CAPTURING THE FULL PICTURE

A JOINT POLICY PAPER ON UNMET MEDICAL NEED IN PHENYLKETONURIA (PKU)

Co-authors:

Kirsten Ahring
Deniz Atakay
Agata Bąk
Fatma Çelik
Merve Esgi
Maria Giżewska
Tobias S. Hagedorn
Gregor Hammerschmidt
Małgorzata Henek
Maria Kozon
Eric Lange
Anita MacDonald
François Maillot
Anna Maria Marzenta
Duncan Noble-Nesbitt
Florentina Perić
Sanja Perić
Júlio César Rocha
Cristina Romani
Stian Skarelven
Francjan J. van Spronsen
Šárka Štěrbová

This paper was funded by PTC Therapeutics. PTC reviewed the Paper for accuracy and compliance purposes only. Harwood Levitt Consulting was engaged to assist throughout the process, including providing writing support.

November 2024

EXECUTIVE SUMMARY

Phenylketonuria *(PKU) is a disease whose severity and burden remains poorly understood. There is a false perception that early diagnosis and a good standard of care have 'solved' the problem, and that all European patients have equal access to such care.*

PKU is a rare inherited genetic disorder resulting from a deficiency in the enzyme that metabolises the amino acid phenylalanine (Phe). If left untreated, PKU causes brain damage, severe developmental, psychological and psychiatric disorders in patients. PKU affects each patient differently throughout their lives depending on the severity of their disease, their age at diagnosis, the treatments they follow as well as a number of other factors. From birth, through adolescence, to old age, patients with PKU require daily, lifelong rigorous management to maintain good health, good nutritional status, good cognition, good psychological health and overall acceptable quality of life.

Although PKU is diagnosed early through newborn screening programmes, and patients are immediately started on a specific nutritional therapy called the 'low-Phe' diet (the standard of care), patients with PKU, their families and their caregivers are faced with substantial health complications, care and social burden and Unmet Medical Need (UMN).

This Joint Policy Paper is the result of a collaboration among patients, clinicians and other key stakeholders directly affected by, and invested in improving, the treatment and care of PKU patients. It aims to raise awareness of PKU, the severity of the disease and to set out the unmet medical needs that still exist for patients with PKU, their families and caregivers.

Unmet Medical Need (UMN) is a critical concept in healthcare, guiding the identification of gaps in treatment and care. It is used to prioritise health resources and drive innovation where they are most needed, ultimately enhancing patient-centred care. PKU is a disease where, despite early diagnosis, low mortality, the general concept of care (dietary treatment) has remained largely unchanged since the 1960s and patients still need better care and treatment options. However, given the low mortality and dietary treatment, PKU is also a disease that could wrongly be perceived as having 'low' UMN.

As the European Union (EU) revises its General Pharmaceutical Legislation (GPL), it plans to include, for the first time, definitions of UMN and high UMN (HUMN) to inform decisions around EU incentives (e.g. market exclusivity and, regulatory data protection periods), this paper aims to contribute to the discussion in EU and national policy and decision-making circles.

PKU provides a concrete example of a rare disease where, despite standards of care existing, significant UMNs remain and the disease and treatment are substantially burdensome on individuals, family and society. Using PKU as a focus, this paper illustrates how any definition of UMN, as well the criteria for determining it, need to be carefully calibrated to be neither too strict nor too narrow. If the unmet needs of patients with PKU are not fully recognised, they cannot be fully addressed.

AUTHORS

Working Group Members:

- **Kirsten Ahring** - *PKU Clinic, Copenhagen University Hospital, Denmark*
- **Deniz Atakay** - *PKU Patient Organization, Turkey*
- **Agata Bąk** - *E.S.PKU Board Member, National University of Distance Education, Spain*
- **Fatma Çelik** - *PKU Patient Organisation, Turkey*
- **Merve Esgi** - *PKU Patient Organisation, Turkey*
- **Maria Giżewska** - *E.S.PKU Scientific Advisory Committee, Pomeranian Medical University in Szczecin, Poland*
- **Tobias S. Hagedorn** - *E.S.PKU Board Member, Germany*
- **Gregor Hammerschmidt** - *E.S.PKU Board Member, Austria*
- **Małgorzata Henek** - *E.S.PKU Board Member, PKU Patient Organisation, Poland*
- **Maria Kozon** - *PKU Patient Organisation, Poland*
- **Eric Lange** - *E.S.PKU Board Member, PKU Patient Organization, United Kingdom*
- **Anita MacDonald** - *E.S.PKU Scientific Advisory Committee, Birmingham Children's Hospital, United Kingdom*
- **François Maillot** - *University of Tours, France*
- **Anna Maria Marzenta** – *President, Comete ASMME (Associazione Studio Malattie Metaboliche Ereditarie)*
- **Duncan Noble-Nesbitt** - *E.S.PKU Board Member, Medigold Health, United Kingdom*
- **Florentina Perić** - *PKU Patient Organisation, Croatia*
- **Sanja Perić** - *PKU Patient Organisation, Croatia*
- **Júlio César Rocha** - *NOVA Medical School, Universidade Nova de Lisboa & Reference Centre for IMD, ULS São José, Lisboa, Portugal*
- **Cristina Romani** - *Aston University, United Kingdom*
- **Stian Skarelven** - *E.S.PKU Board Member, PKU Patient Organisation, Norway*
- **Francjan J. van Spronsen** - *E.S.PKU Advisory Scientific Committee, University of Groningen, Netherlands*
- **Šárka Štěrbová** - *PKU Patient Organisation, Czech Republic*

