Beneath the Surface

A European Position Paper on the Neurocognitive Impact and Care of PKU

Contents

Executive summary

On the surface, there is a clear route for diagnosing and managing the rare condition, phenylketonuria (PKU). Yet, PKU is a hidden illness with many facets that are not always physically obvious to others, including the medical professionals who treat patients. Due to newborn screening, people living with PKU are now diagnosed early and are advised to adhere to strict low protein dietary therapy for life.[1] Despite this progress, patients are still living with the subtle but debilitating effects of their condition, often alone and in silence.

> "PKU has many shades. If we focus only the medical side, we will lose the emotional part of the patient."
>
> – PKU Patient, Italy

PKU impacts patients' lives in hidden ways every day – as this position paper explores. This may be caused directly by unnoticed subtle neurocognitive challenges with concentration or managing low mood,[2] or the challenge of managing lifelong treatment in family, social and work settings.[3] The focus of this position paper is the impact of PKU on the brain and, in turn, its impact on the wider lives of those living with the condition.

PKU is a rare metabolic condition which limits a person's ability to break down protein, and which if left unmanaged can lead to cumulative toxic effects on the brain, affecting around 1:10,000 newborns in Europe.[4] People living with PKU are often able to successfully self-manage phenylalanine (Phe) levels and lead full and independent lives - attending school and university, building fulfilling careers, and having a family. However, the hidden brain-related burdens of PKU are an additional challenge for individuals with PKU to manage, on top of the existing burden of managing a life-long condition. This is what this paper seeks to change, by calling for more support and funding to help patients better identify and manage every day challenges, such as depression or anxiety.

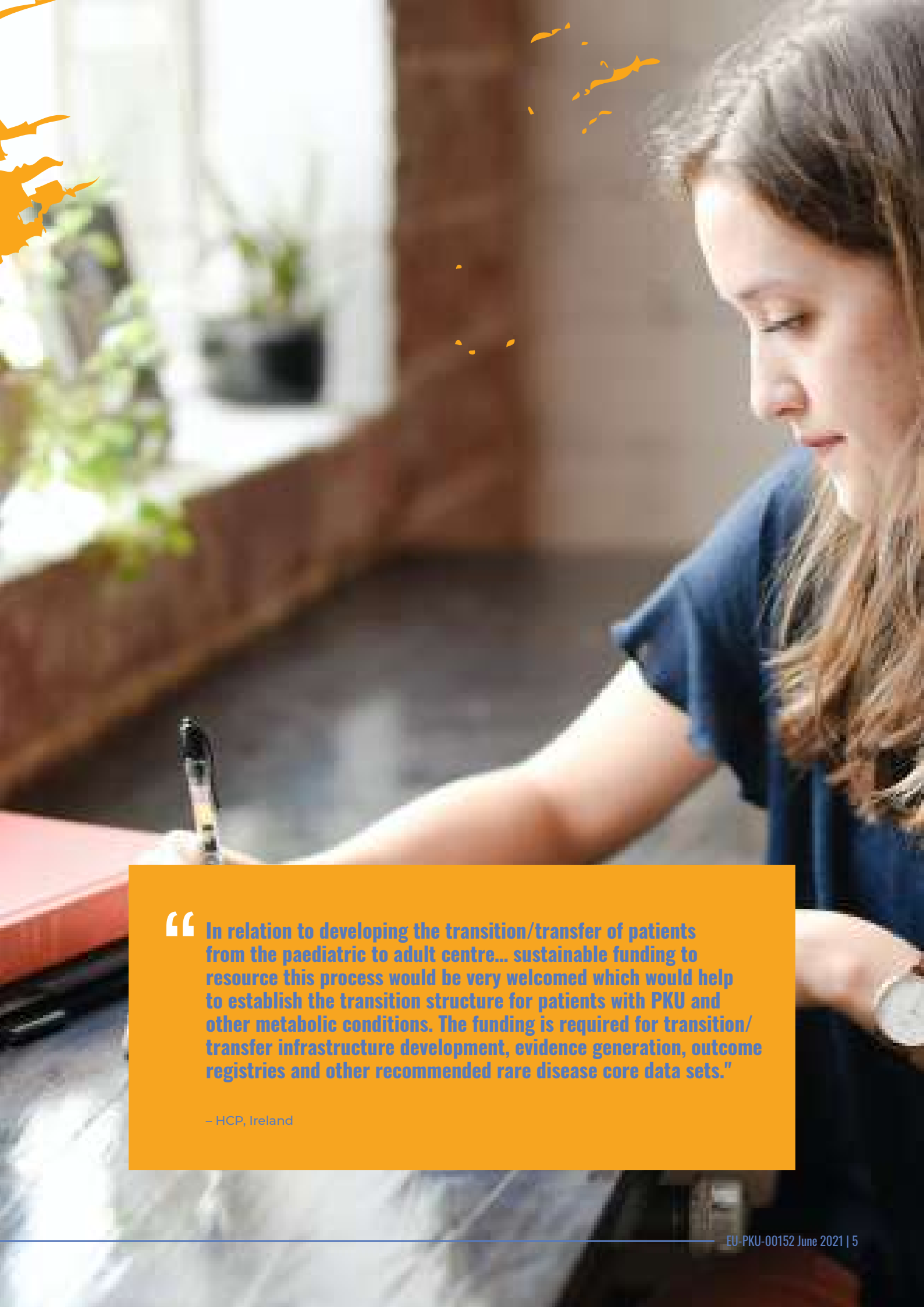
> "In retrospect, I must say that PKU has afflicted me more than I liked to admit when my Phe levels were high."
>
> - PKU Patient, Germany

This paper is set against a climate in which much stigma still exists around mental health. However, mental health disorders in Europe are a growing problem that have been exacerbated in recent years by external factors, such as the COVID-19 pandemic. [5] There is still a long way to go to enable patients across Europe to talk openly about any impacts on their mental health that they may experience as a result of their condition, outside of physical symptoms. However, this paper aims to show that this is a shared experience, and highlights that the situation is improving in many countries.

> "I was very fortunate, to be in an environment where I could speak openly about my PKU. And developing that as an ability, when I was a child, it helped. I don't feel ashamed in saying I have a genetic condition."
>
> – PKU Patient, Italy

This paper is part of the Live Unlimited PKU campaign, which aims to raise awareness of PKU as a life-long condition, and to support everyone living with the condition to ask policymakers to provide better access to specialist and frequent adult care. The campaign membership is made up of patient groups from across Europe, all of which can be found under available resources at the end of the paper. The campaign is funded and developed by BioMarin in collaboration with these patient organisations.

A thorough review of existing evidence and literature from across Europe of the neurocognitive and psychosocial impact of PKU has been undertaken to form the basis of this paper. The paper also presents the views and insights from several people living with PKU and expert clinicians from across Europe, who were interviewed as part of the project. Based on this evidence, the Live Unlimited PKU campaign is calling on governments and policymakers to prioritise four key calls to action to address the requirements outlined in this paper.



> "In relation to developing the transition/transfer of patients from the paediatric to adult centre... sustainable funding to resource this process would be very welcomed which would help to establish the transition structure for patients with PKU and other metabolic conditions. The funding is required for transition/transfer infrastructure development, evidence generation, outcome registries and other recommended rare disease core data sets."
>
> – HCP, Ireland

Key calls to action in Europe

1 Service providers should tailor care models to provide psychosocial and practical support for all patients with PKU, providing adolescents and adults with the opportunity to discuss the holistic impact of their condition with trained specialists. To further support patients to be able to access this support, modelling of the current and anticipated management landscape should be conducted in order to understand where incentives could best be deployed to encourage clinicians to specialise when training. This could include:

- **Consistent provision and access to psychologists.** In terms of specialist types, the positive impact of psychologists, neuropsychologists and even social workers was pronounced, vastly improving patient care and wellbeing.[6]
- **Regular opportunity for mental health monitoring.** Due to the increased risk for neurocognitive and psychosocial issues in PKU patients, regular mental health monitoring is needed[7] – especially given that even early-treated PKU patients experience neurocognitive symptoms that can go unnoticed, such as social functioning.[8]
- **Adequate funding and resources for clinicians to follow-up with patients once a year, for life,**[9] and in particular to support with transition care for adolescents, making sure patients are set up with the right neurocognitive support for their adult lives.
- **Incentives for specialists to remain in a professional setting** where they are able to support PKU patients, alongside a review of the incentives and programmes which encourage clinicians to specialise in areas of expertise which are less common, but are very much needed by the patient community.
- **Resources and dedicated training for families and carers of PKU patients**, who remain the greatest source of support for children and adolescents with PKU on a day-to-day basis.

