

# ADULT PHENYLKETONURIA: TRANSITION MANAGEMENT AND FOLLOW-UP

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**ABSTRACT** – This review explores the challenges in adult phenylketonuria (PKU) management, focusing on the transition to adult care, long-term follow-up, and treatment adherence.

Relevant literature was identified through a PubMed search using keywords such as “phenylketonuria,” “transition process,” “adults,” and “clinical management.” Studies were screened based on relevance, emphasizing neurological and metabolic complications, adherence determinants, and clinical outcomes. Additional insights were drawn from clinical guidelines and consensus statements.

Transitioning from pediatric to adult care is critical but inconsistently implemented, with gaps in specialized services. Multidisciplinary teams, including metabolic specialists and dietitians, are essential for addressing the medical and psychosocial needs of adults with PKU. Plasma phenylalanine levels have limited utility in predicting outcomes, as complications such as obesity and insulin resistance often emerge despite early treatment. Novel therapies, such as pegvaliase, improve dietary flexibility but pose challenges with adherence and accessibility. Digital tools and telemedicine hold promise for enhancing patient engagement.

Structured transition processes, interdisciplinary collaboration, and personalized care strategies are essential for effective adult PKU management. Future priorities include refining assessment protocols, addressing psychosocial barriers, and ensuring access to advanced therapies. Comprehensive, patient-centered care remains crucial to improving outcomes and quality of life.

**KEYWORDS:** Phenylketonuria, Substrate reduction therapy, Transition.

**ABBREVIATIONS:** BMD: Bone mineral density; MRI: Magnetic resonance imaging; PAH: Phenylalanine hydroxylase; Phe: Phenylalanine; PKU: Phenylketonuria; T2D: Type 2 diabetes; WM: White matter.

## INTRODUCTION

Phenylketonuria (PKU) is a rare autosomal recessive disorder caused by mutations in the *PAH* gene, leading to a deficiency of the enzyme phenylalanine hydroxylase (PAH), which catalyzes the conversion of the essential amino acid phenylalanine (Phe) into tyrosine<sup>1</sup>. PKU has an incidence rate in Europe of approximately 1 in 10,000-15,000 births, although higher rates are observed in certain countries, such as Italy, where it occurs in 1 in 4,500 births<sup>2</sup>.

The type of genetic mutation determines the level of PAH activity, which may be completely absent or partially impaired. Over 1,000 mutations have been identified in the *PAH* gene and are catalogued in the PKU-specific PAHvdb database<sup>3</sup>. Mutations, such as splicing, nonsense, and out-of-frame insertions or deletions, typically result in the complete loss of PAH function (null mutations), whereas missense mutations and specific in-frame indels lead to defective PAH production. Null mutations in both alleles lead to classical PKU, characterized by blood Phe levels exceeding 1,200  $\mu\text{mol/L}$  in untreated individuals.

This enzyme deficiency results in elevated blood Phe levels and its accumulation in the brain, causing a range of severe and irreversible clinical manifestations, including intellectual disability, epilepsy, behavioral disorders, and clinical features such as acquired microcephaly, seizures, psychological signs, and generalized hypopigmentation of skin (including hair and eyes)<sup>1</sup>.

A simple screening test for PKU was developed in the 1960s and became a mandatory component of newborn screening in Italy in 1992<sup>4</sup>. Early detection and intervention are critical, as they prevent intellectual disability and support a normal or near-normal quality of life and intelligence quotient<sup>5</sup>.

The primary treatment for PKU is a low-Phe diet, which includes low-protein foods supplemented with Phe-free protein substitutes, such as L-amino acids, glycomacropeptides, and slow-release large neutral amino acids, to meet protein requirements<sup>6</sup>.

Until 2018, the only approved pharmacological treatment for PKU was sapropterin dihydrochloride, an oral form of tetrahydrobiopterin, a cofactor essential for PAH function. However, sapropterin is effective only in patients with residual PAH activity and is therefore unsuitable for those with classical PKU, who lack any residual enzyme function<sup>7</sup>.