OBSERVERS

- **Thomas Bols** – *Head of Government Affairs and Patient Advocacy, EMEA & APAC, PTC Therapeutics*
- **Christian Frenzel** – *Associate Director Patient Engagement, PTC Therapeutics*
- **Ioannis Tomazos** – *Executive Director, Head of Health Economics & Outcomes Research, PTC Therapeutics*

TRANSPARENCY STATEMENT

This joint policy paper is the result of a collaborative project with a diverse group of stakeholders, including patient groups, clinicians, and academics. The views expressed represent a consensus reached through deliberation and exchange. All participants contributed to this paper independently and retained their autonomy throughout the drafting process.

This paper was funded by PTC Therapeutics. PTC reviewed the Paper for accuracy and compliance purposes only. Harwood Levitt Consulting was engaged to assist throughout the process, including providing writing support.

TABLE OF CONTENTS

FOREWORD

Phenylketonuria (PKU) is a disease whose severity and burden remains poorly understood. There is a false perception that diagnosis has 'solved' the problem, that a high standard of care exists, and that European patients have equal access to such care. There is a critical need for more robust, patient-centred policies to drive research, innovation and improved care in PKU. At the same time, the European Union (EU) is revising its General Pharmaceutical Legislation (GPL), which will include, for the first time, definitions of unmet medical need (UMN) and high unmet medical need (HUMN). These policy discussions are crucial, as the definitions chosen and criteria retained will influence the perception of the unmet medical need status of a given disease (including PKU) and, therefore, will shape the future health investment and healthcare landscape in the decades to come.

This Joint Policy Paper is the result of a collaboration between patients, clinicians and other key stakeholders directly affected by, and invested in improving, the treatment and care of PKU. It aims to raise awareness of PKU and its severity, and to set out the unmet medical needs that still exist for patients with PKU, their families and caregivers. If the unmet needs of patients with PKU are not fully recognised, they will not be fully addressed, with consequences for the patients, their families and caregivers, as well as the healthcare system and society as a whole. This paper contributes to the discussion on the definition of unmet medical need: it provides a concrete example of disease which shows why any definition must be carefully crafted and, above all, should not be too strict or too narrow.

1. Introducing PKU

PKU is a rare genetic disorder resulting from a deficiency in the enzyme that metabolises the amino acid phenylalanine (Phe). For people living with PKU, high blood Phe levels are toxic for the brain. If left untreated, it causes brain damage and severe development disorders. Even when PKU is being managed, high levels of Phe can impair IQ and cause issues with movement and coordination, as well as other cognitive functions including thinking, memory, attention and learning, affecting decision-making and social interactions.

In addition to cognitive challenges, people with PKU may also experience mental health difficulties, including depression, anxiety, social withdrawal and fatigue. These mental health problems can be caused both by the disease itself and the burden of following the strict treatment regimen. If metabolic control is poor, additional physical problems can develop, such as muscle stiffness tremors, seizures (epilepsy), balance issues (ataxia), and problems with visual-spatial skills. There is also a higher risk of obesity, nutritional deficiencies, eating disorders, cardiovascular disease, and weak bones.

At the same time, long periods of low-Phe levels can also be detrimental, and are associated with anorexia, alopecia, listlessness, faltering growth, osteopenia. As such, maintaining well-balanced Phe levels is essential to avoid both the serious complications of high Phe and the risks associated with levels that are too low.

Although PKU can be identified early through newborn screening programs, and the vast majority of patients are immediately started on the traditional 'low-Phe' diet, managing PKU remains challenging and very burdensome. Even strict adherence to the diet, which is extremely burdensome, does not result in optimal outcomes when cognition and health is compared to that of unaffected populations.

PKU affects each patient differently throughout their lives depending on factors such as the severity of their disease, their age at diagnosis or the treatments they follow. From birth, through adolescence, to old age, patients with PKU require daily, lifelong rigorous management to maintain good health, good nutritional status, good cognition, good psychological health and an overall acceptable quality of life. This takes a toll on patients and their families as well as being expensive for society at large. Despite these efforts, patients with PKU, their families and caregivers are still faced with significant unmet needs.

PKU in numbers

PKU is a rare disease with an overall global prevalence estimated at 1 in 23,930 live births[1], and 1 in 10,000 in Europe.[2]

While country comparisons are challenging as there are variations in definitions of PKU, there is also significant variation in rates across Europe:

- In The Netherlands around 1 in 18,000 newborns are affected by PKU.[3]
- In France the incidence is around 1:16,500 newborns.[4]
- Portugal, Norway, Sweden, Denmark, and Belgium also have low PKU prevalence, ranging from 1 in 10,500 to 1 in 13,000 births.[1]
- Poland, Croatia, the UK, and Spain are faced with a slightly higher prevalence, with 1 in 8,000 to 1 in 10,000 births affected.[1,5]
- Slovenia, Belarus, Estonia, and Russia report around 1 in 7,000 births affected.[1]
- Italy,[1] Ireland,[2] Germany,[1] Czechia,[1] Austria,[1] Slovakia,[1] and Turkey[6] have the highest prevalence, with around 1 in 4,000 to 1 in 6,000 births affected.

