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# PHENYLKETONURIA: A NARRATIVE REVIEW OF GLOBAL PREVALENCE, DIETARY MANAGEMENT, EMERGING THERAPIES, AND THE ROLE OF NUTRITIONAL SUPPLEMENTATION

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## Abstract

***Background***: *Phenylketonuria (PKU) is an inborn error of metabolism that is an autosomal recessive, caused by the deficiency of phenylalanine hydroxylase (PAH), resulting in toxic phenylalanine buildup and avoidable intellectual disability without treatment. Although six decades of newborn screening and dietary management have been made, adherence, global access disparities, and new therapeutic options are considered a challenge that requires updated evidence synthesis.*

***Purpose:*** *This narrative review critically analyzes PKU through the lenses of its prevalence trends on the global spectrum, dietary management approaches, novel pharmacological and biological interventions, and nutritional supplementation.*

***Methods:*** *A systematic literature search was carried out on PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar to identify articles published in the period between January 2015 and March 2026. Following screening, 32 articles comprising peer-reviewed articles, systematic reviews, meta-analyses, and clinical guidelines were identified and thematically synthesised.*

***Findings:*** *The prevalence of global classic PKU is about 6 per 100,000 neonates with significant regional differences due to consanguinity (Turkey highest, 38.13 per 100,000; Thailand lowest, 0.3 per 100,000). Most low- and middle-income nations do not have universal newborn screening, and under-ascertainment is a result. Dietary management is still the cornerstone therapy, but early-treated patients do an average of 0.46 standard deviations worse than healthy controls on cognitive measures, and adherence in adults reduces to 40-60%. New treatments are sapropterin (working in 2050% of patients) and pegvaliase (reaching blood phenylalanine 360 000 mol/L in 60.7% of adults) but access and safety issues restrict their use. Gene therapy and mRNA-based approaches show preclinical promise. Nutritional supplementation using glycomacropeptide-based formula enhances palatability and bone parameters, though micronutrient deficiencies (vitamin D, B12, iron, zinc) and decreased bone mineral density are still prevalent in non-adherent patients.*

***Conclusions:*** *PKU is an avoidable etiology of intellectual disability, but inequities in newborn screening and access to treatment exist globally. Dietary management is good but not enough to achieve the best long-term results. New*

*treatments have revolutionary possibilities but demand equal opportunity. Nutritional supplement is necessary and should be given priority. The next decade of PKU care is characterized by addressing the global disparities.*

## 1. Introduction

Inborn errors of metabolism (IEMs) are rare, inherited metabolic disorders that arise from defects in enzymes or transport proteins; there are more than 1,000 reported IEMs, but the incidence of these disorders is about 1 in 2,500 live births. Phenylketonuria (PKU; OMIM 261600) is a typical aminoacidopathy (Turkel et al., 2020). The genetic defect of the hepatic phenylalanine hydroxylase (PAH) enzyme, which is unable to convert phenylalanine (Phe) into tyrosine with tetrahydrobiopterin (BH4), is the cause of PKU (Elhawary et al., 2022). This causes hyperphenylalaninemia and tyrosine deficiency with toxic accumulation of Phe in the blood and CSF. Uncontrolled, PKU can result in intellectual disability, epilepsy, behavioural disorders, microcephaly and hypopigmentation (Smith et al., 2021; Hillert et al., 2020). Since the 1960s, newborn screening (NBS) has been the method of choice for early diagnosis and dietary therapy to avoid neurological damage, which is now carried out by tandem mass spectrometry (Dóczi et al., 2026). Changing the adult Phe level is critical since a high level of Phe in adults has negative effects on executive functioning and mood (Van Spronsen et al., 2021). Moreover, PKU is also used as a model to develop enzyme replacement, chaperone and gene therapies (Vinueza, 2023).

The prevalence of PKU is regionally, consanguinity and adoption of NBS dependent. The prevalence of classic PKU is 6.002/100,000 neonates worldwide (Shoraka et al., 2020). Dóczi et al. (2026) found a prevalence of 0.84 of hyperphenylalanema and 0.29 of classic PKU per 10,000 live births. According to Hillert et al. (2020) there are about 450,000 PKU cases worldwide, which is 1 per 23,930 live births. Turkey has the highest prevalence due to consanguinity (de Oliveira & Bjoraker, 2021), while Iran reports 16.7 per 100,000, Japan 1 in 125,000, and Thailand 0.3 per 100,000 (Faraji et al., 2026; Shoraka et al., 2020). Under-ascertainment, late diagnoses, and avoidable disability are consequences of a lack of universal NBS in many LMICs (van Wegberg et al., 2021; Dóczi et al., 2026).