To address the need for an alternative treatment for patients with null residual activity, pegvaliase, a pegylated recombinant Phe ammonia lyase derived from *Anabaena variabilis*, was developed. Pegvaliase reduces blood Phe levels by substituting for PAH and converting Phe to ammonia and trans-cinnamic acid<sup>8</sup>. Approved for patients aged 16 years and older with Phe levels exceeding 600  $\mu\text{mol/L}$  despite prior treatment with available therapeutic options, pegvaliase improves blood Phe control and facilitates a protein intake aligned with general dietary recommendations, enabling greater diet flexibility<sup>9</sup>.

Sepiapterin is a promising oral therapy for individuals with phenylketonuria. This new drug is well tolerated and results in significant and clinically meaningful reductions in blood Phe concentration in participants with varying disease severity<sup>10</sup>.

The life expectancy of patients with inherited metabolic disorders, including PKU, has increased in recent decades, enabling many to reach adulthood. European guidelines<sup>11</sup> emphasize the need for a structured transition process from pediatric to adult care, as PKU patients require continuous follow-up at specialized metabolic centers. Moreover, in 2022, a collaboration between the adult metabolic working group of the Italian Society for the Study of Inherited Metabolic Disorders and Neonatal Screening (SIMMESN) and the European Reference Network for Hereditary Metabolic Disorders (MetabERN) resulted in “The Statement of Udine”, to guide further steps towards improvements in inherited metabolic medicine in adults<sup>12</sup>.

However, there is no national consensus or specific guidelines to manage this transition, and long-term follow-up endpoints beyond blood Phe levels remain undefined.

This narrative review aims to highlight the challenges and significance of managing adult PKU patients, focusing on the transition to adult care and long-term follow-up. It examines the clinical implications of PKU in adulthood, particularly neurological and metabolic complications, and identifies critical factors for patient adherence.

## METHODS

A PubMed search using keywords and combinations such as “transition process,” “phenylketonuria,” “adults,” “clinical management,” “follow-up,” “neurological complications,” “insulin resistance,” “dyslipidemia,” “obesity,” and “phenylalanine levels” led to the identification of 227 papers. The search focused on human studies published in English. Based on their relevance to the topic, using full-text or abstract reviews as needed, 42 articles were screened by the authors.

Relevant data were extracted from each study, emphasizing current practices, experiences, and recommendations related to the transition process, as well as patient attitudes and beliefs. Additionally, the analysis investigated potential lifelong neurological and metabolic comorbidities in adult patients with PKU, as well as patient perceptions and beliefs regarding the healthcare services available to them.

## LITERATURE REVIEW

### The Transition Process

The transition from pediatric to adult care in PKU, which can involve a shift from dietary therapy to new treatment options such as substrate reduction therapy, is a critical period marked by changes in daily routines, logistics, and psychological dynamics. This period affects the patient, the family, and the metabolic centers involved in care<sup>13</sup>.

European guidelines<sup>11</sup> recommend a structured transition process, initiated in adolescence around 12 years old, with the actual transfer to adult care occurring between the ages of 16 and 18 years old, depending on individual needs. Some successful cases<sup>14,15</sup> have been reported in which adult PKU patients transitioned smoothly from pediatric to adult care, with teams discussing patient-specific issues well in advance of the transition.

A study<sup>14</sup> of 96 patients with PKU (56 females, 40 males; median age, 32 years; range, 18-62 years) coordinated a decade-long transition and specialized adult care program. Over the last 3 years, 81% of transferred patients continued to attend regular clinic visits, maintaining stable metabolic control, with median blood Phe concentrations mostly within the therapeutic range (median 673.0  $\mu\text{mol/L}$ , range 213.0-1,381.1).

In another retrospective study<sup>15</sup> of 55 PKU patients, the 2-year periods before and after transitioning to adult care were compared. Results showed a statistically significant increase in median annual blood tests [11 (7-15) vs. 14 (7-20);  $p=0.002$ ] and clinical appointments [5 (4-6) vs. 11 (8-13);  $p<0.001$ ], along with a decrease in the percentage of blood Phe levels under 480  $\mu\text{mol/L}$  [51 (4-96)% vs. 37 (5-85)%;  $p=0.041$ ], indicating improved metabolic control and patient adherence following the transition to adult care.