[1] Hillert, A., Anikster, Y., Belanger-Quintana, A., et al. (2020). The Genetic Landscape and Epidemiology of Phenylketonuria. *Am J Hum Gene*, 107(2):234-250.
[2] Phenylketonuria. (2020). *Orphanet.*
[3] Verkerk, P.H., Vaandrager, G.J., Sengers, R.C. (1990). Vijftien jaar landelijke screening op fenylketonurie in Nederland; vierde verslag van de Landelijke Begeleidingscommissie Phenylketonurie [15 years of national screening for phenylketonuria in The Netherlands; 4th Report of the National Commission for Management of Phenylketonuria]. *Ned Tijdschr Geneeskd*.134(52):2533-6.
[4] Arnoux, J.-B., Douillard, C., Maillot F., et al. Health economic impact of patients with phenylketonuria (PKU) in France – A nationwide study of health insurance claims data. *Molecular Genetics and Metabolism Reports*. 2024 41; 101134.
[5] Phenylketonuria. (2023). UK National Health Service (NHS).
[6] Knowledge on rare diseases and orphan drugs. (2020). *Orphanet*.

2. A standard of care whose general concept has not evolved since the 1960s – and that imposes a high treatment burden on patients

As no cure exists for PKU, the primary goal of treatment is maintaining blood-Phe levels within a defined target range. As Phe is an essential amino acid present in all proteins of natural origins (both plant and animal), this is achieved through a low-Phe diet, achieved through a low-protein diet supplemented with protein substitutes. This diet has been the foundation of the standard of care for the disease since it was introduced in the 1950s.

Although it has been gradually refined over time, the principles of the diet have remained largely unchanged. It requires the elimination of protein-rich foods, including animal and dairy products – but also the majority of plant-based proteins such as legumes, nuts, and seeds. Essentially, most patients with PKU mainly eat foods with a naturally low protein content (such as specific fruits and vegetables (for example: carrots, apples, pears) and specifically manufactured low protein starch-based foods (e.g. low-protein bread and pasta).

On its own however - as protein is a critical nutrient that contributes significantly to essential functions such as the maintenance of muscle mass, bone health, immunity or the production of hormones - the low-Phe diet is also not nutrient-rich enough to ensure full growth and development, especially in children and teenagers. Low-protein diets must therefore be combined with additional nutritional supplements to ensure patients' full dietary needs are met. These must be taken 3 to 4 times daily and are not palatable. On top of this, the range of available supplements are often limited between and within countries, and are associated with complex administrative processes.

The strictness of the low protein diet follows the severity of the disease, with patients with more severe PKU requiring stricter Phe restriction; having lower tolerance for natural proteins. Because the diet is very burdensome, most patients do not achieve effective blood Phe control on dietary treatment alone and the risk of exceeding their Phe tolerance is high, especially as Phe tolerance can also fluctuate because of many factors (such as growth, or illnesses), that can be hard to predict and manage. PKU patients therefore require constant monitoring to adapt their diet accordingly to maintain Phe levels within the target range.

Following the introduction of the first diagnostic tests for PKU in the 1960s, systematic neonatal PKU screening has become the norm throughout Europe,[7] and all newborns diagnosed with PKU are commenced on a low-Phe diet from early infancy. While in the 2000s, limited medicinal treatments for PKU were developed with the goal of increasing Phe tolerance and improving blood Phe control. They have so far only been effective for a small subset of patients, are usually only complementary to the low-Phe diet, and may be associated with side effects.

As such, despite the low mortality in PKU, patients and caregivers are often left with a standard of care whose concept has not substantially changed in 60 years and that negatively impacts almost all aspect of their lives. Indeed, the current standard of care for PKU is highly burdensome on patients. All current treatments for PKU, including dietary management, are highly restrictive, often unfeasible and impractical and may cause secondary issues such as obesity and eating disorders, social anxiety, and isolation.

While for the general, healthy populations it is well accepted that restrictive dietary management is not an effective treatment for obesity, a grueling dietary treatment is still expected to be the 'norm' for patients with PKU. Inadequate dietary control can result in reduced mental processing capabilities, attention deficit, insomnia, mood swings, fatigue, and tremors, creating constant worry for patients and caregivers. Parents for example, may fear sending children to nursery or other events outside of their control due to fears other will not safely manage their child's dietary restrictions.

Many catering services do not provide low- protein food, limiting the ability of people with PKU to socialize and lead a normal life. The difficulties inherent in dietary management may also lead to poor adherence, loss to follow up, problems maintaining a job, a potential increase in the risk of accidents when driving, employment issues, and poor performance generally.

[7] That said, there are still countries in Europe where screening for PKU is not standard, or where the whole population of newborns are not screened, e.g. Albania, Kosovo or Montenegro. See Koracin, V., Mlinaric, M., Baric, I., et al. Current status of newborn screening in Southeastern Europe. *Frontiers in Paediatrics*. 2021 9.