2 To fully understand the impact of PKU on concentration, mood and quality of life, and support regular conversations to aid this, this campaign further calls for the integration of existing or new tools to allow insightful and meaningful discussion between patients and clinicians. Collaboration between policymakers, clinicians and the patient community will further support the embedding of these tools into pathways and guidelines. This might include:

- **Pathway review and redesign** based on patient and clinical insight, and involving opportunities for all stakeholders to suggest areas which can be remodelled using tools which better support patients to deal with all aspects of the neurocognitive aspects of their condition.
- **The development of patient-powered campaigns to drive awareness of and confidence in using** the services, tools and opportunities available for patients to discuss various aspects of their condition in their locality.
- **HRQoL to be monitored as part of standard treatment**, and more research conducted into appropriate tools – such as questionnaires which accurately capture the impact of PKU on QoL, including social aspects.[10]
- **Encouraging and incentivising healthcare professionals** to identify the challenges faced by families and be aware of risk factors associated with lower parental well-being, in order to achieve better family adjustment and health outcomes.[11]
- **Periodic assessment of developmental progress** to identify neurocognitive deficits, allowing appropriate therapies to be offered in response.[12]

3 There are points in which the neurocognitive impact of PKU becomes more pronounced and in turn can have a greater impact on work, life and relationships – for example, with young adults transitioning to self-management and for women with PKU who are pregnant. This position paper calls on policymakers, clinicians and the patient community to review current management guidelines to identify where and how individualised care plans will better support PKU patients. In addition, this paper recognises the positive impact of some practices which have arisen during the recent Covid-19 pandemic, including the greater use of telemedicine. This paper suggests a patient-led review of these changes, with a view to maintaining elements which mitigate barriers to access. In practice, this might include:

- **Encouraging a move towards individually tailored PKU management practices** according to the patients' needs. This can include individually tailored blood Phe target levels, the use of newer medications, follow-up appointment scheduling and strategies to improve treatment adherence, more detailed nutritional assessments, blood tests, and neurocognitive functioning assessments.[13]
- **Introduce goal setting and action planning into tracking and management** with adolescents, to provide patient with responsibility as they take over from parental oversight. This may be best achieved via digital tools.
- **Patient-led review of the impact of telemedicine and digital tools** with a view to identifying post-pandemic opportunities to retain these where they best support individualised care, access to specialists and improve the support network.
- **Reviewing and removing barriers to services** including provision and location of adult centres, cost and insurance (where applicable), educational level and the need to balance work with disease management. Working closely together, policymakers, clinicians and patient organisations should identify and recommend where additional funding and resources would deliver the most impact for patients in need.

4 Finally, there are broader gaps in the understanding and prioritisation of rare diseases within national health systems across Europe, and stigma still exists which prevents meaningful discussion on dietary treatment, mental health and quality of life. While it is important not to lose sight of specific PKU needs, organisations and clinicians working within the rare disease community at large should also consider where to collaborate and leverage a larger and combined voice in order to drive change in shared areas of interest. In addition, this paper calls on policymakers and governments to urgently review the prioritisation of rare diseases within the health system, including:

- **Collaborative campaigning** with the wider rare disease network to highlight common issues and desired goals, i.e. longer appointment times for chronic conditions; access to psychologists.
- **Greater priority and funding** to the care of rare diseases within health systems, including greater patient access to therapies, centres of excellence and specialists.
- **Campaigns which support patients to live a full life** without stigma, including resources and workshops for peers, family and carers to better support people with PKU and public initiatives and partnerships which work to reduce workplace and school stigma, particularly related to diet, mental health or cognitive function.
- **Insightful, patient-led research** into the relationship between social cognition, psychological adjustment, and quality of life with optimal illness control in PKU.[14] It is possible that enhanced psychological and pharmacological treatment of psychiatric symptoms may alleviate subtle cognitive deficits, particularly in the areas of complex attention and speed of information processing.

Contributors to the paper

The patient groups involved in the Live Unlimited PKU campaign have been instrumental in developing this position paper. They have provided concrete and constructive input to help shape the position paper. Thanks goes to all campaign members, without whom, this paper would not be possible.

Interviews were conducted with seven medical professionals and five people living with PKU from across Europe. These interviews lasted one hour and were structured according to a series of questions, designed to understand the individual perspectives of the interviewees and gather their insights on the key findings from the literature review.

Interviewees were selected based on their experience of living with PKU or their expertise and knowledge of managing patients with PKU in Europe, and were offered honorariums in exchange for their time.

We would like to thank the following individuals for their contribution to this paper.

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Beneath the Surface: an introduction

A rare metabolic condition which directly impacts the brain

PKU is a rare metabolic condition which limits a person's ability to break down protein, and which if left unmanaged can lead to cumulative toxic effects on the brain, affecting around 1:10,000 new-borns in Europe.[4]

PKU is caused by deficiency in an enzyme called phenylalanine hydroxylase (PAH), which leads to high Phe levels in the blood and brain.[9] High Phe levels can cause disruptions in serotonin and dopamine levels, negatively impacting mood, learning, memory, and motivation. This happens as a result of incorrect quantities of neurotransmitters (signalling molecules that brain cells use to communicate with each other), as well as Phe being directly toxic to the brain. These changes are thought to explain why high Phe levels can affect the way a person with PKU thinks, feels, and acts.[15]

> "For me, I usually have emotional instability when my Phe levels are high... I get more sensitive sometimes, I get more irritable. It really affects my emotions."
>
> – PKU Patient, Turkey

Controlling Phe levels is crucial for PKU patients because of the potential side effects of prolonged high Phe concentrations, such as possible damage to executive function (mental skills such as memory and self-control and attentiveness).[16] However, the main treatment for PKU patients in Europe is a restricted low protein dietary therapy for life, which, unfortunately, can itself be associated with significant burdens.[1] As a result, European guidelines set out clear goals for adult treatment, one of which is to achieve normal neurocognitive and psychosocial functioning,[1] and it is the pursuit of this goal that has determined the path of this paper.

> "I never had any symptoms; it is more of a feeling. For instance, I might have a tendency to get angrier sometimes or react differently according to my Phe levels."
>
> – PKU Patient, France

Defining the neurocognitive impact of PKU

It can be hard to determine, assess and measure the impact of cognitive defects, as by their very function, they affect how a person feels, thinks and is able to articulate their symptoms. The term 'cognitive' is used broadly in psychology to refer to thought, and other related processes of the brain. The term 'neurocognitive' was applied to these various processes to emphasise that they can lead to measurable and often disruptive symptoms.[6] Neurocognitive disorders can also be applied to negative changes that are acquired during one's life, meaning that patients may experience a decline in executive function (EF), that was not present from childhood.[2] For some patients with PKU this can be the case, as neurocognitive aspects of the condition can impact intellectual quotient (IQ), attention and information processing.[17]

> "It's a question of framing – it's what we look at in psychology. Normally [adult PKU patients] will report a good quality of life. But – when you go deeper, and discuss the detail, then you suddenly realise, 'yes', there are neurocognitive problems. Even difficulties with emotional wellbeing."
>
> – Medical psychologist, Germany

The Neurocognitive Disorders Work Group of the American Psychiatric Association agreed on six principal areas of cognitive function to help clarify neurocognitive disorders:[18]

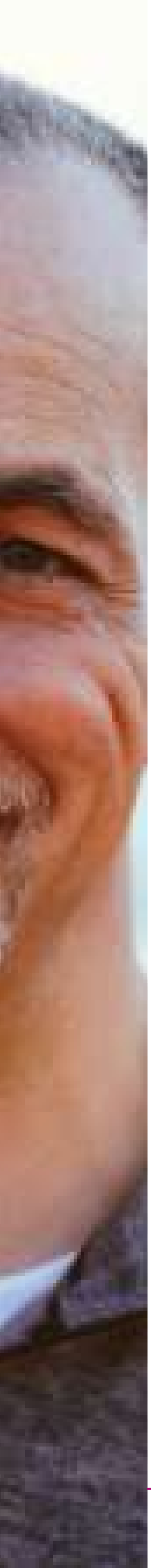
- Complex attention
- Executive function
- Learning and memory
- Language
- Perceptual-motor function
- Social cognition

Understanding and assessing the psychosocial impact of PKU

Psychosocial characteristics is a term used to describe a person's psychological development in relation to his/her/their social and cultural environment.[19] Psychosocial characteristics can include difficulties in social situations, such as:[2]

- Forming relationships
- Achieving independence
- Healthy emotional development
- Attaining educational goals

The psychosocial impact of PKU can sometimes mean that patients experience subtle discrepancies in executive functions (EF), such as a reduction in processing speed, social difficulties, or emotional problems that can go unnoticed for years.[2] Poor EF may affect a patient's ability to adhere to important treatment regimes, in turn leading to negative psychosocial consequences that are not always visible to those around them.