We recently described a case<sup>16</sup> that underscores the importance of establishing a transition program to address the evolving needs of patients with PKU. The case involved a 22-year-old male diagnosed with PKU at birth, presenting with a Phe level of 1,314  $\mu\text{mol/L}$  and confirmed to have compound heterozygosity in the *PAH* gene. Under care at the Bambino Gesù Pediatric Hospital (OPBG) in Rome, he adhered to a Phe-restricted diet (500 mg/day, supplemented with protein equivalents), maintaining Phe levels <600  $\mu\text{mol/L}$ . The patient showed no response to a prolonged tetrahydrobiopterin test and, by age 20, began demonstrating poor adherence to his diet. After 3 months of Phe levels consistently >1,000  $\mu\text{mol/L}$ , substrate reduction therapy with pegvaliase was initiated. Given the patient's age and treatment needs, his care transitioned to the adult metabolic center at Fondazione Policlinico Gemelli (FPG). OPBG and FPG collaborated on training sessions covering PKU management, dietary therapy, and patient care, culminating in a formal transfer of care. At FPG, pegvaliase therapy commenced with ongoing coordination between OPBG and FPG during the induction, titration, and maintenance phases. The centers adjusted pegvaliase dosing and gradually liberalized his diet based on periodic Phe measurements, promoting the patient's autonomy in managing his health. Currently, the patient receives 20 mg/day of pegvaliase, follows a liberalized diet, and maintains Phe levels consistently <300  $\mu\text{mol/L}$ <sup>16</sup>.

A consensus among Italian experts<sup>13</sup>, established through three rounds of surveys and structured interviews, provided a pathway for an effective transition. The plan includes preparatory training for both pediatric and adult teams, familiarization of the patient and family with the transition process, designation of appropriate facilities and a transition coordinator, and organized meetings between teams. The importance of a transition coordinator who facilitates the process, as well as the role of patient associations, was strongly emphasized.

The transition not only marks a shift in the care setting but can also involve a change in treatment type. Substrate reduction therapy, available for patients over 16 years, provides greater flexibility in diet and social activities, potentially improving treatment adherence during adolescence. However, vulnerable patients may experience anxiety or psychological challenges due to changes in treatment or the potential occurrence of drug side effects, which could negatively impact their commitment to treatment<sup>17</sup>. Metabolic centers and patient associations can enhance motivation and adherence to treatment by raising awareness of therapeutic alternatives and their psychosocial benefits while addressing concerns about adverse effects<sup>13</sup>.

Clinical experience has further highlighted specific barriers to effective transition and treatment adherence, including limited adult metabolic expertise and inadequate training in transition processes. A survey<sup>18</sup> of 77 European Reference Network centers for Hereditary Metabolic Disorders found that only 40% of metabolic pediatricians had received training in transition management, and there was a lack of personnel dedicated to coordination. An Italian study<sup>19</sup> involving 21 adult PKU patients noted the scarcity of specialized adult PKU centers as an unmet need, which can create patient dissatisfaction, reduce adherence to transition, and, in some cases, lead to treatment discontinuation.

Consequently, patients often maintain long-term loyalty to pediatric centers, where care is managed from diagnosis through adulthood<sup>20</sup>. A US study<sup>21</sup> of 50 PKU patients who transitioned to adult care reported that patients valued their established relationships with pediatric teams and the familiarity of treatment plans. The loss of these established relationships could lead to anxiety and reduced motivation, potentially affecting adherence to new treatments<sup>13</sup>.

The transition process also represents a psychological milestone as patients shift from parental oversight to independent disease management. Some patients express feelings of inadequacy or confusion regarding the responsibility of managing their condition, which can result in non-compliance or disengagement from treatment and follow-up<sup>19,20</sup>.