3. Remaining high unmet need: PKU's impact across the lifespan

Despite the advances in the diagnosis and treatment of PKU, the daily lives of people with PKU are ruled by the disease from the moment they are born to the end of their lives. Patients with PKU require specific healthcare support throughout their lives. Furthermore, the efforts required to manage the disease and ensure Phe levels are kept within an acceptable range, impact not only the physical health, cognitive health and mental health of patients with PKU, their families and caregivers, but their ability to participate fully in society (from going to school, holding a job, maintaining relationships and socializing). Indeed, patients with PKU, their families and caregivers, have many remaining unmet health (a), healthcare-related (b), and social needs (c)

a. Remaining unmet health needs

As a result of the disease and the diet, patients with PKU face numerous direct physical and mental health needs. The daily life of a patient with PKU is a constant struggle to maintain Phe levels within a target limit. However, variations in patients nutritional needs linked, for example, to age, growth speed, sporting activity, illness) mean that an individual's dietary Phe tolerance levels are not a constant, but rather regularly fluctuate. The reality is that, for a variety of reasons, most patients with PKU do not achieve effective blood Phe controls throughout their lives, even when strictly adhering to their dietary management. The current standard of care is therefore inherently flawed, as patients are still at risk of disease progression and symptom development. Even early- and well-managed patients experience hidden disabilities, including defects in mental functioning, such as reductions in mental processing capacity, social difficulties, psychiatric issues as well as physical problems such as deficits in bone health and emotional problems that can remain unnoticed for years.

Furthermore, the inability to control blood Phe levels fully places a significant emotional burden on patients and their caregivers, as they are often anxious that even the slightest mistake could result in cognitive damage. At the same time, the management of PKU remains highly 'patient dependent' and children are reliant on their parents to adhere to their dietary management. This takes a toll on patients and their families day to day, creating anxiety and often hopelessness at the "inevitable slip-up". In fact, patients report that adhering to the diet causes as much if not more anxiety than the disease itself. PKU patients are often in need of professional psychological support, which not only increases the economic burden but also strains the capacity of social or psychological services. However, despite this toll, psychological support for PKU patients is not widely available.

Finally, the overall clinical burden on patients with PKU in general is exacerbated by the risk of comorbidities. While there are still gaps in our understanding of the full spectrum of these comorbidities, as well as which result directly from PKU and which are associated with the treatment (e.g. diet), existing data clearly supports an increased prevalence of certain conditions. These include anxiety and depression[8] and cardiovascular issues, as well as higher rates of obesity linked to the diet.[9]

While conditions like osteoporosis and kidney disease have been mentioned in various studies, the evidence is not yet strong enough to confirm a direct relationship to PKU or its treatment in a consistent way. The reality, however, is that our current understanding of the long-term health impacts of PKU is still evolving, particularly because the first generation of patients who received consistent treatment from birth is only now reaching older age.

b. Remaining unmet healthcare-related needs

The management challenges and healthcare needs due to PKU are largely unmet, as some medical settings are often ill-equipped to provide the necessary care and overlook the specific requirements of this rare disease.

Firstly, healthcare systems are often not set up appropriately to care for PKU patients beyond childhood. Many specialised PKU teams are housed within pediatric centers, and there is a lack of age-appropriate care and information beyond childhood. This can lead to non-adherence or loss-to-follow up

[8] Bilder, D. A., Kobori, J. A., Cohen-Pfeffer, J. L., et al. Neuropsychiatric comorbidities in adults with phenylketonuria: a retrospective cohort study. *Molecular genetics and metabolism.* 2017 121; 1:8.

[9] Trefz, K. F., Muntau, A. C., Kohlscheen, K. M., et al.,. Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities-a retrospective study of German health insurance claims data. *Orphanet J Rare Dis*. 2019 14; 1:16.

during the transition from childhood to adulthood. This lack of knowledge is caused by a lack of education on nutrition and rare diseases generally, and PKU specifically, at medical schools.

At the same time, the general lack of understanding of PKU within wider medical settings is due in part to the fact that the evolution of PKU has not yet been fully described, particularly – but not only – as patients with PKU get older. More studies are needed to understand the impact of ageing on PKU, as well as how PKU and the diet affects or is affected by other comorbidities and their treatment (e.g. diabetes, osteoporosis, cardiovascular disease, dementia, or kidney disease). This can compromise treatment for both PKU and the additional diseases that the patient must be treated for. In fact, many hospitals do not provide PKU compliant special low-protein food.. Protein substitutes may be difficult to tolerate leading to gastrointestinal symptoms such as reflux, abdominal pain or diarrhea. They have been associated with an imbalance of bacteria in the gut, affecting nutrient absorption, inflammation, and affecting digestive health. This may lead to unusual comorbidities and increase the burden on dietitians and physicians, especially where expertise is limited or there is limited care capacity.

Related to this, PKU patients face significant healthcare costs, with substantial expenditures on pharmaceuticals, outpatient care and dietary management. This is caused either directly by PKU through frequent healthcare visits, blood tests, medications, protein substitutes, and low-protein foods, or indirectly by related health issues that add to the financial burden on both patients and the healthcare system.

Finally, and in relation to the diet itself, many patients throughout Europe have difficulties accessing special low-protein foods and protein substitutes.[10] These products are significantly more expensive than “regular” food and not uniformly reimbursed across Europe, and where they are, often only for children. These extra costs present a significant barrier, particularly for patients from lower socio-economic backgrounds. On top of this, special low protein foods are not available in regular supermarkets, and some dietary companies are even withdrawing some from the market. These barriers create inequality in access to treatment and dietary options and foods across and within EU countries and represent a significant problem for PKU health. For example, early diagnosis can lose its value if families give up their dietary treatment over time because they are unable to afford or access low-protein products and necessary supplements.

c. Remaining unmet social needs

Finally, PKU patients, their families and caregivers still incur a high number of social unmet needs. As indicated above, PKU patients and their families often require consistent lifelong financial support as the monthly cost of low-Phe foods and nutritional supplements are significantly higher than ‘normal’ food. This financial disadvantage can be amplified by difficulties maintaining full-time employment, linked to reduced ability to focus, sustain attention, learn or memorize information, as well as the need for tailored accommodations in social, employment and educational settings. These issues not only hinder educational achievements but also limit career opportunities, further contributing to a sense of social exclusion. The strain extends to families and caregivers, who often reduce their working hours or leave employment altogether to provide necessary care, intensifying the economic pressure. The burden of care also leads to increased stress and anxiety, particularly concerning the availability of special nutritional products, which becomes a major concern during travel or holidays.

