-0.81) |
| Age groups | | | | | | | |
| Up to 20 years | 20 (3.3) | 10 (2.9) | 18 (10.3) | 9 (2.4) | Modelled is probability of being in the higher age band: OR <1.0 indicates lower of odds, ie., younger subjects. | | |
| 21-30 years | 36 (4.8) | 25 (7.3) | 8 (4.6) | 21 (5.5) | | | |
| 31-40 years | 61 (8.1) | 35 (10.3) | 25 (14.3) | 43 (11.4) | | | |
| 41-50 years | 147 (19.6) | 59 (17.4) | 44 (25.1) | 87 (23.0) | OR=0.85 (0.67-1.07) | OR=0.45 (0.33-0.60) | OR=0.78 (0.63-0.97) |
| 51-60 years | 250 (33.3) | 118 (34.7) | 48 (27.4) | 110 (29.0) | | | |
| 61-70 years | 161 (21.4) | 64 (18.8) | 20 (11.4) | 80 (21.1) | | | |
| >70 years | 69 (9.2) | 27 (7.9) | 8 (4.6) | 20 (5.3) | | | |

In 40-50% of patients, general practitioners (GPs) recognised the symptoms and referred to an appropriate specialist, while in over 25% of cases, GP did not recognised DS and did not refer patients to a specialist. Only 25% of patients obtained a correct diagnosis within one year after first symptoms, while more than 15% waited longer than 10 years (*Table 2*). Consequently treatment was delayed. Sub-analysis of data from Croatia, Germany, Italy and the UK did not show statistically significant differences among countries, despite significant differences in healthcare systems, especially financing. According to the Organisation for Economic Co-operation and Development (OECD), cost 'per Capita' in Croatia (1504 eur) was 2-4 times less than in the other three countries[3]. However, Croatia is the only country with mandatory movement disorders education for GPs. Results of our study indicate that management of dystonia patients could be positively correlated with specialist medical education, especially GPs. When translating the impact of DS, delayed diagnosis and treatment economic savings are evident. Each year of d layed diagnosis (Croatian data) increases healthcare costs 3-5 times for DS patients (GP visits, hospital stays, tests, medicine and productivity loss due to absence from work).

| TABLE 2 | UK | Germany | Italy | Croatia | Germany/UK | Italy/UK | Croatia/UK |
|---|---|---|---|---|---|---|---|
| N | 751 | 340 | 175 | 379 | | | |
| GP assessment | | | | | | | |
| No referral (0) | 221 (29.4) | 87 (25.6) | 50 (28.6) | 94 (24.8) | Modelled is probability of a "better" decision by the GP: OR >1.0 indicates higher odds, ie., "better" decision by a GP. ORs are adjusted for gender, age-band and type of dystonia. | | |
| Erroneous referral (1) | 159 (21.2) | 74 (21.8) | 31 (17.7) | 53 (14.0) | | | |
| Correct referral (2) | 324 (43.1) | 149 (43.8) | 72 (41.1) | 198 (52.2) | | | |
| Missing data | 47 (6.3) | 30 (8.8) | 22 (12.6) | 34 (9.0) | OR=1.11 (0.86-1.42) | OR=0.98 (0.70-1.36) | OR=1.54 (1.19-1.98) |

## Conclusions

This study represents a first attempt of evaluating the economic benefits of addressing major treatment gaps, especially delayed diagnosis, in DS care. Significant efforts is needed to organise specialist movement disorder centers and to introduce sub-specialised education for general neurologists (GNs) and general practitioners (GPs). Consequently, positive socio-economic impact should be achieved.

## Acknowledgements:

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### References:

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# Phenylketonuria (PKU) Care Pathway Analyses

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# Background

Phenylketonuria (PKU) is an inborn error of amino acid metabolism, caused by deficiency of the enzyme phenylalanine hydroxylase Newborn screening (NBS) programs have been implemented in most European countries, to enable early introduction of dietary management as untreated, alterations in chemical balance can lead to severe intellectual disability. This development prompted the establishment of PKU clinics, that eventually also attended to patients with other inherited metabolic disorders European PKU management guidelines have recommended target Phe levels for children and adults, monitored through serial blood tests with advice given to patients regarding changes to their diet, if required.The recent introduction of two distinct pharmacologic options ie oral pharmacologic chaperone subcutaneous enzyme therapy) enables achievement of Phe level targets, with potential for the relaxation of the diet Longterm outcomes amongst early treated individuals suggest there may be on going difficulties which may be intrinsic to PKU and/or its management. In particular, psycho social issues and putative co morbidities (such as obesity) require further elaboration whilst the added value of novel therapies need to be established.