Thematic analysis of these neurocognitive and psychosocial impact

These two interconnected symptoms, the direct neurocognitive and toxic effect on the brain, and the daily psychosocial impact of living with the chronic and rare condition PKU, provide guidance towards the best care and support for patients. However, these terms are meaningless unless their impact on real quality of life is understood.

The following five themes were uncovered as a result of talking to clinicians and people living with PKU about how this terminology and literature translated into clinical practice and real-life outcomes. The following sections in this paper outline key findings, conclusions and data related to each theme.

- Mental health and mood
- Concentration
- Social impact
- Relationships
- Work and education

Mental health and mood

The experience of poor mental health is common across Europe

Although the term 'mental health' is interpreted differently across Europe, good mental health can commonly be viewed as a state of wellbeing in which an individual can cope with the day-to-day challenges and stresses of life, work productively, and is able to make a contribution to his or her community.[1] Poor mental health disorders can be characterised by symptoms such as troubled thoughts, emotions, behaviour and relationships with others, and are extremely common in Europe.

But stigma and differing views complicate the opportunity to set standards and goals for care

Despite the prevalence of mental health disorders in Europe being well documented, an unmet need exists in providing adequate attention and treatment for these illnesses. One European Commission report from 2017 found that "although effective treatments exist, around 56% of patients with major depression receive no treatment at all."[20]

> 110 million people (12% of the population in Europe) in 2015 experienced poor mental health, with 80 million people reporting anxiety or depression.[21]

This lack of treatment may in part be due to diverse attitudes throughout Europe to talking openly about mental health. Many people who require treatment for anxiety or depression in Europe do not receive it, or even a diagnosis.[20] During interviews with a range of patients and clinicians from across Europe, one clinician in Hungary noted that there was a significant disparity in openness towards mental health within the country, with those based in cities found to be much more open to discussing the topic, while rural communities were more fiercely constrained by stigma. Conversely, a patient from Sweden described how mental health was spoken about comfortably and liberally within their country.

Understanding the experience of poor mental health and low mood in PKU

People with rare conditions such as PKU can often experience poor mental health and low mood. In a 2019 UK study, of 286 respondents which examined the impact of mental health on daily life in adults with PKU, the only one of its kind, it was estimated that 50% of PKU patients report symptoms of anxiety or depression.[22]

This was further qualified in an interview with an expert in metabolic diseases in Spain, who described a disproportionate number of young patients with PKU being prescribed medication to cope with the psychological symptoms, including anxiety and depression. Low mood was also reported by PKU patients themselves. In an interview with a patient from Turkey, she described how high Phe levels caused her to experience emotional instability, feeling increasingly sensitive and irritable.

> "When I was 13 or 14 in middle school, I remember some moments when I was so sensitive. I wasn't depressed but from the outside you would think I was depressed because I was so emotional over everything. At some points, I would get really angry."
>
> – PKU Patient, Turkey

These symptoms are thought to be largely a result of the additional complexities that come with managing a complex condition, including stress and unpredictability, regular visits to different healthcare settings and, in some instances, lifelong management of an illness that is not always well understood by peers.[3]

A cycle which reinforces low mood and poor mental health

For patients with PKU, the resulting impact on anxiety and depression can be seen as two-fold:

1. The direct effect of PKU on the brain, resulting in low mood, anxiety and depression.
2. The broader impact of managing a lifelong condition causing mental health factors to arise.[14]

Depression and anxiety can be experienced by patients with PKU due to several factors and as a result, the root cause of the conditions is not always clear. While the causes of poor mental health are varied, many patients manage symptoms of anxiety and depression as part of their everyday life. The complexity involved in understanding the origins of poor mental health and mood was identified by various clinicians in interviews, all of whom affirmed these symptoms are present in their patients. One clinician from Spain spoke to the high social impact of PKU, which will be examined in throughout this paper, expressing that it is "difficult to understand why it happens. I think that the main reason is the metabolic condition...but there should be additional research to understand what's happening to them."

All of this means that the daily impact of PKU is often hidden and symptoms are managed in silence

Despite these symptoms, patients are often able to successfully self-manage Phe levels and lead full and independent lives - attending school and university, building fulfilling careers, and having a family. However, the hidden burden of poor mental health and low mood is an additional challenge for individuals with PKU to manage, on top of the existing burden of managing a lifelong condition.

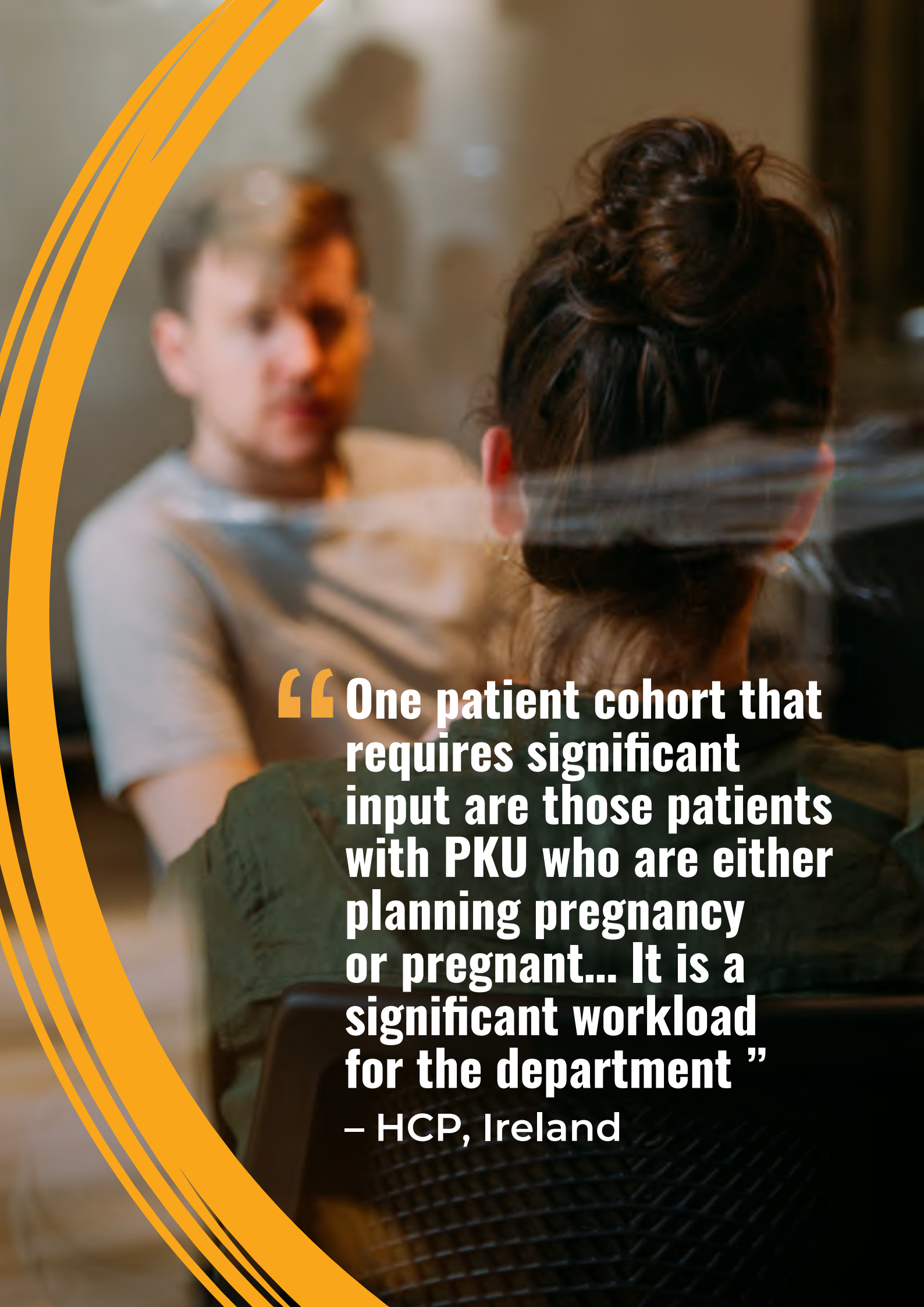
Diagram 1: The two-fold impact of PKU on mood

In one Italian study of 92 patients, 30% of patients reported feeling ashamed of their dietary restrictions and negative towards their treatment as a result.[11] This was echoed by a PKU patient interview from Germany, who said that "there are a lot of people with PKU who feel ashamed of going to the doctor". When interviewed, a clinical dietitian from Denmark noted that it would be helpful to have access to more research about the link between depression, anxiety and PKU, "because it's a rising problem, for all of us... to see what PKU actually does, to see if we could do more to prevent this from happening...can we talk to them, can we make them feel better about their condition?"