Indeed, constant compromise and daily schedules are necessary to avoid activities that could disrupt their Phe levels. People affected by PKU often cannot easily eat outside of their houses, making going to school or the workplace difficult, and thus further hampering their participation in society. Families face additional financial burdens due to the high cost of secondary treatments stemming from inadequate PKU management, along with expenses for travel and accommodation to access specialized care. Social participation is further hampered by the need for home modifications to accommodate dietary restrictions and by the exclusion experienced by children at school due to their different dietary needs. Finally, gaps in knowledge and the lack of education on PKU also limits the support and understanding available to patients. This gap exacerbates the social isolation and anxiety experienced by PKU patients, where further education and understanding can help improve the quality of life for those affected by PKU.

The psychosocial impact extends to healthy siblings, who may feel neglected or burdened by the special attention their affected sibling requires, which can contribute to a pervasive sense of isolation within the family. These challenges underscore the urgent need

[10] Pena, M. J., Almeida, M. F., van Dam, E., et al. Special low protein foods for phenylketonuria: availability in Europe and an examination of their nutritional profile. *Orphanet J Rare Dis*. 2015 10;1:6.

for a comprehensive approach that addresses both the social and psychological needs of patients with PKU and their families, ensuring better integration and support in all aspects of life.

d. Specific needs of individual types of patients

Patients with PKU are not affected by their disease in the same way. Depending on their age, personal situation, severity of PKU (individual Phe level tolerance), gender, socio-economic status, etc., patients' needs are very individualised.

- **Newborns and young children**

For newborn babies, while newborn screening (NBS) is now policy across the European Union, it is not universally practiced throughout Europe.[11] Indeed, treatment should be initiated before the age of 10 days, and every four weeks' delay in starting treatment causes a decline of approximately 4 IQ points. Children's rapid changes in nutritional needs however, require that the diet be continuously updated, posing particular challenges for parents who are in need of detailed nutritional information and education. Ensuring NBS and treatment during early childhood is thus particularly risky, and young children with PKU are completely dependent on their caregivers, who often report feeling overwhelmed and lacking information and reassurance by parents who have been through the same situation. Lastly, many school children may have additional educational problems and needs requiring extra assistance at school. However, this is not commonly assessed, as PKU is considered resolved.

- **Teenagers**

Teenagers can feel highly isolated as they lose the support of pediatric facilities and the close monitoring of their parents, putting at risk their adherence to the diet. Indeed, it is in the transition between childhood and adulthood care that many PKU patients are 'lost-to-follow' up. In addition, even when it does not affect intellectual development, non-adherence can significantly increase levels of anxiety, depression and hyperactivity, which can create difficulty in forming stable relationships and socializing, amplifying feelings of depression and loneliness. Furthermore, nutritional deficiencies are a particular challenge, due to the higher nutritional requirements of this age group. This is the time that treatment often goes wrong and is hard to recover. Current evidence suggests that even with advances in dietary treatments, 'optimal' growth outcomes are still not achieved in individuals with PKU.

- **Patients who are lost to follow up**

Adolescents and young adults with PKU face significant challenges as they transition from pediatric to adult care, often resulting in a substantial proportion of patients being lost to follow-up (LTFU). This vulnerable period requires robust support systems, yet many PKU patients, lacking sufficient guidance and continuity of care, disengage from medical oversight during adolescence and early adulthood. Studies estimate between 33% and 77% of adult PKU patients become LTFU,[12] leaving them at increased risk of poor health outcomes, cognitive decline, and the potential development of comorbidities.

Without consistent care, adherence to the low-Phe diet becomes difficult, further exacerbating the risk of long-term complications. The gaps in research surrounding the specific needs of LTFU patients, including how to re-engage them and the impact of untreated PKU on their overall health, highlight an unmet medical need. This issue requires better strategies for patient retention, better transition programs between pediatric and adult care, and targeted interventions aimed at reducing the risk of patients falling through the cracks during this critical life stage.

- **Adults**

Adult PKU patients regardless of sex, age, or circumstances, must adhere to their PKU therapy to fulfill their social roles, and gain professional and personal success. In order to do so, they require the highest possible standard of care. Adulthood is a time when additional health problems often appear and their treatment requires cooperation with PKU doctors as well as other specialized doctors.

However, the standard of care for adult PKU patients across Europe varies significantly. Many adults continue to receive care in children's hospitals from pediatricians and medical teams primarily focused on pediatric care. Managing comorbidities or other health conditions in adults with PKU requires close collaboration with their PKU medical team. This can be challenging if the patient is under the care of pediatric specialists. Moreover, there is limited understanding of how other health conditions affect adherence to the low Phe diet, or how PKU and this diet interact with the treatment of other health conditions. There remain

[11] See for example in Bulgaria or Romania, where despite the policy of neonatal screening, over 10% of newborns were not screened. See Zerjav Tansek M, Groselj U, Angelkova N, et al. Phenylketonuria screening and management in southeastern Europe - survey results from 11 countries. *Orphanet J Rare Dis*. 2015 May 30;10:68.