As highlighted in the recent Italian consensus document<sup>13</sup> on the management and pharmacological treatment of PKU, an integrated multidisciplinary and transversal approach throughout pediatric and adult care is deemed important. This approach involves collaboration among the pediatrician, a dietitian, and a psychologist to support the patient through the transition to an internist. There is a general consensus on the need for strong doctor-patient communication and supportive relationships with healthcare providers to foster engagement and adherence during the transition period and subsequent treatment. Educating the patient, enhancing their awareness of PKU management in adulthood and available treatment options, and providing adequate support are critical components of effective transitional care<sup>22</sup>.

## CLINICAL MANAGEMENT AND FOLLOW-UP OF THE ADULT PATIENT WITH PKU

### Clinical Indicators of the Adult Patient with PKU

Given the complex picture of adherence to either a free or restricted diet depending on treatment options, adults with PKU require lifelong management. This includes regular blood Phe monitoring, attendance at specialized adult outpatient clinics with age-appropriate education programs, and ongoing metabolic control to monitor for potential complications such as neurological and metabolic disorders.

### *Neurological alterations*

Since the introduction of newborn screening programs for PKU, most patients receive early and continuous treatment from birth, which prevents severe complications through dietary restrictions, with or without additional therapeutic interventions.

Despite early diagnosis and treatment, late-onset neurological symptoms may emerge in adulthood, especially in cases where treatment has been discontinued after childhood or in the presence of severe genetic mutations. These manifestations often include cognitive impairment, psychiatric symptoms, and social or behavioral challenges. The timing of symptom onset varies widely, ranging from weeks to up to 20 years after treatment discontinuation<sup>23</sup>. However, the prevalence of these complications in the adult PKU population is not well characterized<sup>24</sup>.

The neurological phenotype of early-treated PKU (ETPKU) patients remains poorly defined, particularly regarding their neurological, neurocognitive, and neuroimaging characteristics, the proportion of affected individuals, and the influence of metabolic control and treatment burden on these features. Neurological symptoms are frequently related to motor function, with tremor and hyperreflexia being the most common signs. Although rare, more severe symptoms, such as ataxia, optic atrophy, spastic quadriparesis, and altered muscle tone and reflexes, have also been reported<sup>24</sup>.

Phe levels are the primary biomarker for monitoring PKU in adulthood, with European guidelines<sup>11</sup> recommending plasma Phe levels of 120-600  $\mu\text{mol/L}$ . However, studies in the literature have shown mixed results regarding the correlation between Phe levels and neurological outcomes. A study<sup>25</sup> investigating neurological outcomes in 57 ETPKU patients (mean age 23.6 years) compared with controls found that PKU patients exhibited increased tremor (28% vs. 15%) and significantly reduced fine motor skills, including hand steadiness, dexterity, and speed. However, no significant differences in Phe levels were observed. Conversely, a prospective study<sup>26</sup> of 19 ETPKU patients (median age 41 years) showed a significant correlation between plasma Phe levels and motor-evoked potential latency (Pearson correlation coefficient  $r=0.48$ ,  $p=0.030$ ), suggesting an association between Phe levels and motor function impairment.

Certain brain regions may become increasingly vulnerable to the neurotoxic effects of Phe with advancing age<sup>27</sup>, and individual variations in Phe uptake at the blood-brain barrier have been reported<sup>28</sup>. Future studies should standardize neurological assessments alongside Phe measurements to clarify the relationship between Phe levels and neurological outcomes<sup>23</sup>. Understanding how Phe levels influence the range, frequency, and severity of neurological issues in adult PKU patients will support the development of evidence-based treatment guidelines<sup>24</sup>.

Studies<sup>29</sup> link the neurological manifestations of PKU to its underlying neuropathophysiology, which includes decreased levels of monoaminergic neurotransmitters (serotonin, dopamine, noradrenaline) and abnormal cerebral myelination, seen as white matter (WM) lesions on magnetic resonance imaging (MRI). Conventional MRI techniques (FLAIR/T2-weighted imaging and diffusion-weighted imaging) provide a valuable, non-invasive method for detecting brain changes and gaining insights into the pathophysiology of ETPKU in adults<sup>23</sup>. In ETPKU patients, overt brain atrophy is rare; however, MRI often reveals increased T2-weighted signals in the periventricular WM, brainstem, and cerebellum<sup>30</sup>. The severity of WM abnormalities appears to be influenced by patient age and dietary adherence, with older age and/or elevated Phe levels linked to greater WM involvement. In contrast, WM abnormalities are less severe in patients with adequate dietary control<sup>31,32</sup>.

