

Beneath the Surface Position Paper

A European Position Paper on the Neurocognitive, Psychological and Mental Health Impact of PKU

B:OMARIN

LIVE UNLIMITED 

Executive summary

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.¹ PKU is caused by deficiency in an enzyme called phenylalanine hydroxylase (PAH), which leads to high phenylalanine (Phe) levels in the blood and brain.^{2,3}

PKU can impact patients' lives in hidden ways every day. In PKU patients, high Phe levels can cause disruptions in serotonin and dopamine levels, negatively impacting mood, concentration and motivation.^{4,5} Studies have found that as a result of their condition, PKU patients are more likely to experience poor mental health, undergo social difficulties when forming relationships and face attainment challenges in the workplace or at school.^{5,6,8}

Over the last decade, there has been a transformation in the understanding of PKU on the brain, with some cognitive deficits formally recognised as features of PKU itself.

The 'Beneath the Surface' position paper explores the neurocognitive, psychosocial and mental health impact of PKU and, in turn, its impact on the lives of those living with the condition.

“**PKU has many shades. If we focus only the medical side, we will lose the emotional part of the patient.**

- PKU Patient, Italy

“**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

Research Methodology

This paper was developed in collaboration with the patient groups involved in the Live Unlimited PKU campaign and is funded and developed by BioMarin. The Live Unlimited PKU campaign aims to raise awareness of PKU as a life-long condition, and support everyone living with the condition to ask policymakers to provide better access to specialist and frequent adult care.

This paper was developed through a review of existing evidence and literature from across Europe, focusing on the neurocognitive, psychosocial and mental health impact of PKU. The paper also presents the views and insights from seven medical professionals and five people living with PKU from across Europe, who were interviewed as part of the project. These interviews lasted for one hour and were structured according to a series of questions, designed to understand the individual perspectives on the key findings of the literature review.

The Beneath the Surface position paper, developed under the PKU Live Unlimited Campaign, has been funded and developed by BioMarin in collaboration with 10 patient advocacy groups across Europe.

Key Findings from the Research

The following five themes were uncovered as a result of the literature review and from talking to the clinicians and people living with PKU about the neurocognitive, psychosocial and mental health impact of PKU:



Mental Health and Mood:

As a result of their condition, people with PKU can often experience poor mental health and mood swings. In a 2019 UK study of 286 respondents which examined the impact of mental health on daily life in adults with PKU estimated that 50% of PKU patients report symptoms of anxiety or depression.⁶



Concentration:

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.⁹ Even patients with more controlled Phe levels can also struggle with concentration.⁶



Social Impact:

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.⁵



Relationships:

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.⁶ In one survey, 44% of adult patients reporting that they felt socially excluded due to their PKU,⁶ while another survey showed that 36% of patients reported feeling embarrassed by their formula.¹⁰



Work and Education:

The hidden aspects of PKU can impact a patient's ability to reach their full potential at work or at school. 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.⁸



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



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

JUNE 2024
EUCAN-PKU-00097

Key calls to action in Europe

Based on the evidence of the position paper, the Live Unlimited PKU campaign is calling on governments and policymakers across Europe to prioritise four key calls to action to address the requirements outlined in this paper. More details on these calls to action can be found in the full position paper.

1 Service providers should **tailor care models to provide psychosocial and practical support for all patients with PKU**. This should include:

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- **Consistent access to psychologists**, enabling regular mental health monitoring
- Funding and resources for clinicians to **follow-up with patients annually, for life**¹¹
- **Incentivising specialists to remain in professional settings** where they can support PKU patients

3 Policymakers, clinicians and the patient community should review current management guidelines to **identify how individualised care plans can be designed to better support PKU patients**.

This research should be facilitated through public and patient involvement and might include:

- Encouraging healthcare professionals to **use more individualised approaches to care management**, such as tailored blood Phe target levels
- Reviewing pathways to **understand how telemedicine can be used to support individualised care**
- Holding a patient-led review to **identify where additional resources are needed to overcome current barriers** to accessing care

2 Policymakers, clinicians and the patient community should collaborate to **embed tools into existing pathways to allow patients to have meaningful discussions with clinicians** on their concentration, mood and quality of life.

This might include:

- Pathway audits to **identify where tools can be introduced to better support patients** in managing the psychosocial aspects of PKU
- **Periodic assessments on patients' developmental progress** to identify neurocognitive deficits¹²
- Encouraging healthcare professionals to **introduce tools that monitor the wellbeing of families of PKU patients** to support family adjustment¹⁰

4 Organisations and clinicians working across the entire rare disease community should **consider where to collaborate to drive change in shared areas of interest** and should encourage policymakers to prioritise rare diseases within the health system.

This may include:

- **Collaborative campaigning amongst rare disease groups** to highlight common issues and advocate for greater funding for supporting rare disease patients
- **Supporting public initiatives and partnerships** which encourage rare disease patients to live a full life without stigma

“ **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.**

- Healthcare Professional, Ireland

¹ Loeber JG. Neonatal screening in Europe; the situation in 2004. *J Inher Metab Dis*. 2007;30(4):430–438

² NORD (2019). Phenylketonuria. Available at: <https://rarediseases.org/rare-diseases/phenylketonuria/>. [Accessed April 2022]

³ van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;162(12). <https://doi.org/10.1186/s13023-017-0685-2>

⁴ PKU (2021). How PKU Affects the Brain. Available at: <https://www.pku.com/about-pku/phe-in-the-brain/>. [Accessed April 2022]

⁵ Gentile, 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.

⁶ 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

⁷ Gentile, 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.

⁸ Mütze, U., Roth, A., Weigel, J.F.W., et al (2011). Transition of young adults with phenylketonuria from pediatric to adult care Mutze. *J Inher Metab Dis*, 34(3), pp. 701-9. doi: 10.1007/s10545-011-9284-x. Epub 2011 Feb 9.

⁹ 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)

¹⁰ Cazzorla, C., Bensi, G., Blasucci, 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.

¹¹ 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)

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.