[12] See references within Androux et al. (2024).

significant gaps in research and knowledge regarding the well-being of adult PKU patients at critical life stages, such as during menopause, or when facing life threatening conditions like cancer.

- **Pregnancy and Maternal PKU**

Pregnant women have to monitor their Phe-levels even more strictly, as metabolic fluctuations are higher during pregnancy. Phe-levels that go over the target limit can be detrimental to both the mother and fetus. The consequences of maternal PKU range from intellectual disability to congenital heart defects in the baby. Sexual education for PKU patients, particularly for younger PKU patients, is particularly important as unplanned pregnancies or pregnancies caught late can be dangerous given the need for management. The anxiety created by the condition and the impact of an unforgiving, strict, expensive and demanding diet on themselves and the baby can deter PKU patients from having children altogether. Maternal PKU mothers need support post pregnancy and often receive very little. Furthermore, children of women with PKU are not comprehensively monitored long term and may be at risk of ADHD and other development issues.

- **Late and Undiagnosed PKU Patients**

The unmet needs of late and undiagnosed PKU patients are often largely forgotten. This is particularly remarkable as late diagnosed patients make up a large group within the PKU community. Furthermore, issues around NBS or more recent implementation of NBS policies in countries such as Moldova means the population of late diagnosed PKU patients in the EU could substantially increase after further EU-enlargement. With regards undiagnosed patients, while numbers are difficult to estimate, it is expected that there are undiagnosed patients with PKU within homes for mentally handicapper individuals. These groups also include a disproportionate amount of patients from migrant backgrounds.[13]

Late or undiagnosed patients are at a higher risk of having cognitive deficits, neurological impairment, and other dysfunctions, impacting quality of life and their independence, and requiring specialist, lifelong care. This is particularly problematic in countries with poor social care systems that struggle to look after people with disabilities, placing those PKU patients in particular positions of vulnerability. Furthermore, in some cases, late diagnosed PKU patients who have already developed disabilities refuse completely to undergo treatment following their diagnosis, and therefore worsening their situation. In other cases, late diagnosed patients may be denied treatment due to lack of carer capacity.

- **Ageing with PKU**

The first children to have been diagnosed with PKU and to have followed the low-Phe diet throughout their lives are getting older and we do not yet fully understand how PKU affects comorbidities linked to ageing such as Parkinson's or Dementia. As their independence declines, patients may worry about maintaining their diet while relying on others. There is also some evidence suggesting that late diagnosed patients with PKU, now often in their 60s and 70s, may have a higher mortality rate. Furthermore, classic PKU patients with inadequate dietary treatment are at an increased risk of suffering from bone and joint disorders. This underscores the critical need for more research and a higher standard of care for adult PKU patients

[13] Van Wegberg AMJ, Trefz F, Gizewska M, et al., Study Group on Missed PKU and Missed to Follow-up. Undiagnosed Phenylketonuria Can Exist Everywhere: Results From an International Survey. *J Pediatr.* 2021 Dec; 239:231-234.e2.

4. A definition of Unmet Medical Need that reflects the needs of patients with rare diseases like PKU

Unmet Medical Need is a critical concept in healthcare, guiding the identification of gaps in treatment and care. It is used to prioritize health resources and drive innovation where they are most needed, ultimately enhancing patient-centered care. PKU is a disease where, despite ease of diagnosis (through newborn screening), low mortality and an existing standard of care, patients still need better care and treatment options. However, given the low mortality and existing treatments, PKU is also a disease that could wrongly be perceived as having 'low' unmet medical need.

In the context of revising the EU's General Pharmaceutical Legislation (GPL), the European Commission is proposing a shift from its current broad definition, which defines UMN as any "condition for which there exists no satisfactory method of diagnosis, prevention or treatment … or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advance to those affected." The updated definition is expected to include a narrower, criteria-based definition, introducing clinical concepts of high morbidity and mortality, and which would also include a category for High Unmet Medical Need (HUMN) – see box. The potentially narrow focus on clinical impact, however, could neglect important factors such as health-related quality of life, the broader socio-economic impact of the disease and the acceptability of, and responsiveness to, existing treatments for patients - factors often taken into account in other jurisdictions' definitions (like the Food and Drug Administration (US), the Therapeutic Goods Administration (Australia), or Health Canada (Canada)). Such a definition could render invisible the critical, complex and multifaceted nature of the unmet medical needs of patients and society.

The new definition of UMN will be crucial because it will impact innovation in healthcare and will be used in many settings beyond the European Union to categorize and rank diseases. Indeed, it will have an impact even before the entry into force of the GPL (expected in 2028), particularly on national HTA and payer bodies, who may be influenced by the definition to establish the 'value' of a new medicine. If the specificities of all disease areas are not recognised within the new definition of UMN, there is a risk that innovation may be discouraged, especially in disease areas where standards of care or treatments already exist, even if they do not allow for an acceptable quality of life.