> "PKU never made me stop doing the things I wanted to do. When I went to university, I lived in a flat alone. So that I could experience working life."
>
> – PKU Patient, Italy

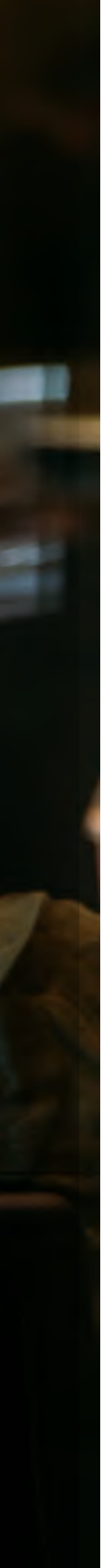
The impact of poor mental health and low mood is further exacerbated by the need to focus on and manage the more obvious aspects of a chronic condition. An internal medicine specialist in Hungary, observed that "because [PKU patients] are focussed on the everyday process, they do not have time, energy to take care [of their] mood. It's enough to take care [of] the every day." This was echoed directly by a patient from Turkey, who reported: "When you get older your days get busier...you don't have a lot of time for yourself in the day...it's hard to always be attentive [to managing the condition]."

The impact on mood and mental health is often overlooked and not openly discussed, either by friends, family or healthcare professionals. This can cause further isolation for patients and is indicative of a culture where these symptoms are managed in silence. This silence means that many patients do not recognise these factors as a symptom of their disease,[23] which means adequate psychological support has not been realised for many patients.



“One patient cohort that requires significant input are those patients with PKU who are either planning pregnancy or pregnant... It is a significant workload for the department ”

– HCP, Ireland



The impact of PKU on anxiety, mood and depression can complicate important life milestones, such as pregnancy

One study, which surveyed 300 women with PKU in the UK, found that 73% expressed concerns, fears and distress about pregnancy and two thirds of women who had at least one pregnancy stated that having PKU made pregnancy more stressful and difficult.[24] This stress appears to be predominantly the result of two, closely interlinked factors: concern around causing harm to the baby, and fear about their ability to manage a strict diet during pregnancy.[24]

This significant impact of mental health also continued post-pregnancy, where 48% of women experienced low mood or sadness, and 41% experienced depression.[24] One clinician interviewed from Ireland discussed the strain on hospital resources to accommodate maternal PKU patients, who could often require in-patient admission if their condition proved difficult to manage alongside pregnancy.

Just as adolescents struggle to manage their treatment regimes alongside the responsibilities of adult life, 33% of new mothers said they could not manage their PKU and care for their baby.[24]

Non-specialists often find themselves supporting the emotional needs of patients

The need for multidisciplinary healthcare teams (MDTs) to treat patients living with PKU is well-established, and the Live Unlimited PKU campaign and associated partners has long called for access to MDTs, including a psychologist, for all adults in Europe. But the reality is far from perfect.

> A 2010 European survey of patients with PKU found that only 12% currently have access to a multi-disciplinary team consisting of specialist physicians, nutritionists, specialty nurses, psychologists and clinical biochemists.[25]

This paper found that a number of clinicians interviewed who did not have a speciality in psychology were left to tend to the emotional needs of their patients, despite the absence of specialist training and expertise.[25] The lack of access to psychologists was affirmed by several clinicians throughout the interviews, who often expressed frustration and dealt with the issue in a number of different ways. A clinician, Hungary, described how he was limited to helping patients manage the strictly medical aspects of their condition, as he was unable to refer them to specialist support to help with difficulties relating to their social life. He stated: "we are a medical team, we are not a social team, and unfortunately we don't have a social nurse or somebody who might support his or her private life or social [life]. We need to focus on his or her medical conditions." In contrast, one clinical dietitian interviewed from Denmark revealed she often provided her patients with broader care, including much-requested emotional support, alongside the nutritional advice she was equipped to provide.

One interviewee who specialised in metabolic medicine described how the numbers of PKU patients with depression or anxiety was extremely high, resulting in "a massive workload for a part time clinical psychologist".

The clinician stated that "Although we have some access to clinical psychology (part time psychologist with service) in the adult centre more is required", and went on to describe that the ideal solution would be a "full drop-in service so that if patients have issues or concerns they can access the service on a daily basis."
– Metabolic specialist, Ireland

Concentration

The impact of PKU on concentration remains the most common neurocognitive symptom

A wealth of existing studies demonstrate that difficulty concentrating is one of the most commonly cited neurocognitive impacts of PKU. Several studies have reported that high Phe levels, if prolonged, can have a negative impact on cognitive function, including concentration and reaction times.[26, 27]

Patients report this as a 'brain fog', which can manifest and affect executive functioning

Patients with PKU often report symptoms of "brain fog", which affect their ability to concentrate. Research has indicated that PKU patients, in comparison to the broader population, struggle more with memory, problem-solving skills and strategy.[28] Even patients whose Phe levels are more under control can also struggle with concentration.[27]

Several specialists were able to describe their observations on the effect of PKU on patients' concentration. An internal medicine specialist, Hungary, found that while most of his patients would, on the surface, appear to be the same as anyone else living in Hungary, a subset would experience problems focussing and have a lower IQ compared to the average population. Other symptoms he observed included challenges with motor skills and executive functioning.

> In a survey of respondents regarding desired outcomes from new treatments, 43% said lifting the fog would be a desired outcome. [29]

The knock-on effects continue to go unnoticed and unchecked

As poor concentration can impact daily life and development, the results which explore this impact are crucial to uncovering how the neurocognitive impact can be effectively managed, supported and reduced. Without developing a good level of concentration, focus, and memory, patients may struggle to fulfil the responsibilities associated with adulthood, including acquiring and maintaining employment, managing money, raising a family and driving.[2,30] However, without standardised tests to assess the impact of PKU on QoL, the broader aspects of living with PKU and the knock-on effects of symptoms may continue to go unnoticed and unchecked.

One patient interviewed had a teacher who would go around the class and choose people to answer questions on the spot and at random. As the patient struggled to follow along during a lecture, often reading through the material after class to catch-up, this teaching style caused difficulties and anxiety.

PKU Patient, Sweden, describing how, although they had never felt their issues with concentration to be a significant burden, they had once been forced to email a teacher about difficulties concentrating for long periods of time.

Over the last decade, there has been a transformation in the understanding of PKU on the brain, with some cognitive deficits now thought to be a feature of PKU itself, rather than a secondary effect caused by poor diet control. As highlighted by one clinician from Italy, additional research is needed to understand the impact of fluctuating Phe levels on concentration.

While patients can achieve good Phe control with diet management and reduce the impact of brain fog, there remains an elevated risk of low mood, anxiety and attention disorders across adult life, and specific research into these symptoms may well uncover novel treatment options to provide greater relief from such symptoms when compared to diet.[14]


Beautiful,
free photos.

Social impact

The subtle effects of neurocognitive symptoms can make everyday socialising more challenging

Living with PKU can challenge the way you live your life, particularly in relation to the highly restrictive diet and the need to constantly monitor Phe levels. Reports have found that even early and well-treated PKU patients can experience social difficulties and emotional problems that can go unnoticed for years,[2] the impact of which is broadly being considered under 'quality of life'. This was captured in an interview with a patient, Turkey, who described: "I'm always trying to be attentive. Then I get tired. When I get tired I panic, is it because my Phe levels are high? It's like a little circle that I'm in."

One study found that while patients highly valued social interactions, they also identified that their mood could impact their ability to socialise.[11] An Italian study found that Phe levels regularly affected patients' mood:

25%
reported fatigue

14%
reported irritability (n = 16; 14%)

13%
reported mood swings (n = 14; 13%).[23]

n = 111

Interviews with clinicians uncovered various lines of thinking on how to accurately assess and measure the impact of the disease on quality of life, but these are not recommended routinely in all countries. For example, an internal medicine specialist, Hungary, advised that neurocognitive aspects of PKU in patients should be measured in two ways. Firstly, on an ad-hoc basis, with patients reporting specific problems that lead to a broader discussion about the challenges they are facing. Secondly, through the more formal use of the Cambridge Neuropsychological Test Automated Battery (CANTAB) tools. These can be used every five years to measure a patient's mood and other neurocognitive symptoms, allowing changes to be measured over time. Additionally, another clinician interviewed from Spain suggested that a real-time monitoring tool for use in clinics would be useful to help explore the relationship between Phe levels and the neurocognitive symptoms being presented.