The exact neuropathophysiological relationship between WM abnormalities and neurological deficits remains unclear, and the severity of neurological symptoms does not consistently correlate with the extent of WM abnormalities<sup>33</sup>.

### Metabolic alterations

Insulin resistance and type 2 diabetes (T2D) involve widespread disruptions in metabolic physiology, affecting glucose, fat, and amino acid metabolism. Disturbances in Phe and tyrosine homeostasis have been associated with insulin resistance<sup>34</sup>. In a study of 263 non-obese Indian and Chinese men [body mass index (BMI)  $\sim 24$  kg/m<sup>2</sup>], insulin resistance was correlated with elevated levels of various amino acids, including Phe<sup>35</sup>.

Although the roles of amino acids in insulin signaling and glucose uptake remain unclear, elevated blood levels of aromatic and branched-chain amino acids have been observed in T2D patients<sup>36</sup>. An animal study<sup>37</sup> demonstrated that Phe modifies insulin receptor  $\beta$ , thereby inactivating insulin signaling and impairing glucose uptake. As a result, mice fed a Phe-rich diet, aspartame (a Phe precursor), or overexpressing human phenylalanyl-tRNA synthetase developed insulin resistance and T2D symptoms.

Moreover, a low-Phe diet supplemented with low-protein foods and Phe-free amino acid mixtures, often adopted by PKU patients, leads to high consumption of carbohydrates and fats to meet energy needs, which may increase the risk of obesity and associated comorbidities. However, the evidence in adult PKU populations remains inconsistent<sup>38</sup>.

Burton et al<sup>39</sup> reported a higher obesity rate in PKU individuals than in matched controls (5.35% vs. 2.25%,  $p < 0.0001$ ). Similarly, Azabdaftari et al<sup>40</sup> found that adult PKU patients had higher BMI than controls ( $27.6 \pm 5.4$  kg/m<sup>2</sup> vs.  $23.4 \pm 6.4$  kg/m<sup>2</sup>,  $p < 0.001$ ), with 50% of female PKU patients classified as obese compared with 18% of male patients<sup>40</sup>. In contrast, a multicenter study<sup>41</sup> involving European and Turkish centers reported that PKU adults in 83% of the participating centers had lower rates of overweight than the general population; however, females still exhibited higher obesity rates (median prevalence of 20% in females vs. 7% in males). In a study<sup>42</sup> of 37 PKU patients following a Phe-restricted diet with essential amino acid supplementation, no higher incidence of overweight or obesity was reported compared with 26 healthy siblings. However, patients with lower adherence to treatment (<50%) showed a higher prevalence of overweight and abdominal obesity.

In a study<sup>43</sup> of 22 treated PKU patients (mean age 38.7 years) compared with 14 controls (mean age 35.2 years), total cholesterol and low-density lipoprotein (LDL) cholesterol levels were significantly lower in PKU patients (179.4 mg/dL vs. 200.9 mg/dL,  $p < 0.02$ , and 79.5 mg/dL vs. 104.1 mg/dL,  $p < 0.0038$ , respectively). These results suggest a negative impact of Phe on lipoprotein plasmatic concentration and potential interference of Phe with cholesterol synthesis or LDL regulation. Conversely, Azabdaftari et al<sup>40</sup> found that patients with PKU (ages 18-47) had significantly higher systolic and diastolic blood pressure, resting heart rate, and BMI compared to 28 controls. Total and non-high-density lipoprotein (HDL) cholesterol levels were also elevated. In contrast, HDL cholesterol levels were significantly lower in PKU patients, potentially increasing their cardiovascular risk. However, the clinical significance of these findings remains unclear<sup>40</sup>.

