PUBLICATION SUMMARY

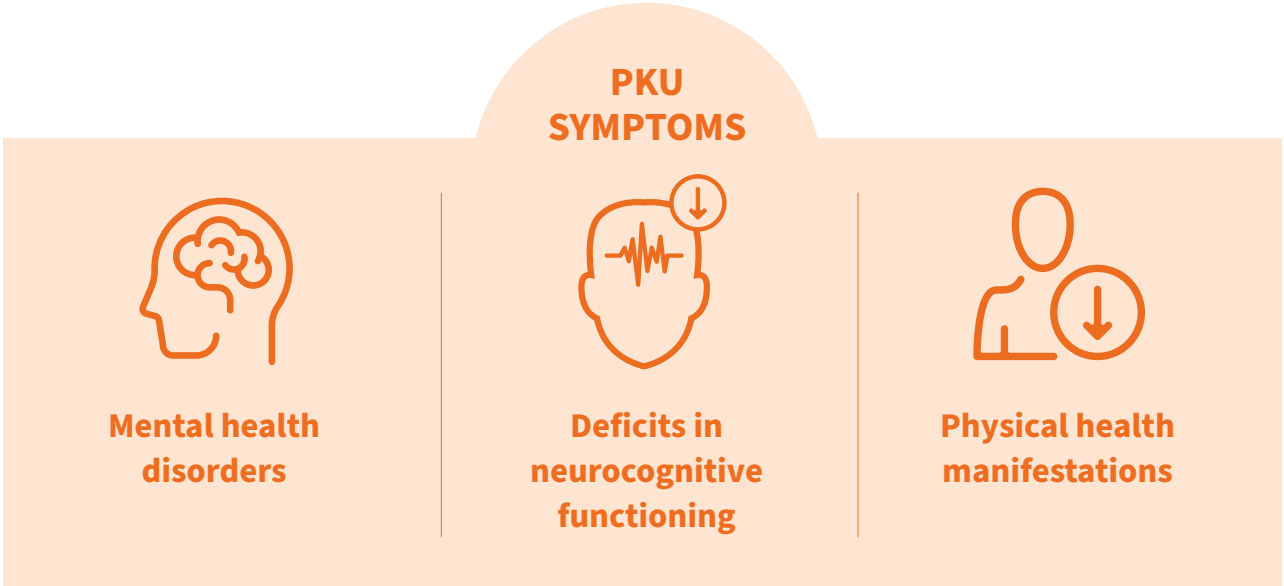
Expert Panel Provides Strategic Recommendations for Managing Adolescents and Young Adults With PKU[1]

Burton BK, Hermida Á, Bélanger-Quintana A, et al. Management of early treated adolescents and young adults with phenylketonuria: development of international consensus recommendations using a modified Delphi approach. *Mol Genet Metab*. 2022;137(1-2):114-126.

This summary is based on the publication referenced above and is not comprehensive. This publication was supported and funded by BioMarin and should be reviewed in its entirety.

Despite early treatment, many adolescents living with phenylketonuria (PKU) become lost to follow-up (LTFU) care as they transition to adulthood.

A decline in clinic attendance and relaxation in adherence to medical nutrition therapy in these patients often results in increased blood phenylalanine (Phe) levels, which in turn may interfere with effective management of PKU symptoms.



PKU care has historically focused on pediatric patients, with few programs or resources established to support the transition to adulthood. This pediatric focus has led to limited guidance on management and optimizing outcomes for better quality of life in adolescents and young adults.

Reaching consensus on PKU management

Over 2 days, 25 international experts in PKU gathered virtually to discuss the management of patients between the ages of 10 and 24 years old.

Panelists who were PKU clinical care experts had, on average:

20
years of experience

AND MANAGED UP TO

2,500
patients collectively across all age ranges

Recommendations were developed based on pre-meeting survey results and a live panel discussion. These recommendations were voted on during the second virtual meeting, using a modified Delphi approach to achieve consensus ≥70%.

The modified Delphi approach included 3 rounds of voting:

1st ROUND

Anonymous voting with expert-provided feedback

2nd ROUND

Statements with <70% consensus were revisited and revoted on following discussion among the experts

3rd ROUND

Statements that did not achieve consensus in the 2nd round were revised and anonymously revoted on

37 recommendations were developed across 5 key areas of PKU management

1 General physical health

Consensus Statements 1 to 5

Many adolescents and young adults with PKU experience physical health comorbidities that require special attention.