Managing care for a chronic condition adds to the stress and challenge of socialising

While the neurocognitive impacts of PKU can directly lead to social issues, the broader burden of managing a chronic, rare and dietary condition like PKU can result in social challenges too. For example, rare disease patients often report feeling isolated due to living with a condition which those around them are unlikely to understand. In a recent survey, over 50% of rare disease respondents said they faced isolation from friends and family which was caused or amplified by their rare disease.[31] In the same research, patients acknowledged that they were tired of explaining their PKU to friends or colleagues, and often preferred to avoid socialising altogether as a result.[31]

Talking about PKU can stimulate feelings of embarrassment and affect self-esteem

As examined earlier, although the psychosocial aspects of PKU may be reduced by controlling Phe levels, the primary management programme for patients is focused on a strict, life-long diet, which can often lead to feelings of social isolation and exclusion where food is a part of socialising. This can happen particularly in certain social settings, such as restaurants, at parties, or on work trips. While dietary conditions have received greater attention in recent years, for people with rare diseases like PKU, being able to quickly discuss dietary needs in a social setting without stigma, and with a level of understanding, is still not a reality for most across Europe.

In one UK study, PKU patients reported that they found their treatment to be a major cause of embarrassment, upset and frustration, which often resulted in a lack of adherence to the diet for many patients.[22] Similarly, an Italian study found that non-adherent patients reported their non-compliance to be a result of the emotional distress caused by feeling different to their peers in social situations.[23]

This finding was reflected across several interviews. During an interview, a clinical dietician from Denmark described how "we hear quite often that [adolescent PKU patients] are not comfortable taking their amino acid supplements in high school. They are embarrassed about it." This was echoed by a clinical psychologist from Germany, who had observed that PKU patients will often refer to their PKU as an allergy to avoid relaying details of their condition, calling for a "huge focus on self-esteem" to help such patients.

As such, many people with PKU find themselves in a position where the neurocognitive impacts of PKU make socialising difficult, but the most common method of minimising such neurocognitive impacts (a strict diet that controls Phe levels) can exacerbate the feelings of anxiety and social isolation already experienced.

“I don’t think I’ve ever encountered anyone who has the slightest idea of what PKU is. That’s only happened once or twice in my life.”

“Before treatment, every day was a struggle. Eating at school, eating at restaurants, feeling left out in social situations.”

- PKU Patient, Sweden

Adolescents experience this challenge keenly at a time of social pressure, identity-forming and a desire of independence

Many teenagers transitioning from paediatric to adult settings can find social situations and building relationships with others more challenging due to their PKU. This may be due to the loss of metabolic control that is often seen within this age group, or to the situational factors associated with managing a strict treatment regime at a challenging life stage. One patient from Sweden revealed that she had never spoken to anyone about the neurocognitive impact of PKU apart from her parents. The same patient stated that this had been very stressful for her parents to have the "burden" of her PKU on their shoulders, citing fear of how the condition would turn out in the future as a primary cause of this stress. Another patient from Germany described how she now regretted resisting the dietary restrictions "imposed" by her parents, as they only wanted the best for her.

Like peers in this age-range, teenagers with PKU also face peer-pressure and a desire for increased independence, which can result in a lack of adherence to treatment.[7] This behaviour may be adopted to alleviate some of the social stigma teens associate with their PKU, but can also ultimately exacerbate some of the behavioural symptoms these patients face due to uncontrolled Phe levels. Studies have found that during the transition to adulthood, adherence to treatment significantly reduces as a consequence of a desire for independence and reduced parental control, social factors and organisational difficulties.[7]

> One study found that 61.5% of adults had poor metabolic control, compared to just 25.5% of children.[29]

A desire to 'be normal' means adolescents rebel against their management and become 'lost' to clinical follow up at this crucial time

Many adults with PKU in Europe are either "lost" in the transition process from paediatric care to adult care or must continue to be seen in a paediatric setting, which is no longer suitable.[32] One Italian study from 2020 reported that adults had a strong desire to be treated away from the paediatric setting and suggested this may encourage non-adherent adults to comply with treatment.[23] One medical psychologist interviewed, Germany, described the situation in which patients with PKU are lost in follow up after the age of 18 as "unethical". For these patients, their adherence rate to the treatment is generally low and they have an increased risk of developing comorbidities that need regular controls.[32] The same interviewee described how many of the adolescent PKU patients she treated are "so tired of their PKU", resulting in a reluctance to adhere to treatment.

In a separate interview, one patient described the cumbersome administrative processes involved with transitioning from adolescent (student) healthcare to adult. They stated that no assistance or information on these procedures was provided in advance, and young people with PKU can often find this generates considerable stress.

> "They just hope if they stop thinking about it, if they stop being compliant with the diet, that it will disappear and of course, it won't, it will just get much worse."
>
> – HCP, Denmark

One patient described to this clinician how mentally she began to feel healthier, if she stopped adhering to her diet as she was not constantly reminded of her condition.
There is considerable variation across Europe in terms of how patients living with PKU are managed once they reach adulthood (normally accepted as 18 years old in Europe). For instance, the clinical community in Italy has yet to determine which subset of doctors should be responsible for adult PKU patients, whereas in Denmark, a single centre is equipped to support individuals throughout their life.

An additional burden for adult patients to contend with is a growing concern and sense of unknown about what the future looks like for PKU patients, particularly as they transition from adult to geriatric care. In most European countries, someone transitions to geriatric care at the age of 65, which is based primarily on retirement age.[33] The first generation of early-treated adults with PKU (the first patients to receive new-born screening and lifelong management of PKU) are beginning to reach their 50s in Europe. To date, there has been little exploratory research on the geriatric care pathway.

Researchers have also expressed concerns around the unknown effects of high Phe levels on ageing brain as there is limited evidence on this topic.[34] One study found that, based on a neuropsychological assessment in adults with PKU, neurocognitive impairment was present particularly in older adult patients. However, 'older' patients in this research context referred to patients in their thirties, suggesting a research gap that needs to be urgently addressed as PKU patients age.[35]

Several interviewees expressed concerns about what the experience of ageing with PKU would look like. For instance, an Italian patient described "a gap in the ageing process for PKU patients. Existing clinical data talks about how the life will be for an adult. This is where there is a gap...the ageing process is little known". In addition, several patients reported being "curious to see how our lives will be when we're in our 80s and 90s".

Relationships

Misunderstanding, disbelief and challenges with concentration can make forming relationships more difficult.

Enjoying personal, professional and family relationships successfully provides support, joy and stability for everyone – whether you live with a rare disease, or not. However, a 2017 EURORDIS survey of 2689 rare disease patients found that 70% reported having difficulties socialising and building relationships with other people, due to their rare condition, and 43% reported having problems communicating with others.[31] One study found that patients with rare diseases (non-PKU) reported the misunderstanding and disbelief from others regarding their illness as a major cause of interpersonal problems.[24]

In a further challenge for PKU patients, some of the neurocognitive outcomes associated with PKU, such as difficulty concentrating and reduced processing speed, can lead to problems forming interpersonal relationships,[2] even among those treated from birth.

For instance, Bilder's review of psychiatric symptoms and disorders in PKU found that children with early-treated PKU still commonly experienced lower social competence. In the same paper, adults with early-treated PKU were also reported to experience issues with social isolation, withdrawal and lack of autonomy.[16] These symptoms can lead to challenges forming and maintaining strong relationships. Additional research in the field, although scant, has suggested that difficulties forming relationships stem from the neuropsychological, behavioural and social symptoms that some patients report throughout their lives, attributable to their PKU.[14]

Looking 'normal' can put pressure on patients to explain, defend and proactively discuss their condition

Like many rare conditions, PKU is a hidden illness with comorbidities and symptoms which are not always visible to others. Some patients report challenges with relationships due to a lack of awareness from others, describing that they can feel misunderstood or scrutinised by these individuals.[22]

> "I think maybe I feel [anxiety] is less interesting than if it was something visibly physical that would happen to me that people would feel is interesting. I don't think I feel that having a bit more general anxiety is worth mentioning to people I don't know well."
>
> – PKU patient, Sweden

Support networks play a crucial role in adherence to treatment

Adolescent and adult patients may feel more isolated when the responsibility for managing their condition falls to them alone, and they are unable to rely on family, friends or social networks for support.[23] In these circumstances, adherence to any sort of treatment can be particularly challenging, and studies have indicated that support from family or friends can be beneficial for following the treatment regime.[11] Given that adherence to treatment is higher in childhood, parental support and involvement in condition management is crucial for many of those living with PKU.[11]

> "The role of relatives in the early years and of parents is absolutely crucial. It seems to me that today the system does not help them at all to manage their daily lives, which are affected by this heavy burden (sometimes with several PKU children in the same family)."
>
> – PKU Patient, France

While it is known that neurocognitive and psychosocial effects may be improved by adhering to treatment, this can be very challenging. Literature has indicated that treatment adherence requires a patient to be able to effectively plan, exercise self-control and resist dietary discretion,[14] all of which can be more challenging when executive functioning is impaired – or when socialising and building important relationships.