Dietary therapy is used to restrict the use of natural proteins, while ensuring adequate nutrition (MacDonald et al., 2020). Target blood Phe levels are 120-360 µmol/L for children under the age of 12 years and 120-600 µmol/L for 12 years and older (van Wegberg et al., 2017). Phe-free amino acid formula, which delivers 75-85% of protein requirements, and glycomacropeptides (GMP) formula, which enhances palatability (Daly et al., 2021; Ney et al., 2016). Adherence is difficult, ranging from 40-60% of adults achieving target levels (Jurecki et al., 2017; Ford et al., 2018). Pegvaliase (PAL enzyme replacement) – phase 3 trials showed 60.7% of patients had Phe ≤360 µmol/L at 24 months, but this is subject to monitoring for hypersensitivity (Thomas et al., 2018; Hydery & Coppenrath, 2019). In 20–50% of responsive patients, the synthetic BH4 analog, sapropterin (Kuvan®), can be used to allow a relaxation of diet. AAV vectors and mRNA are being explored as gene therapy approaches (Grisch-Chan et al., 2019; Bailey & Mackay, 2024). Treatment needs to be tailored to phenotype and genotype (Van Spronsen et al., 2021).

Supplements are added to the diet to make up for deficiencies. Protein is provided by phe-free formulas and GMP products, while deficiencies are corrected through fortification, such as vitamin B12, iron, zinc, calcium and vitamin D (Anton-Păduraru et al., 2025). DHA supplementation is beneficial for brain function (Alanís-Bernal et al., 2025), and tyrosine is conditionally essential (van Spronsen et al., 2021). These barriers are poor palatability, food aversion and the unequal access to food on a global level (Ford et al., 2018; van Wegberg et al., 2021). Biomarkers should be monitored routinely, particularly vitamin D, B12, ferritin, zinc and selenium, and bone health should be

monitored: 23% of adults with PKU have osteopenia and 9% osteoporosis (de Castro et al., 2020). Although dietary control has been attempted for many years, results are far from satisfactory. This decreases after adolescence, with only 40-60% of adults meeting target Phe levels. The lifelong restrictive diet, poor palatability, and social isolation are an unsustainable burden (Ford et al., 2018). There remain inequities globally, with the majority of low and middle-income countries still not having universal NBS, and thus, late diagnosis and irreversible damage (van Wegberg et al., 2021). There are still a number of evidence gaps concerning the comparative effectiveness and long-term effectiveness of emerging therapies that hinder clinical guidance (Van Spronsen et al., 2021; Hydery & Coppenrath, 2019).

### 1.1 Aim

To critically review PKU global prevalence, dietary management, emerging therapies, and nutritional supplementation.

### 1.2 Objectives:

1. Evaluate global PKU prevalence and factors contributing to regional variations.
2. Review dietary strategies and emerging therapies, comparing efficacy and safety.
3. Assess nutritional supplementation's role, including formulas, micronutrients, and compliance barriers.

### 1.3 Research Questions

1. What is the global prevalence of PKU, and how does it vary across regions?
2. What are current dietary strategies and emerging therapies for PKU, and how do they compare in efficacy and safety?
3. What role does nutritional supplementation play in comprehensive PKU management?

## 2. Literature Review

### 2.1 Global Epidemiology and Prevalence Patterns of Phenylketonuria

The knowledge of the worldwide distribution of PKU is crucial in planning healthcare, resource allocation, and creating specific screening and intervention programmes. Hillert et al., (2020) conducted a landmark study to provide the most detailed analysis of the epidemiology of PKU to date, analyzing genotypes and metabolic phenotypes of 16,092 affected individuals in 51 countries and 17 world regions. The researchers estimated the number of people living with PKU to be about 450,000 worldwide, with the global prevalence of the condition being 1:23,930 live births, 1:4,500 in Italy and 1:125,000 in Japan. The distribution of phenotypes across the globe included 62% classic PKU, 22% mild PKU and 16% mild hyperphenylalanemia. Notably, the research found that there was a gradient in the distribution of genotype and phenotype across Europe with classic PKU being more common in the east and milder phenotypes in the southwest and south. This genetic heterogeneity has direct clinical consequences with genotype-based prediction of phenotype with 88% accuracy and genotype-based prediction of BH4 responsiveness with 83% accuracy allowing tailored therapeutic selections.