### *Osteoporosis and Osteopenia*

European guidelines<sup>11</sup> recommend that follow-up outpatient visits for adult PKU patients should include a comprehensive assessment. This involves taking a detailed medical and dietary history, collecting anthropometric data (e.g., BMI), conducting physical and neurological examinations, and addressing treatment outcomes, such as neurological and psychiatric issues, behavior, and mood. Additional investigations should focus on potential nutritional deficiencies (particularly iron and vitamin B12), neurocognitive function, and bone mineral density (BMD), which is assessed using dual-energy X-ray absorptiometry scanning. PKU dietary treatments may contribute to low BMD, a potential risk factor for skeletal fractures<sup>11</sup>. However, the clinical significance of these findings remains inconclusive, with limited evidence of an increased fracture risk in PKU patients<sup>44</sup>.

In a meta-analysis of ETPKU patients, Demirdas et al<sup>44</sup> reported lower BMD Z-scores in PKU patients than healthy subjects. For total body (three studies; n=133), lumbar spine (seven studies; n=247), and femoral hip (two studies; n=78), the respective Z-scores were -0.45 (95% CI: -0.61, -0.28), -0.70 (95% CI: -0.82, -0.57), and -0.96 (95% CI: -1.42, -0.49), all within the normal reference range<sup>44</sup>.

A separate study<sup>45</sup> of 183 adult ETPKU patients (aged 18–46 years; median age, 28 years; all premenopausal females) found that BMD was lower at most skeletal sites compared to the general population. However, low BMD (Z-score  $\leq$ -2) was observed in only 5.5%, and no specific risk factors for low BMD in PKU patients were identified.

Current guidelines<sup>11</sup> recommend performing a dual-energy X-ray absorptiometry scan during late adolescence. If the results are normal, further scanning is unnecessary. In cases of abnormal results, follow-up, with or without treatment modification, is advised after 1 year.

### **Determinants of Patients' Adherence to the PKU Management and Follow-Up**

Beyond clinical symptoms, various factors influence the lifelong follow-up of adult PKU patients, who report diverse attitudes and beliefs toward PKU treatment.

Key determinants of adherence to dietary and therapeutic regimens include patients' perception of their condition, with some even denying the diagnosis. An Italian survey<sup>46</sup> revealed that many adults lack an adequate understanding of PKU and its long-term risks, with 40% of respondents not considering it a disease. Although 85% reported regular Phe monitoring, nearly half recorded high plasma levels (>600  $\mu$ mol/L in the last 6 months), and 31% were unable to report their levels. Dietary adherence was also low, with increased consumption of natural protein sources and reduced use of amino acid supplements. Another study<sup>19</sup> found that individuals adhering to treatment had a positive attitude, strong organizational skills, and awareness of the clinical and psychosocial consequences of high Phe levels. In contrast, non-adherent individuals showed limited acceptance of their diagnosis and reduced awareness of adult-onset risks. A UK survey<sup>47</sup> further linked knowledge to adherence, with those strictly following or returning to the PKU diet showing higher knowledge scores than those who had ceased dietary restrictions. In another UK survey conducted by Ilgaz et al<sup>48</sup>, including 65 adult PKU patients and nine caregivers of adult patients, only 32% of respondents followed a Phe-restricted diet with protein substitute intake as prescribed. The remaining respondents were either partially adherent or did not follow dietary restrictions. Additionally, 19% (n=14/74) of participants had not attended a clinic review within the previous 2 years. Less than half (44%) of the respondents reported performing blood spot tests for Phe levels at least monthly; only 32% felt adequately informed about the risks associated with high Phe levels in adulthood<sup>48</sup>.

Indeed, adults with PKU frequently report the lack of adequate education about their condition in adulthood and pharmacological options, as well as the lack of social platforms for information exchange and peer support, which may enhance adherence to treatment<sup>19</sup>.

Dietary restrictions and clinical management often negatively affect quality of life and social interactions, which in turn impact treatment adherence. In Borghi et al<sup>19</sup>'s study, non-adherent patients expressed feelings of isolation and discomfort from dietary restrictions, along with a sense of individual burden and social exclusion. Psychological challenges, including feelings of anger, guilt, and shame about the condition, were also reported by adolescents and adults with PKU, contributing to low self-esteem, confidence issues, and social isolation<sup>49</sup>.