The importance of support networks came through strongly in the interviews conducted for this paper, with several healthcare professionals citing conversations with their patients' families or partners as the only way to gather an accurate picture of how an individual is coping. A clinician interviewed from Portugal described how the first barrier to understanding the neurocognitive impact of PKU is often the conversation with the patient, which was difficulty echoed by a specialist in metabolic disease:

> "I have to ask the same question to their partner, to their parents, to their friends, to the people who are living with them because sometimes they are really not self-aware of what is happening. It is the other people who are really aware.'
>
> – Specialist in Metabolic Disease, Spain

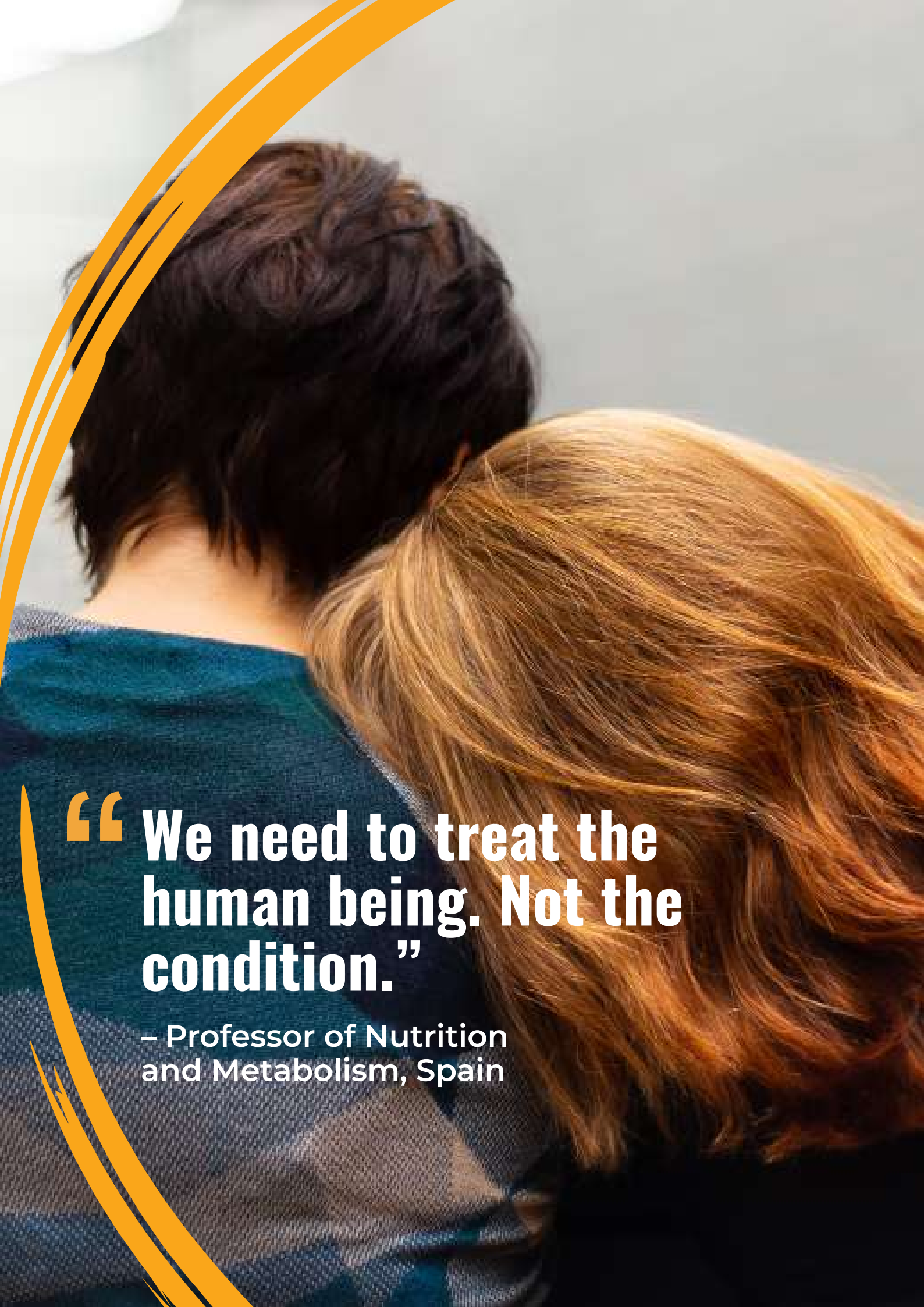
Relationships with HCPs are key, yet healthcare professionals are time poor and many centres lack psychological and dietary support.

Agreed standards of care needed to help adults comply with treatment is set out in the 2017 European guidelines, which recommends adults with PKU are seen once a year for the entirety of their life.[1] Unfortunately, registry data suggests that not all patients are seen once a year, and that this lack of continued care can have serious neurocognitive consequences for some patients.[25]

A study from Italy explored the perceptions that non-adherent patients had towards healthcare professionals, finding that these patients were disengaged with the healthcare system and sometimes felt angry towards their medical team.[23] Patients reported that while their healthcare professionals tried to be helpful, they often lacked knowledge about how best to manage PKU, apart from the restrictive diet.[23] In order to improve care for people with PKU, improved understanding, and the use of language and tools between patients and doctors are crucial, as a relationship with the healthcare system must be maintained in order to have a high chance of adherence and management of PKU.[27]

> "It takes a lot to go that extra mile and ask for help.... I don't know if I could have gotten that help [psychological support] if I asked for it. It is not something that I've been offered."
>
> – PKU Patient, Sweden

In addition, many patients find it helpful to be introduced to other people with PKU who are struggling or have struggled with similar aspects of the condition to them. For example, when interviewed, one clinician from Denmark spoke to how she connects her patients with other people with PKU who are in the same situation, as well as holding summer camps and other activities to bring these groups together.



“We need to treat the human being. Not the condition.”

– Professor of Nutrition and Metabolism, Spain

These challenges around interacting with healthcare professionals are not just experienced by those with PKU, but by patients with rare diseases more broadly. Due to the low prevalence of their condition and lack of professional knowledge, this appears to be a common issue among those with uncommon diseases.[37]

> "It can be uncomfortable having to explain to a regular doctor what PKU is all the time…I don't think I've ever experienced a doctor knowing what PKU is. This makes me feel unsafe."
>
> – PKU Patient, Sweden

Trust, understanding and recognition of the hidden burden is an important part of the patient-doctor relationship

When interviewed, a clinical nutritionist, Portugal, spoke to his belief that "we need to pay attention to the reality of the patient", and how he focuses heavily on shifting the dynamic between the doctor and patient in order to do so. He believes once you understand the patient's social life, the impact of the restrictive diet can be improved. The interviewee cited an example of a patient he was seeing whose dietary treatment was not working and how, through listening to her and uncovering that she was undergoing high-pressure exams, he altered her treatment approach and she started to feel better. A desire to see this approach used more widely was expressed by one patient from Turkey, who stated: "We need to adapt the diet to our lives, because now we are adapting our lives to the diet."

A survey by EURORDIS [2017], found that rare disease patients rated their healthcare experience just 2.5 out of 5, substantially lower than chronic disease patients, due to a feeling that their specialists lacked knowledge or information.[31] Patients and carers reported wanting more support with how they felt about their health emotionally.[38] For those with PKU, these feelings may be exacerbated by a lack of specialists in the adult space, particularly psychologists and nutritionists.[38]

Several patients and clinicians interviewed expressed their concern that patients with PKU did not have access to a psychologist, with one patient from Italy stating: "I feel like if I had [a psychologist] I would probably discover more about me. I'm sure that there are some side effects on my social life that I don't realise or don't pay attention to. But if I could work with a psychologist, I'm sure I would realise them."

Work and education

Hidden effects of PKU manifest throughout life, meaning individuals have to work harder to match peers

Like those challenges experienced in managing relationships, the hidden aspects of PKU can impact a patient's ability to reach their full potential at work or at school. For example, issues with concentration can have a knock-on effect on job performance.[2]

One German study of 48 respondents found that just 19% of adult patients with PKU had achieved their senior high school diploma, compared to the 38% of the general population.[40] A second study in Germany found that the majority of patients with late diagnosed PKU had attended special educational schools.[41] In this second study, PKU patients who had received continuous treatment achieved higher graduation levels.

> "On-going research in the department is examining how the cohort of adults with PKU compare to adults without PKU.. in relation to success in completing second and third level education and achieving follow up gainful employment."
>
> – HCP, Ireland

Factors relating to adherence can also impact an individual's ability to reach their full potential at work. For example, in one survey:

36%
of patients reported feeling embarrassed by their formula[11]

33%
highlighted that such products are not easy to use outside the home environment[11]

34%
had challenges finding the right food when travelling[11]

One interview with a clinician, Germany, revealed that although patients with PKU who suffer significant cognitive impairment are confronted with considerable stigmatisation, and often struggle to find or maintain employment, they are often not considered impaired enough to warrant any assistance from the state.