# Methods and Findings

Three independent metabolic units (based in Ireland, UK and Spain), dealing with children and/or adults with IEM examined staffing and resources, PKU patient care pathways (including practice relating to the implementation of European guidelines), and potential economic implications. Patients were asked to complete the following instruments (EQ5D5 L, and a Neophobia scale), to assess concerns involving anxiety/depression, quality of life and aversion to certain foods.Medical records were reviewed to ascertain the proportion of patient achieving Phe level targets, and the presence of comorbidities.For adults, there was a determination of the extent to which patients met criteria for metabolic syndrome. Discussions were held with Health Economics advisors and a specialist in health care systems delivery (reported separately). In the course of data collection, opinions were sought from a patient advocate and an independent expert representing MetabERN.

## Patient testimonies:

***Irish experience:***

*"Having PKU is having a tag for the rest of my life."*

*"Just annoying counting exchanges not being ableto eat what you want and be normal."*

***Spanish experience:***

*"I lapsed with diet between young adult and middle-aged adult. I lost touch with the metabolic unit at first, and now I returned back since PKU affects my short-term memory and agility of mind"*

***UK experience:***

*"To be good at diet you need full support - home & medical - if one part is missing you fall off the wagon."*

*"People don't seem to realise the mental and physical toll it takes on you as a person having PKU, they seem to think, 'Oh it's just a food thing, I'm sure it can't be that bad'."*





**Table 1. Summary of patient characteristics and clinic interactions**

| CATEGORY | | Ireland<br>Mater Misericordiae University Hospital, Dublin (>18 years) | Spain<br>Hospital Clínico Universitario de Santiago (>18 years) | UK<br>Birmingham Children's Hospital (12-16 years) |
|---|---|---|---|---|
| **Cohort size** | n (%) | n (%) | n (%) | n (%) |
| | Total Sample | 50 (100) | 31 (100) | 33 (100) |
| | Male | 14 (28) | 9 (29) | 16 (48.48) |
| | Female | 28 (56) | 22 (71) | 17 (51.52) |
| | mPKU | 8 (16) | / | / |
| **Age Years ± SD**<br>***Female category does not include mPKU** | Total Sample | 38.8 + 10.1 | 32.1 + 10.4 | 13.1 + 1.3 |
| | Male | 35.3+ 9.5 | 34.6 + 12.8 | 13.5 + 1.3 |
| | Female | *42.1 + 10.2 | 31.1 + 9.5 | 12.7 + 1.2 |
| | mPKU | 33.5 + 9.4 | / | / |
| **Genotype:**<br>**Three Most Common Alleles, n (%)** | | 39 (78%) Irish patients had genetics results<br><br>R408W: 23 (59)<br>F39L: 8 (20.5)<br>R243*; I65T; 1315+1G>A: 6 (15.4) | 29 (87.9%) Spanish patients had genetic results<br><br>R261Q: 7 (24.1)<br>IVS10: 6 (20.6)<br>E280K: 4 (17.2) | Not available |
| **Mean Number of Clinic Attendances per patient per year ± SD** | Total Sample | 1.3 + 0.8 | 1.6 + 0.9 | 1.2 + 0.8 |
| | Male | 1.2 + 0.4 | 1.6 + 0.8 | 0.8 + 0.6 |
| | Female | 1.0 + 0.2 | 1.7 + 0.9 | 1.2 + 1.0 |
| | mPKU | 2.4 + 1.2 | / | / |
| **Mean number of Additional Dietetic Reviews per patient per year ± SD** | Total Sample | 0.3 + 1.4 | Not Reported | 2.2 + 2.1 |
| | Male | 0 | Not Reported | 1.8 + 1.8 |
| | *Female* | 0.1 + 0.4 | Not Reported | 2.5 + 2.4 |
| | mPKU | 1.5 + 2.8 | / | / |
| **Mean Number of Healthcare Professionals (HCPs) Seen per patient per year + SD** | Total Sample | 2.6 + 0.8 | 3.2 + 0.8 | 4.7 + 2.0 |
| | Male | 2.4 + 0.8 | 3.2 + 0.4 | 5.3 + 2.1 |
| | Female | 2.6 + 0.9 | 3.3 + 1.0 | 4.2 + 1.8 |
| | mPKU | 3.1 + 0.3 | / | / |