European Commission's Proposal Directive relating to medicinal products for human use (Com(2023) 192 final 2023/0132 (COD))

Article 83: Medicinal products addressing an unmet medical need

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

   a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

   b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. Designated orphan medicinal products (…) shall be considered as addressing an unmet medical need.

It is essential that the UMN definition included in the revised GPL accurately captures the specific needs of all patients. Specifically, any definition of UMN must capture the remaining needs of patients for whom standards of care currently exist, but do not fulfill all the patients' needs. To do so, it is vital that the criteria for UMN and HUMN are carefully crafted to ensure no patients or disease areas are left behind, for example by including metrics related to quality of life, potential comorbidities, or the impact of treatment.

In this sense, PKU is representative of a new paradigm for many rare diseases, where although standards of care exist, they are highly burdensome. Indeed, PKU illustrates how any definition of UMN, as well as the criteria for determining it, need to be carefully calibrated to capture the needs of patients. Getting the definition wrong could put at risk new treatments being developed for diseases where, despite the existing standard of care, better care and treatment options are sorely needed.

On the one hand, a wider definition would highlight potential areas of improvement in health outcomes, quality of life, and foster efforts to reduce the social and economic burden on patients within the existing standard of care. Whereas on the other hand, any proposed narrower, criteria-based definitions of UMN that do not fully capture the full spectrum of health, healthcare and social-related needs faced by patients risk the medical and wider health policy ecosystem (policymakers, payers and HTA bodies) viewing diseases like PKU as 'solved.'

Failing to recognise or define the ongoing needs of people living with PKU – or perceiving the disease area as 'solved - can lead to a lack of political prioritisation, research, underfunding and inadequate patient support, hindering innovation and new treatments becoming available. This would hinder much needed improvement in the PKU treatment and care landscape, where patients with PKU, their families, caregivers and support networks continue to have significant unmet needs

POLICY RECOMMENDATIONS & SOLUTIONS

In light of the EU's revision of the General Pharmaceutical Legislation and the narrow criteria for defining Unmet Medical Need proposed by the European Commission, it is critical that any definition capture the unmet needs of PKU patients, their families and carers.

To ensure any such definition and healthcare policies are truly patient-centred, we propose the following recommendations for policymakers at both national and European Level.

1. **Adopt a broad definition of Unmet Medical Need (UMN) to fully capture the needs of patients, their families and carers**

   UMN should be defined widely to fully capture the needs and experiences of patients and their families. In particular, the criteria should be needs based and include health, healthcare-related and social needs, and fully capture the impacts on quality of life, including the burden of available treatment on patients, families and carers.

2. **Guarantee a collaborative process in the finalisation and implementation of the General Pharmaceutical Legislation**

   European Institutions and other decision-makers must engage with patient groups and clinical experts to ensure their voice and needs are reflected in the final definition of UMN included in the revision of the General Pharmaceutical Legislation.

3. **Patient voices and clinical experts should be systematically involved in the assessment of UMN**

   Regulatory authorities, as well as policy- and decision-makers (including payers), should systematically involve patient voices, clinical experts and healthcare professionals both in shaping and finalising definitions of UMN, as well as assessing UMN in disease areas.

4. **Recognise the limits and ensure the responsible use of definitions of UMN**

   While acknowledging that UMN definitions are necessary for directing funds and political prioritization, ensure that the limitations of UMN definitions, and the risks of unintended negative outcomes when misapplying such definitions (for example by disincentivising innovation in disease areas that might appear 'solved') are explicitly recognised.

5. **Set up patient Registries, foster ongoing dialogue and ensure the periodic review of UMNs**

   Establish registries that track patient outcomes and experiences, which can inform healthcare professionals, health institutions, and industry on the limitations of current standards of care (for PKU patients), and periodically assess existing UMN.

6. **Establish an EU-PKU patients dialogue**

   Set up an annual meet-up to foster dialogue between EU health officials and PKU patient representatives so that more can be done to:

   - Understand PKU and the experiences of patients living with this disease
   - Improve the existing standard of care
   - Close the gap on the unmet medical need that persists