Frustrations of a different nature were also echoed by a patient interviewee, who described how they had not previously felt the need for psychological support. However recently they had determined that during their next check-up they were going to ask for an annual appointment with a psychologist to discuss the intellectual demands of their profession, and to see how they might cope better with them.

Standing out – social stigma and feeling different at school

As explored in previous themes, social aspects of work and school can also be hard to navigate for people living with PKU, with 44% of adult patients reporting that they felt socially excluded due to their PKU.[22] Having to take medication in public places can often make people feel isolated and socially awkward, leading to a lack of adherence. One interview with a neurologist from Italy revealed that once patients fully understand the link between their low Phe levels and their cognitive performance, the patient may be more motivated to adhere to treatment.

PKU patients do not stop experiencing social stigma after they leave school, with one patient interviewee describing how they would need to prepare separate food for an upcoming business trip and would not be able to eat with their colleagues.

Due to the substantial number of patients with cognitive inefficiencies reporting co-morbid mood and anxiety symptoms, academics have called for further research into the contribution of depression and anxiety on the neuropsychological profile in PKU and the impact of these factors on academic attainment.[14]

During an interview, one clinician based in Spain described how, although it was widely thought that well-controlled PKU patients were not impacted neurocognitively, his own experience with his patients has seen that even adherent patients with controlled Phe levels experience difficulties. The clinician stated that in his clinics, many adult patients with PKU were unemployed, meaning that many were still dependent on parents. Further research and tools are clearly needed to better understand the full impact of PKU on academic attainment, particularly considering new treatment advances.

Glossary

This list details the definitions used in this paper.

Phenylketonuria (PKU)

A rare metabolic condition which limits a person's ability to break down protein, often leading to cumulative toxic effects on the brain.

Cognitive

A term used broadly in psychology to refer to thought, and other related processes of the brain.

Neurocognitive

A term applied to various processes to emphasise that they can lead to measurable and often disruptive symptoms.

Psychosocial characteristics

A term used to describe an individual's psychological development in relation to his/her social and cultural environment.

Mental health

A state of wellbeing in which an individual can cope with the day-to-day challenges and stresses of life, work productively, and is able to contribute to his or her community.

Resources available

Live Unlimited PKU Campaign

The Live Unlimited campaign aims to raise awareness of the life-long condition, PKU, and to support everyone living with the condition to ask policymakers to provide better access to specialist and frequent adult care.

Further information about the campaign can be found on: **https://liveunlimitedpku.com/** or you can email the campaign at **LiveUnlimitedPKU@portland-communications.com**

The Live Unlimited PKU campaign has been funded and developed by BioMarin in collaboration with ten patient groups and their memberships: AMMeC (Italy), Cometa A.S.M.M.E (Padua, Italy), Les Feux Follets (France), Svenska PKU-föreningen (Sweden), PKU Aile Derneği (Turkey), FEEMH (Spain), DIG (Germany), PKUAI (Ireland), APOFEN (Portugal) and the Hungarian Society for PKU (Hungary).

AMMeC (Italy)

AMMeC (Associazione Malattie Metaboliche Congenite) is an Italian association for neurometabolic diseases responsible for providing support to patients and their families. The association's objectives include promoting greater knowledge of metabolic diseases, stimulating medical scientific research and prevention, as well as ensuring the adequate training of doctors looking after patients with these diseases.

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Cometa A.S.M.M.E (Padua, Italy)

COMETA ASMME is an Italian association for patients with metabolic diseases, including PKU. The association is committed to supporting people affected by hereditary metabolic diseases and promoting financing research into metabolic disease. In addition, Cometa ASMME focuses on raising public awareness about both the existence and severity of these diseases and making health authorities aware of the specific and continuous medical assistance needed to allow patients to integrate with society.

E-mail: info@cometaasmme.org
Telephone: 049.8962825

Federación Española de Enfermedades Metabólicas Hereditarias (Spain)

Federación Española de Enfermedades Metabólicas Hereditarias (FEEMH) is a non-profit Spanish association with a mission to improve the quality of lives of those affected by hereditary metabolic diseases. The association achieves this through psychological and nutritional workshops, providing subsidy for the purchase of low protein food, raising awareness, collaboration in research, and the expansion and homogenisation of neonatal screening at regional levels.

E-mail: federacion@metabolicos.es
Telephone: +34 910 82 88 20

Svenska PKU-föreningen (Sweden)

Svenska PKU-föreningen is a Swedish organisation founded in 1991 and is part of the Rare Diagnosis Association. The association aims to improve the lives of PKU patients and their families. This is reflected by the association's objectives which include spreading information about PKU, promoting greater choice of diet products and working towards clear guidelines on PKU.

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PKU Aile Derneği (Turkey)

PKU Aile Derneği is a Turkish PKU association with objectives focused around improving the lives of people affected by PKU. These objectives include providing training on the treatment of individuals with PKU, preparing and implementing special education/rehabilitation programmes for people with disabilities, and working in cooperation with relevant institutions on dietary products.

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Les Feux Follets (France)

Les Feux Follets is a French national association of parents of children and adults with inherited metabolic diseases treated by a strict diet, including PKU. The association's mission is to transmit scientific and medical information through professionals, provide advice, enable families to meet and share their experiences and provide administrative support to families. It is important to Les Feux Follets that it brings children, adolescents, adults and people around them to help and support them in their daily management of the disease. It works to achieve this is in many ways, for example, the association organises regional workshops around cooking.

E-mail: lesfeuxfollets@phenylcetonurie.org
Telephone: 06 98 87 31 31

PKUAI (Ireland)

The PKU Association of Ireland (PKUAI), established and managed by a voluntary group of community members, aims to assist and support those living with PKU in Ireland today. PKUAI strives continuously for the best quality of care for those living with PKU through; raising awareness about the rare disease, advocating for more proactive and holistic life-long care from diagnosis of newborns, continuing throughout childhood into older adult-hood and providing a support network for the community. PKUAI believes with a more determined and scientific approach to treating PKU, people living with this rare disease will secure a better quality of life and be better able to reach their full potential.

E-mail: info@pku.ie / communications@pku.ie

Hungarian Society for PKU (Hungary)

Founded in 1990, the Hungarian Society for PKU provides dietary support, summer camps, scholarship programmes, support for events and information materials to families across Hungary.

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APOFEN (Portugal)

APOFEN is a non-profit association which, in Portugal, supports PKU and other inherited metabolic disorders of protein metabolism that, although with different pharmacological approaches, share a low-protein diet. Its mission is to ensure the improvement of the quality of life of patients in a close relationship with all of them. APOFEN promotes several activities throughout the year to accomplish their mission, such as: Mentorship Programme; Family Support Programme, "Young APOFEN" Group, Psychological Support; Campaigns in kinder-gartens and schools; Cultural Weekends for young adults; Summer Camp; National Family Meeting; Regional Meetings (islands); Cooking Workshops and Thematic Meetings.

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DIG PKU (Germany)

The DIG PKU was founded in December 1975 by 8 pairs of parents whose children were diagnosed with phenylketonuria (PKU) Today the DIG PKU has nearly 1,900 members and supports PKU patients, but also those with allied protein metabolism disorders, and their relatives and caregivers.

References

1. Van Wegberg, A.M.J., Macdonald, A., Ahring, K., et al. (2017) The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017; 12: 162. Published online 2017 Oct 12. doi: 10.1186/s13023-017-0685-2

2.Gentille, J.K., Ten Hoedt A.E., Bosch, A.M (2010) Psychosocial aspects of PKU: Hidden disabilities – A review. Mol Genet Metab, 99 Suppl 1:S64-7. doi: 10.1016/j.ymgme.2009.10.183.

3. Nunn, R (2017). "It's not all in my head!" - The complex relationship between rare diseases and mental health problems. Orphanet journal of rare diseases, 12(29). Available at: https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0591-7 [Accessed June 2021]

4. Loeber JG. Neonatal screening in Europe; the situation in 2004. J Inherit Metab Dis. 2007;30(4):430–438

5. Webb R.T., S. McManus, et al. Evidencing the detrimental impact of the COVID-19 pandemic on mental health across Europe. The Lancet. Accessed at: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00029-6/fulltext [Accessed June 2021]

6. Jurecki E.R., Cederbaum, S., Kopesky, J., et al (2017). Adherence to clinic recommendations among patients with phenylke-tonuria in the United States. Mol Genet Metab, 120(3), pp190-197. doi: 10.1016/j.ymgme.2017.01.001.

7. Vockley, J., Andersson, H., Antshel, K., et al (2014). Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genetics in Medicine, 6, pp 188–200.