PKU Comorbidities

- **Obesity/overweight**
- **Type 2 diabetes**
- **Gastrointestinal disorders**
- **Renal disease**
- **Asthma**
- **Allergies, including eczema and rhinitis**
- **Osteopenia, osteoporosis, and osteomalacia**
- **Ischemic heart disease**
- **Nutritional deficiencies**

Panel Recommendations

Screening for comorbidities should be a continuous process, beginning early and ideally performed every 6 months

Discuss preventative measures such as a healthy diet, exercise, sleep hygiene, and weight management with adolescent and young adult patients with PKU

Managing these conditions should go beyond simply focusing on blood Phe, as some comorbidities can be caused by a complex series of pathophysiological reactions

2 Mental health and neurocognitive functioning

Consensus Statements 6 to 21

Many patients struggle to sustain metabolic control past childhood, increasing their risk for comorbidities that can impact psychosocial outcomes.

Most important comorbidities requiring special attention

Anxiety

Depression

Impaired executive functioning

Panel Recommendations

Begin screening for neurocognitive and mental health concerns early in life to reduce the risk of these challenges compounding over time. Quick, valid, reliable, multilingual, and easy-to-download screening tools can help improve the ongoing monitoring of these conditions

Ask neutral, open-ended, age and developmentally appropriate questions during consultations

Consider the genetic, social, and environmental factors behind uncontrolled blood Phe

Address blood Phe levels before managing depression and anxiety in patients with antidepressants and/or anxiolytics

3 Blood Phe target range

Consensus Statements 22 to 24

The current guidelines recommend maintaining blood Phe levels between 120 and 360 µmol/L in the United States, and below 600 µmol/L in the European Union. However, an increasing body of evidence supports the recommended US range, as Phe levels above 240 to 360 µmol/L have been associated with poorer health outcomes in adolescents and young adults.

There was some disagreement among the experts due to conflicting and lacking evidence. However, the panel ultimately recommended that patients should maintain blood Phe levels below 360 µmol/L.

The panel acknowledged that achieving guideline levels with dietary management alone may be challenging. Medical nutrition therapy proved effective in preventing some of the comorbidities of PKU. However, its restrictive nature has been linked to emotional burden on PKU patients. Overall, the blood Phe target range should be set according to available treatment options and their capacity to both lower blood Phe levels and improve patient outcomes.

Panel Recommendations

Further research should be conducted to understand how the restrictive PKU diet may impact adolescent development and mental health

As new treatment options become available, the recommended blood Phe target range should be reevalutated

4 PKU-specific challenges

Consensus Statements 25 to 29

Most adolescents and young adults with PKU face specific challenges on top of the day-to-day obstacles typically experienced by their peers.

PKU-specific challenges:

Feeling guilty for not adhering to dietary restrictions

Feeling shame about their disease and management, leading to social isolation

Long-term impact of PKU, including maternal PKU risks

Low self-esteem and confidence

Disordered eating

Panel Recommendations

Tailored management to address the specific type of disordered eating often associated with adolescent and young adult patients with PKU

Support from PKU and non-PKU peers, education of parents and patients, and improved access to (neuro)psychological, psychiatric and/or social work support

Role-playing how to react in relevant social situations to help adolescents and young adults with PKU better respond to peer pressure and the need to fit in

Individualized and one-on-one maternal PKU education that considers the age and developmental level of the patient

5 Transition to adult care

Consensus Statements 30 to 37

Over time, many adolescents and young adults with PKU decrease or stop adhering to medical nutritional therapy, monitoring of blood Phe, and in-clinic follow-up, leading to blood Phe levels above the recommended target ranges.

Key factors that contribute to adolescent patients becoming LTFU:

Increasing demands in life and risk-taking behavior

Lack of motivation and self-awareness about symptoms

Inadequate transition to adult care

Insurance and financial issues

Panel Recommendations

Encourage use of telemedicine, mobile apps, social media groups, and self-monitoring devices to improve access to care and support

Be flexible and consistently engaged to meet the increasing life demands that patients with PKU face in young adulthood

Adopt a positive empowerment approach to PKU management to allow for better understanding and support of patients

Individualize management and go beyond blood Phe levels, focusing on setting life goals, while also considering the potential mental health and neurocognitive challenges patients face each day

Limitations

As there is limited peer-reviewed literature available on the management of adolescents and young adults, these recommendations are:

- Partly based on the panel's personal opinions and experiences with PKU and other metabolic disorders
- Supported with evidence from literature when available

These recommendations may not be generalizable and implementation will largely depend on:

- Clinical capacity
- Staffing
- Availability of resources of each clinical center

Conclusion

In summary, the expert panel reached consensus across five 5 areas of adolescent and young adult PKU management: general physical health, mental health and neurocognitive functioning, blood Phe target range, PKU-specific challenges, and the transition to adult care.

These recommendations aim to provide clinics with the guidance and tools they need to better support this patient population and may inform PKU management guidelines moving forward

Reference: 1. Burton BK, Hermida Á, Bélanger-Quintana A, et al. Management of early treated adolescents and young adults with phenylketonuria: development of international consensus recommendations using a modified Delphi approach. *Mol Genet Metab.* 2022;137(1-2):114-126.