# Treatment Gaps/Unmet Needs

Dietary management of PKU has prevented development of intellectual disability, but residual problems relating to psychosocial issues and co morbidities may exist that require further exploration There may be vulnerable individuals who exhibit anxiety, which in combination with challenges in their imposed dietary restriction have a significant impact on quality of life. Despite close interaction with metabolic dieticians, it is worth noting a proportion of patients are overweight and/or obese the potential clinical relevance of which with aging necessitates close tracking Examination of the three Metabolic units indicates variability in staffing and resources, the implementation of the European PKU guidelines, the genotype profile of patients and access to novel therapies Increased availability of certain food products has expanded dietetic options for patients, and access to pharmacologic chaperone for some has enabled the relaxation of their` diet. To properly assess the value of novel therapies additional resources are required, to enable close patient follow up, drug dose/supplement adjustments, evaluation of adverse events, and the collection of outcomes data. Patients deemed most likely to benefit from novel therapies should have access, but this requires attention to close monitoring and determination of the added value of treatment, beyond dietary management alone. The experience with health care delivery during the pandemic lockdown requires investigation, as this has altered routine clinical practice, with the introduction of virtual clinic appointments and reporting of results via ` gadgets.

# Recommendations

- A definition of therapeutic goals, beyond maintaining Phe level within target needs to be established, for which data is required in support so clinical operations can be designed to meet patient expectations and address health related concerns.
- Special attention needs to be devoted to addressing psychosocial issues and potential comorbidities which represent added burdens that impact on the patient physical and functional well being.
- A proportion of patient experience high levels of anxiety, as suggested by screening tools that should be part of regular assessment to identify vulnerable individuals with provisions made for psychosocial support, as indicated.
- Support should also be provided to patients to minimize the other burdens, related to the cost of obtaining nutriceuticals and the posting of monitoring blood samples.
- Access to novel therapies provides the opportunity for improved patient management. It is hoped these measures will enable better patient outcomes, but require careful evaluation to ascertain value, given the associated high costs. European guidelines can be used as a benchmark to assess the practice of Metabolic Units but it is evident most units have adapted portions in different ways to suit local capacity.





# Conclusions

The paper describes clinical practice in relation to the diagnosis and management of children and adult patients with PKU, seen at three European metabolic units in Ireland, Spain and the UK dedicated to caring for individuals with inborn errors of metabolism. All three units are current members of MetabERN, a European non profit network established to facilitate access to the best available care and so address the needs across country borders of all patients and their families affected by IMD. European PKU guidelines have been published but its recommendations have been implemented to varying degrees by the three units, to suit local goals. Staff resources and access to supplements, low protein food and the use of saproterin was variable across the the 3 units. Currently, no patients at the time of data collection were managed with pevaliase Longterm studies focusing on quality of life, neurocognitive and psychosocial concerns are necessary, so programs to fully meet patient needs can be developed. Meanwhile, expanding the choice of low protein foods and other therapeutic options may enable optimal care and positive health outcomes for the patient community at large.

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# Health service use and costs associated with Phenylketonuria (PKU) in three European countries: cost analysis and comparison with guidelines

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# Background

Phenylketonuria (PKU) is a rare genetic metabolic disorder. Early intervention in the form of a low-Phe diet is critical in avoiding profound mental disability and severe neuro-psychiatric consequences of the disease. However, these diets are highly restrictive, unpalatable, and can have substantial impact on patients' and caregivers' time. As patients affected by PKU reach adolescence and adulthood, 70-80% of patients do not follow their diets.[1] Guidelines are important to improve diagnosis and management of PKU using a multidisciplinary care approach. 2017 European guidelines for the diagnosis and treatment of phenylketonuria set out a minimum standard of care for patients with PKU,[2] but there is little published evidence of the cost of implementing this guidance or adherence to it. The aim of this analysis was to determine the resource use and costs associated with PKU treatment, and how this resource use compares with recommended European guidelines.

# Methods

We compared the mean resource use per PKU patient at three European sites over a 12 month period and compared this with the recommended standard of care according to European treatment guidelines.[2] Subjects were 33 children (age range 12-16 years) at Birmingham Children's Hospital in the UK, 50 adults (22-63 years) at Mater Misericordiae University Hospital in Ireland, and 31 adults (19-56 years) at the Hospital Clínico Universitario de Santiago in Spain receiving treatment for PKU in April 2021. A health service perspective was taken for the cost analysis. Data were obtained from retrospective reviews of medical notes over the previous 12-month period. Data were collected for each patient on the number of clinic visits with the PKU team, staff attending these clinics, additional consultations with the dietitian, the number of home blood Phe monitoring tests, the average length of all contacts, the cost of protein diets, and the cost of medical treatment with KUVAN® (sapropterin dihydrochloride). All costs were calculated in 2020/21€. Unit costs for clinic visits and dietitian consultations were taken from published sources and converted into € at prevailing exchange rates where appropriate. Home blood Phe monitoring tests included the cost of the test undertaken by the parent/patient and a telephone call with the dietitian to report the results. Annual costs of the protein diet and KUVAN® per patient were based on published market prices.