A meta-analysis and systematic review by Shoraka et al., (2020) reviewed 53 studies with 119,152,905 participants who were conducted between 1964 and 2017 and estimated the prevalence of classic PKU in the world at 6.002 per 100,000 of neonates (95% interval: 5.0 The analysis indicated that there was a significant heterogeneity in different regions (I 2=99%), which was due to variations in consanguinity rates, genetic reserves, method of study and diagnostic cut-off points. Turkey showed the highest level of 38.13 per 100,000 neonates and Thailand showed the lowest prevalence of 0.3 per 100,000. The authors have highlighted that NBS programmes offer the most valid source of data on which to estimate the incidence of a disease but most countries do not have universal screening infrastructure and therefore, they may under estimate the actual disease burden.

Recently, Dóczi et al., (2026) have performed a systematic review and meta-analysis that quantifies the global and regional birth prevalence of hyperphenylalaninemia due to PAH deficiency. The global prevalence of hyperphenylalaninemia was regionally weighted

at 0.84 per 10,000 live births (95% CI: 0.441.24) with classic PKU at 0.29 per 10,000 births total. In North America and Europe, the rate of classic PKU was 0.58 per 10,000 births and 0.67 per 10,000 births, respectively. The authors observed that prevalence trends resembled consanguinity levels and this is why the burden is high in the Middle East and North Africa region and low in Southeast Asia. This paper insists on the necessity of taking into consideration regional demographic aspects when designing PKU screening and treatment services.

The country-specific studies have further explained the variation in PKU occurrence in a region. A systematic review and meta-analysis of PKU prevalence in Iran conducted by Faraji et al., (2026) found the country to be a high-prevalence region with 16.7 per 100,000 population, this prevalence in girls and boys were 15.2 (95% CI: 5.244.2) and 9.8 (95% C The authors explained this high rate by the high rates of consanguineous marriage in the Middle East region, de Oliveira and Bjoraker, (2021) described the serendipitous discovery of PKU cases in Iraq, which they said were not yet widespread and regular screening of metabolic disorders was not done, leading to an underestimation of the burden of the disease in the area.

The health consequences of PKU that remains undiagnosed are immense to the population. A survey by van Wegberg et al., (2021) across 259 patients in 52 countries revealed that 20% of patients had PKU diagnosed late and 55% of patients were born prior to NBS implementation or in an area without NBS. These individuals suffered some preventable neurological damage that underscores the extreme significance of universal implementation of NBS. The article has highlighted that PKU may be undiagnosed in all locations and that healthcare providers must be highly suspicious of the condition especially in immigrants to countries that do not have screening programmes in place.

**2.2 Dietary Management of Phenylketonuria**

The mainstay of PKU management has been dietary therapy, and there is a significant evidence base that it is effective in preventing neurological impairment when implemented early and sustained. The van Wegberg et al., (2017) European PKU recommendations offer detailed guidelines on diagnosis, treatment, and monitoring throughout the lifespan. The recommended target blood Phe levels in children younger than 12 years of age are 120360 µmol/L, and individuals older than 12 years of age is 120600 µmol/L, although more strict (120360 µmol/L) control is advised in pregnancy to avoid maternal PKU syndrome. The guidelines underscore the need to have lifelong treatment, multidisciplinary care, and frequent monitoring of nutritional status and neurocognitive development.

To support the European guidelines, MacDonald et al., (2020) created the PKU dietary handbook, which offers real-world advice on how to address the issue to healthcare workers and patients. The handbook outlines the concepts of dietary management, such as Phe tolerance calculation, Phe-free protein substitutes, low-protein foods, and dietary adherence management of the diet in various life stages. The authors emphasize that protein substitutes provide about 75-85 percent of total protein needs and play a vital role in the prevention of protein malnutrition and the optimal control of metabolism. The handbook also discusses more practical issues such as food neophobia, taste aversion, and psychosocial effects of the dietary restrictions.

The exact effects of long-term metabolic control on cognitive ability have been measured in recent, powerful meta-analyses, which present powerful evidence to advocate intensive lifelong management. A meta-analysis study by Romani et al., (2025) that combined 29 adult and 21 paediatric PKU groups found that those treated early in life underperform on average about 0.46 standard deviations (SD) on all cognitive tests compared to healthy controls. The deficit continued throughout the lifespan, although there was a different pattern of impairment between age groups. There were more homogeneous impairments across domains in children, and a striking dissociation between processing speed as the most profoundly

impaired function (estimate -0.74 SD, 95% CI: -0.99 to -0.49) and accuracy-based tasks such as crystallised intelligence which were relatively preserved. More importantly, the meta-analysis revealed that there was a strong dose-response effect, and every 100 mmol/L change in lifetime blood Phe yielded -0.04 SD reductions in cognitive performance.