8. ESPKU (2015). PKU: Closing the Gaps in Care, An ESPKU benchmark report on the management of phenylketonuria within EU healthcare economies. Available at: https://www.espku.org/wp-content/uploads/2015/06/PKU_report_FINAL_v2_nomarks.pdf [Accessed June 2021]

9. 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, Article number: 171 (2020)

10. Barta A., Sumanzski C., Turgonyi Z., et al. (2020) Health Related Quality of Life assessment among early-treated Hungarian adult PKU patients using the PKU-QOL adult questionnaire. Mol Genet Metab Rep 23: 100589 Published online 2020 Apr 22. doi: 10.1016/j.ymgmr.2020.100589

11. Cazzorla, C., Bensi, G., Biasucci, G. (2018) Living with phenylketonuria in adulthood: The PKU ATTITUDE study. Mol Genet Metab Rep 2018 Jul 11;16, pp. 39-45. doi: 10.1016/j.ymgmr.2018.06.007. eCollection 2018 Sep.

12. Singh, R., Cunningham, A., Mofidi, S., et al. (2016) Updated, web-based nutrition management guideline for PKU: An evidence and consensus based approach. Mol Genet Metab Jun;118(2), pp. 72-83. doi: 10.1016/j.ymgme.2016.04.008.

13. Enns, GM., Koch, R., Brumm, V., et al. (2010) Suboptimal outcomes in patients with PKU treated early with diet alone: Revisiting the evidence. Mol Genet Metab, 101(2-3), pp 99-109. doi: 10.1016/j.ymgme.2010.05.017. Epub 2010 Jun

14. Ashe, K., Kelso, W., Farrand.,S et al (2019). Psychiatric and Cognitive Aspects of Phenylketonuria: The Limitations of Diet and Promise of New Treatments. Front Psychiatry, 10: 561. doi: 10.3389/fpsyt.2019.00561

15. PKU Living (2020). Phe in the brain. Available at: https://www.pkuliving.eu/about-pku/phe-in-the-brain. [Accessed June 2021]

16. Brumm, V.L., Bilder, D., and Waisbren, S.E. (2010) Psychiatric symptoms and disorders in phenylketonuria. Mol Genet Metab, 99(1), pp 59-63. doi: 10.1016/j.ymgme.2009.10.182.

17. Weglage, J., Fromm, J., van Teeffelen-Heithoff, A., et al. (2013). Neurocognitive functioning in adults with phenylketonuria: Results of a long-term study. Molecular Genetics and Metabolism, 110, pp s44-S48

18. Sachdev, P.S., Blacker, D., Blazer, D.G., et al (2014). Classifying neurocognitive disorders: the DSM-5 approach. Nature reviews; Neurology. Advanced online publication, pp. 1-9. Available at: https://escholarship.org/content/qt77g8t63q/qt77g8t63q_noSplash_59d7fbd60fc063e6dba5c393fe7ea300.pdf [Accessed June 2021]

19. Vizzotto A.D.B., de Oliveira A.M., Elkis H., Cordeiro Q., Buchain P.C. (2013) Psychosocial Characteristics. In: Gellman M.D., Turner J.R. (eds) Encyclopedia of Behavioral Medicine. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-1005-9_918

20. P. György, P. Ionela, et al. Joint Action on Mental Health and Well-being. (2017). Available at: https://ec.europa.eu/health/sites/default/files/mental_health/docs/2017_depression_suicide_ehealth_en.pdf [Accessed June 2021]

21. World Health Organization (2018). Fact sheets on sustainable development goals: health targets.Available at: https://www.euro.who.int/__data/assets/pdf_file/0017/348011/Fact-sheet-SDG-Mental-health-UPDATE-02-05-2018.pdf [Accessed June 2021]

22. Ford S, O'Driscoll M, MacDonald A (2018). Living with Phenylketonuria: lessons from the PKU community. Mol Genet Metab Rep, 17: pp 57–63. 10.1016/j.ymgmr.2018.10.002

23. Borghi, L., Moreschi, C., Toscano, A., et al (2020). The PKU & ME study: A qualitative exploration, through co-creative sessions, of attitudes and experience of the disease among adults with phenylketonuria in Italy. Mol Genet Metab Rep. 2020 Jun; 23: 100585. Published online doi: 10.1016/j.ymgmr.2020.100585

24. S. Ford, M. O'Driscoll, et al. (2018). Reproductive experience of women living with phenylketonuria. Mol Genet Metab. (17). Pp. 64-68. Doi: 10.1016/j.ymgmr.2018.09.008

25. Blau, N., Bélanger-Quintana A., Demirkol M., et al. (2010). Management of phenylketonuria in Europe: Survey results from 19 countries. Mol Genet Metab Feb;99(2) pp 109-15. doi: 10.1016/j.ymgme.2009.09.005

26. Evinç SG, Pektaş E, Foto-Özdemir D, et al. (2018). Cognitive and behavioral impairment in mild hyperphenylalaninemia. Turk J Pediatr, 60(6), pp. 617-624. doi: 10.24953/turkjped.2018.06.001.

27. Fonnesbeck CJ, McPheeters ML, Krishnaswami S et al (2013). Estimating the probability of IQ impairment from blood phenylalanine for phenylketonuria patients: a hierarchical meta-analysis. J Inherit Metab Dis 2013 Sep;36(5):757-66. doi: 10.1007/s10545-012-9564-0.

28. Bartus, A., Palasti, F., Juhasz, E., et al. (2018) The influence of blood phenylalanine levels on neurocognitive function in adult PKU patients. Metabolic Brain Disease, 33, pp. 1609–1615 (2018)

29. Brown, C.S. and Lichter-Konecki, U. (2015) Phenylketonuria (PKU): A problem solved? Mol Genet Metab, Mar;(6), pp.8-12. Doi: 10.1016/j.ymgmr.2015.12.004

30. Romani, C., Manti, F., Nardecchia, F., et al. (2019). Adult cognitive outcomes in phenylketonuria: explaining causes of variability beyond average Phe levels. Orphanet J Rare Dis, Nov 28;14(1):273. doi: 10.1186/s13023-019-1225-z

31. Eurordis (2017). Juggling care and daily life: The balancing act of the rare disease community. A Rare Barometer survey. Available at: http://download2.eurordis.org.s3.amazonaws.com/rbv/2017_05_09_Social%20survey%20leaflet%20final.pdf [Accessed June 2021]

32. Ceberio, L., Hermida, A., Venegas, E., et al (2019) Phenylketonuria in the adult patient. Expert Opinion on Orphan Drugs, 7(6), pp 265 – 276. https://doi.org/10.1080/21678707.2019.1633914

33. L. Alderslade. (2020) What age is considered 'old'? Aged Care Guide. Accessed at: https://www.agedcareguide.com.au/talking-aged-care/what-age-is-considered-old [June 2021]

34. A. Romani, F. Manti, et al. (2020). Cognitive Outcomes and Relationships with Phenylalanine in Phenylketonuria: A Comparison between Italian and English Adult Samples. Pub Med. DOI: 10.3390/nu12103033

35. J. Weglage, J. Fromm, et al. (2013). Neurocognitive functioning in adults with phenylketonuria: Results of a long term study. Mol Genet Metab. DOI: 10.1016/j.ymgme.2013.08.013

36. Burlina, A., Leuzzi, V., Spada, M., et al (2021). The management of phenylketonuria in adult patients in Italy: a survey of six specialist metabolic centers. Curr Med Res Opin Mar;37(3), Pp. 411-421. doi: 10.1080/03007995.2020.1847717. Epub 2021 Feb

37. Uhlenbusch, N., Lowe, B. and Depping, M. (2019). Perceived burden in dealing with different rare diseases: a qualitative focus group study. BMJ Open 2019;9:e033353. doi:10.1136/bmjopen-2019-033353

38. Eurordis (2021). Improve our experience of healthcare: Key findings from a survey on patients' and carers' experience of medical care for their rare diseases. Available at: https://download2.eurordis.org/rbv/HCARE/HCARE_FS_long.pdf [Accessed June 2021]

39. Burton, BK., Bradford Jones, B., Cederbaum, S., et al. (2018). Prevalence of comorbid conditions among adult patients diagnosed with Phenylketonuria. Mol Genet Metab Nov; 125(3), pp. 228-234. doi: 10.1016/j.ymgme.2018.09.006. Epub 2018 Sep 12

40. Mütze, U., Roth, A., Weigel, J.F.W., et al (2011). Transition of young adults with phenylketonuria from pediatric to adult care Mutze. J Inherit Metab Dis, 34(3), pp. 701-9. doi: 10.1007/s10545-011-9284-x. Epub 2011 Feb 9.

41. Mütze, U., Thiele A. G., et al. (2016). Ten years of specialized adult care for phenylketonuria. Orphanet Journal of Rare Diseases. 11. 27. https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0410-6

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