Adult PKU patients often face barriers related to limited specialized resources and infrastructure. Many patients express a desire for age-appropriate communication and resources in healthcare settings. A retrospective US study<sup>21</sup> of 50 PKU patients transitioning from pediatric to adult care revealed insufficient access to adult-oriented resources and educational materials in pediatric centers. Similarly,

a Turkish survey<sup>50</sup> indicated that easier access to specialized adult services would improve follow-up and treatment adherence. In the UK survey conducted by Ilgaz et al<sup>48</sup>, the need to provide a high standard and equitable service to adult patients with PKU was also highlighted. Only half of the respondents (50%) described their experience in adult clinics as “good”. However, half of the patients were unable to contact their dietitians with questions or concerns, and only 24% felt they received adequate support<sup>48</sup>.

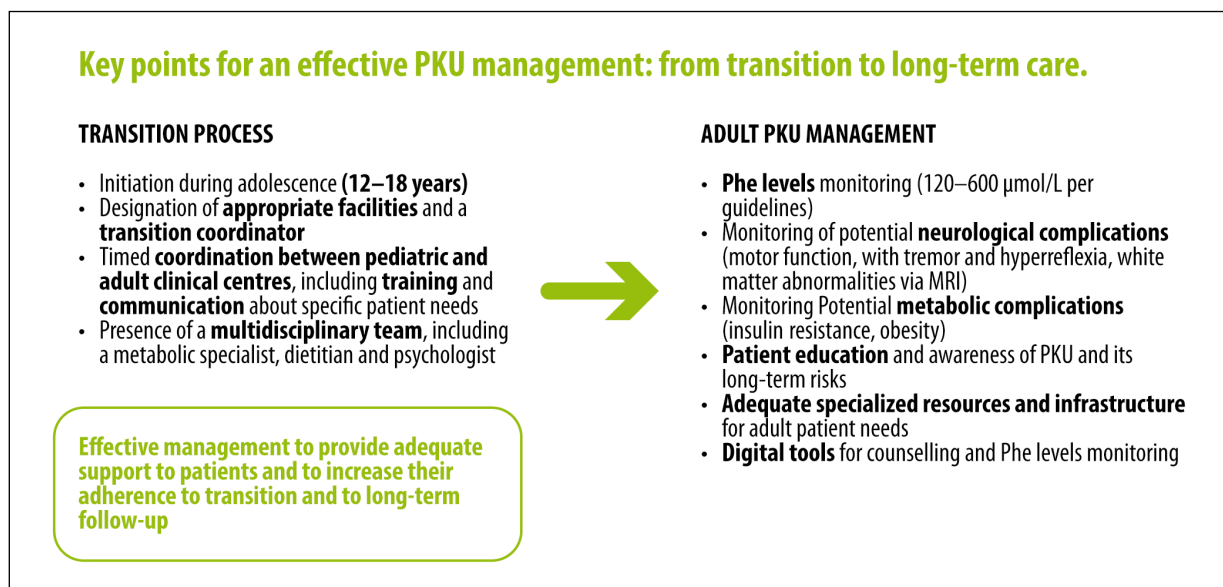
The COVID-19 pandemic significantly accelerated the use of telemedicine, offering video and phone consultations as alternative follow-up methods. A retrospective study<sup>51</sup> comparing pre-pandemic in-person clinic visits with pandemic-era telemedicine found improved metabolic control, with a higher proportion of samples showing Phe levels within recommended ranges and increased Phe tolerance in patients on low-Phe diets. On the other hand, a UK survey<sup>52</sup> reported that patients were less likely to engage *via* video (64%) or phone (50%) than in-person consultations (80%). In-person visits remain important for physical examinations and counseling, although providing a range of options could enhance overall patient engagement and adherence.