BIBLIOGRAPHY

- Ahring, K., Bélanger-Quintana, A., Dokoupil, K., et al. (2011). Blood phenylalanine control in phenylketonuria: A survey of 10 European centres. *European Journal of Clinical Nutrition*, 65(2), 275-278.
- Ahring, K., Bélanger-Quintana, A., Burlina, A., et al. (2024). Management of phenylketonuria in European PKU centres remains heterogeneous. Molecular Genetics and Metabolism, 141(1), 108120.
- Arnoux, J.-B., Douillard, C., Maillot F., et al. (2024) Health economic impact of patients with phenylketonuria (PKU) in France – A nationwide study of health insurance claims data. *Molecular Genetics and Metabolism Reports*, 41, 101134.
- Beghini, M., Pichler, M., Tinnefeld, F. C., et al. (2024). Poor adherence during adolescence is a risk factor for becoming lost-to-follow-up in patients with phenylketonuria. *Molecular Genetics and Metabolism Reports,* 39, 101087.
- Bilder, D. A., Kobori, J. A., Cohen-Pfeffer, J. L., et al. (2017). Neuropsychiatric comorbidities in adults with phenylketonuria: a retrospective cohort study. *Molecular genetics and metabolism*, 121(1), 1-8.
- Burton, B. K., Jones, K. B., Cederbaum, S., et al. (2018). Prevalence of comorbid conditions among adult patients diagnosed with phenylketonuria. *Molecular genetics and metabolism*, 125(3), 228-234.
- Cazzorla C et al. (2018. Living with phenylketonuria in adulthood: The PKU ATTITUDE study. *Molecular Genetics and Metabolism Report*s, 16, 39–45.
- Demirkol, M., Giżewska, M., Giovannini, M., & Walter, J. (2011). Follow up of phenylketonuria patients. Molecular Genetics and Metabolism, 104, S31-S39.
- European Society for PKU and Allied Disorders Treated as PKU (E.S.PKU). (2012). PKU: Closing the Gaps in Care; An ESPKU benchmark report on the management of phenylketonuria within EU healthcare economies.
- Esgi, M., Ergun, H., Kaya, N. Y., et al. (2024). Phenylketonuria from the perspectives of patients in Türkiye. *Orphanet Journal of Rare Diseases*, 19(1), 78.
- Ford, S., O'Driscoll, M., & MacDonald, A. (2018). Living with Phenylketonuria: Lessons from the PKU community. *Molecular genetics and metabolism reports*, 17, 57-63.
- Hagedorn, T.S. (2024) Phenylketonurie: Wie Betroffene die seltene Erkrankung erleben. *Forum Sanitas – Das informative Medizinmagazin,* 2 August 2024, 31.
- Hillert, A., Anikster, Y., Belanger-Quintana, A., et al. (2020). The Genetic Landscape and Epidemiology of Phenylketonuria. *Am J Hum Gene*, 107(2):234-250.
- Ilgaz, F., Pinto, A., Gökmen-Özel, H., et al. (2019). Long-term growth in phenylketonuria: A systematic review and meta-analysis. *Nutrients*, 11(9), 2070.
- Knowledge on rare diseases and orphan drugs. (2020). *Orphanet.*
- MacDonald, A., Davies, P., Daly, A., et al. (2008). Does maternal knowledge and parent education affect blood phenylalanine control in phenylketonuria? *Journal of human nutrition and dietetics*, 21(4), 351-358.
- MacDonald, A., Smith, T. A., de Silva, S., et al. (2016). The personal burden for caregivers of children with phenylketonuria: a cross-sectional study investigating time burden and costs in the UK. Molecular genetics and metabolism reports, 9, 1-5.
- MacDonald, A., Van Wegberg, A. M. J., Ahring, K., et al. (2020). PKU dietary handbook to accompany PKU guidelines. *Orphanet Journal of Rare Diseases*, 15, 1-21.
- Newbould, E., Pinto, A., Evans, S., Ford, S., O'Driscoll, M., Ashmore, C., Daly, A., & MacDonald, A. (2021). Accidental Consumption of Aspartame in Phenylketonuria: Patient Experiences. *MDPI*. Nutrients, 13(2), 707. https://doi.org/10.3390/nu13020707
- Pena, M. J., Almeida, M. F., van Dam, E., et al. (2015). Special low protein foods for phenylketonuria: availability in Europe and an examination of their nutritional profile. *Orphanet Journal of Rare Diseases*, *10*, 1-6.
- Phenylketonuria. (2023). *UK National Health Service (NHS).*

- Phenylketonuria. (2020). *Orphanet*.
- Rodrigues, C., Pinto, A., Faria, A., et al. (2021). Is the phenylalanine-restricted diet a risk factor for overweight or obesity in patients with phenylketonuria (PKU)? A systematic review and meta-analysis. Nutrients, 13(10), 3443.
- Romani, C., Olson, A., Aitkenhead, L., et al. (2022). Meta-analyses of cognitive functions in early-treated adults with phenylketonuria. *Neuroscience & Biobehavioral Reviews,* 143, 104925.
- Trefz, K. F., Muntau, A. C., Kohlscheen, K. M., et al. (2019). Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities-a retrospective study of German health insurance claims data. *Orphanet journal of rare diseases*, 14, 1-16.
- Van Spronsen, F. J., Ahring, K. K., & Gizewska, M. (2009). PKU—What is daily practice in various centres in Europe? Data from a questionnaire by the scientific advisory committee of the European Society of Phenylketonuria and Allied Disorders. *Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism*, 32(1), 58-64.
- Van Spronsen, F. J., van Wegberg, A. M., Ahring, K., et al. (2017). Key European guidelines for the diagnosis and management of patients with phenylketonuria. The lancet Diabetes & endocrinology, 5(9), 743-756.
- Vardy, E. R., MacDonald, A., Ford, S., & Hofman, D. L. (2020). Phenylketonuria, co-morbidity, and ageing: a review. Journal of inherited metabolic disease, 43(2), 167-178.
- Verkerk, P.H., Vaandrager, G.J., Sengers, R.C. (1990). Vijftien jaar landelijke screening op fenylketonurie in Nederland; vierde verslag van de Landelijke Begeleidingscommissie Phenylketonurie [15 years of national screening for phenylketonuria in The Netherlands; 4th Report of the National Commission for Management of Phenylketonuria]. *Ned Tijdschr Geneeskd*.134(52):2533-6.
- Wegberg AMJ, MacDonald A, Ahring K, et al. (2017). The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet Journal of Rare Diseases*. 2017;12(1):162.
- Zerjav Tansek, M., Groselj, U., Angelkova, N., et al. (2015). Phenylketonuria screening and management in southeastern Europe: Survey results from 11 countries. *Orphanet Journal of Rare Diseases*, 10, 68.