# Results

Among 33 children (mean age 14 years) treated for PKU in the UK the mean (standard deviation, SD) clinic visits per patient and home blood Phe monitoring tests per patient over a 12-month period were 1.2 (0.8) and 36 (26), respectively (*Table 1*). For children aged 18 years and under European guidelines recommend 2 clinic visits per annum and monthly home blood Phe monitoring tests. 27% of the sample met the recommended guidelines for clinic visits and 79% for home blood Phe monitoring. Among 50 adults (mean age 39 years) treated for PKU in Ireland the mean (SD) clinic visits per patient and home blood Phe monitoring tests per patient over a 12-month period were 1.3 (0.8) and 11 (22), respectively. For adults aged over 18 years European guidelines recommend 1 clinic visit per annum and monthly home blood Phe



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monitoring tests. 100% of the sample met the recommended guidelines for clinic visits and 16% for home blood Phe monitoring. Among 31 adults (mean age 32 years) treated for PKU in Spain the mean (SD) clinic visits per patient and home blood Phe monitoring tests per patient over a 12-month period were 1.7 (0.9) and 5 (4), respectively; 100% of the sample met the recommended guidelines for clinic visits and 7% for home blood Phe monitoring. The mean (SD) total cost of contacts (clinic visits, additional dietitian consultations, home blood Phe monitoring tests) was €1072 (€795) for children in the UK, €591 (€833) for adults in Ireland and €438 (€223) for adults in Spain, though different cost components were included in each. When the costs of the protein diet were added the mean total costs increased to €17 253 (€4380) for children in the UK and €14 191 (€6342) for adults in Ireland. 3 children in the UK dataset were receiving KUVAN® at a mean annual cost per child taking the drug of €77 516 (€20 978). When these costs were included the mean total costs across all children in the sample increased to €25 428 (€24 835). No adults in the data from Ireland were receiving treatment with KUVAN®. 5 adults in the Spanish dataset were receiving KUVAN® at a mean annual cost per adult taking the drug of €46 827 (€26 626). When these costs were included the mean total costs across all adults in the Spanish sample increased to €14 474. Health service contacts accounted for 4-6% of the total costs in both children and adults affected by PKU.

**Table 1. Health care resource use and costs for people affected by PKU per annum at three European sites**

| | **UK** Birmingham Children's Hospital | **Ireland** Mater Misericordiae University Hospital | **Spain** Hospital Clínico Universitariode Santiago |
|---|---|---|---|
| | **Children** | **Adults** | **Adults** |
| **Observations** | 33 | 50 | 31 |
| **Age, years (mean, (range))** | 14 (12 to 16) | 39 (22 to 63) | 32 (19 to 56) |
| **Clinic visits per annum (mean, (SD), [% patients meeting European guideline])** | 1.2 (0.8) [27] | 1.3 (0.8) [100] | 1.7 (0.9) [100] |
| **Home blood Phe monitoring tests per annum (mean, (SD), [% patients meeting European guideline])** | 36 (26) [79] | 11 (22) [16] | 5 (4) [7] |
| **Additional dietitian visits (mean, (SD))** | 2.2 (2.1) | 0.3 (1.3) | |
| **Cost of clinic visits, € (mean, (SD))** | 210 (135) | 359 (423) | 348 (189) |
| **Cost of additional dietitian visits, € (mean, (SD))** | 152 (146) | 10 (46) | * |
| **Cost of home blood Phe monitoring tests, € (mean, (SD))** | 711 (514) | 221 (431) | 89 (74) |
| **Cost of protein diet, € (mean, (SD))** | 16 180 (4153) | 13 600 (6101) | 6483** |
| **Cost of KUVAN®, € (mean whole sample, (SD), [mean those prescribed only {SD}))** | 8174 (26 946) [77 516] {20 978} | 0 | 7552 (20 026) [46 827] {26 626} |
| **Total cost (contacts only)** | 1072 (795) | 591 (833) | 438 (223) |
| **Total cost (contacts + protein diet)** | 17 253 (4380) | 14 191 (6342) | 6921** |
| Total cost (contacts + protein diet + Kuvan) | 25 428 (24 835) | 14 191 (6342) | 14 474** |

* No data are available. ** Includes costs of Phe-free supplements only (protein supplements are self-paid by the patient). Total costs only were available so an SD is not reported

# Conclusions

A multidisciplinary care approach in the management of PKU is essential. Recommended European PKU guidelines have been implemented to varying degrees across the three units. The costs of health service contacts for people affected by PKU are modest compared with the costs of the protein diet and treatment with KUVAN®. Further research would be beneficial to understand the reason for the lack of adherence to recommended monitoring guidelines despite, and to identify strategies to encourage better monitoring.

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