Digital tools, such as apps that calculate Phe levels in food (e.g., Fenilanometer) or provide travel support, protein-free product information, and therapy updates, are of growing interest to adult PKU patients<sup>19</sup>. Improved access to Phe and results and self-monitoring capabilities can further increase adherence by simplifying follow-up processes for patients and caregivers. Wada et al<sup>53</sup> recently reported on the PheCheck system, which combines a portable ammonia detection device with Phe ammonia-lyase to estimate plasma Phe levels, showing a strong correlation with traditional high-performance liquid chromatography (coefficient of determination  $R^2=0.97$ ).

Finally, European guidelines<sup>11</sup> emphasize the importance of a multidisciplinary care team to provide optimal, comprehensive care for adult PKU patients. This includes regular monitoring of clinical complications, dietary management counselling – especially when enzymatic replacement therapy is used – and psychological support. The care team should consist of a metabolic physician and a dietitian experienced in inherited metabolic disorders for patients of all ages. Additional psychological and social work support is recommended to help both adherent and non-adherent patients address treatment-related challenges and maintain motivation. The inclusion of a neurologist is also advised to conduct regular neurological assessments and manage potential complications<sup>22,49</sup>.

## CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Adult PKU management is a cornerstone of care for inherited metabolic diseases, reflecting advancements in treatment and an increasing emphasis on improving quality of life in long-term care. This review highlights the multifaceted challenges and key considerations involved in transitioning from pediatric to adult care, managing adult PKU patients, and addressing factors that influence treatment adherence (Figure 1).



**Figure 1.** Key points for effective PKU management: from transition to long-term care.

A structured transition from pediatric to adult care is critical. While European guidelines<sup>11</sup> provide a framework, their inconsistent implementation leaves many patients with limited access to specialized adult care services. Studies emphasize the importance of multidisciplinary teams, including metabolic specialists, dietitians, psychologists, and neurologists, to address the complex medical, dietary, and psychosocial needs of adults with PKU. The inclusion of transition coordinators and patient advocacy groups has proven effective in improving adherence and outcomes during this pivotal period<sup>11,22</sup>.

Emerging evidence on late-onset neurological symptoms and metabolic complications in adult PKU patients underscores the limitations of traditional biomarkers, such as plasma Phe levels, in predicting long-term outcomes. Neurological manifestations, including motor deficits and psychiatric symptoms, require further research to clarify their relationship with metabolic control and WM abnormalities. Similarly, the metabolic phenotype of adult PKU patients, characterized by increased risks of insulin resistance, obesity, and dyslipidemia, calls for robust longitudinal studies to uncover underlying mechanisms and effective interventions<sup>23,39</sup>.

The advent of new therapies, such as substrate reduction therapy with pegvaliase, offers promising opportunities for more flexible dietary management and improved quality of life. However, these treatments also present challenges, including ensuring adherence, addressing psychological readiness, and managing potential adverse effects. Patient-centered digital tools and telemedicine have shown the potential to enhance engagement and adherence, particularly during the COVID-19 pandemic. Nonetheless, these technologies require further refinement to ensure equitable access and effectiveness across diverse populations<sup>51,53</sup>.

Validated neurological and metabolic assessment protocols that integrate biomarkers, imaging, and clinical outcomes are essential for improving long-term monitoring. Advances in genetic profiling and metabolic phenotyping hold promise in guiding individualized treatment strategies, optimizing efficacy, and minimizing adverse effects. Tailored educational programs and support networks within both clinical and community settings are critical to empowering patients in self-management and fostering adherence. Assessing the cost-effectiveness and accessibility of advanced therapies, such as pegvaliase, will provide valuable insights for policy decisions and equitable healthcare delivery. Establishing international registries and longitudinal cohorts will further illuminate the natural history of PKU, treatment outcomes, and emerging complications.

## CONCLUSIONS

In conclusion, while substantial progress has been made in understanding and managing adult PKU, ongoing interdisciplinary collaboration, innovative research, and patient-centered care are essential to addressing the unmet needs of this growing population. As therapeutic options expand and patient expectations evolve, the overarching goal remains to improve overall health and quality of life through comprehensive, evidence-based care.

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