Compliance with dietary therapy is a major issue during the management of PKU in the long term. Jurecki et al., (2017) carried out an in-depth study on adherence trends of patients with PKU in the United States, and their results showed that the adherence to clinic-recommended adherence and maintenance of target blood Phe levels decreased progressively with age (childhood, adolescence, adulthood). It was only around 40-60 percent of adults who were within the recommended target ranges in their blood Phe levels. but the Factors related to poor adherence were older age, loss of insurance, and perceived burden of dietary restrictions. The research also pointed out the necessity of better supports and other treatment choices to patients with dietary compliance issues.

A qualitative study by Ford et al., (2018) offered meaningful information about the experience of PKU people. The study has outlined key themes such as the weight of a life-long diet, social isolation due to food-based activities, coping with the diet in various social settings, and the psychological effects of the condition through a deep interview with adults with PKU. Participants explained that protein substitute tasting was perceived as a huge load and that they have several methods of disguising bad flavours. The paper has emphasised the significance of patient-centred care models that consider the psychosocial aspects of PKU management and deal with obstacles to the best adherence.

Nutritional sufficiency of the PKU diet has been studied in a few studies. Demirdas et al., (2017) conducted a systematic review of micronutrient status, essential fatty acid profiles and bone health among PKU patients. It was discovered that the prevalence of vitamin D deficiency and lower bone mineral density among adult patients with PKU were high due to limited dairy consumption and altered metabolism of vitamin D. Suboptimal levels of vitamin B12, iron, zinc and selenium were also reported in a subset of patients, especially those who had low compliance with prescribed protein supplements. Regular assessment of nutritional biomarkers and proper supplementation to avoid deficiencies were the recommendations that were given by the authors.

Rodrigues et al., (2021) performed a systematic review and meta-analysis of 15 studies to ascertain whether a phenylalanine-restricted diet subjects patients with PKU to overweight or obesity. The meta-analysis established no difference in body mass index (BMI) between patients with PKU and healthy controls and this provided no support to the hypothesis that a Phe-restricted diet was a risk factor in the development of overweight. Nevertheless, there was a subgroup of patients with classical PKU who were much heavier than healthy controls and the authors stressed that patients with PKU have to be followed in their lifetime with individual nutritional counselling and systematic nutritional status monitoring. In another systematic review of 18 articles investigating bone status in PKU, de Castro et al., (2020) discovered that low bone mineral density is a common finding, with reported osteopenia prevalence of 23-48% and osteoporosis prevalence of 9-14% in adults. The review affirmed the high prevalence of vitamin D deficiency and the importance of a continuous nutritional monitoring and intervention measures to maximise long-term bone health outcomes.

Daly et al., (2020) have reported the evolution of protein substitutes, which has been traced back to the early years of casein hydrolysates and the contemporary amino acid mixtures and GMP-based formulas. The review has demonstrated a positive change in nutritional composition, palatability, and convenience, and also admitted that taste acceptability is still a serious obstacle to most patients. The authors observed that GMP-based formulas are a significant innovation, with a more physiological amino acid profile and better satiety when compared with the conventional amino acid mixtures.

Daly et al., (2021) have followed the historical progression of protein substitutes by starting with the earliest experimental applications of these vital products in a 2-year-old child with PKU on chemist-formulated amino acid mixtures to present-day recipes. The review described the development of early casein hydrolysates to modern L-amino acid mixtures, introduction of bioactive glycomacropeptide (GMP) as casein substitute base since 2008, and the physiomimic technology in 2018 of coating amino acids with a polymer to allow slow release and a better physiological profile. The review has emphasized the continuous enhancement in nutritional composition, palatability and convenience and has noted that taste acceptability is a major obstacle in many patients. The researchers observed that GMP-based formulas are a significant innovation, with a more physiological amino acid profile, and possibly better bone and gut health, nitrogen retention, and blood phenylalanine regulation than conventional amino acid mixtures. It was concluded that the efficacy of the protein substitute ultimately depends on its nutritional profile, amino acid composition, dose, timing, distribution, and sufficient energy intake and that these products receive insufficient attention but that their pharmacological effects and clinical benefit are critical in the management of PKU.

**2.3 Novel Pharmacological and Biological Therapies.**

The treatment of PKU has evolved greatly beyond dietary control and now pharmacological and biological therapy has been developed which addresses various facets of the underlying metabolic abnormality. Longo et al., (2025) conducted a thorough review of PKU, assessing the unmet needs and the necessity of newborn screening and chronic treatment alternatives. The literature available was reviewed by an international team of experts who considered treatment internationally to evaluate patient benefit. The review noted that there are countries that have not been able to introduce newborn screening programmes or that do not use a treatment-for-life approach. The current issues facing persons with PKU are poor access to cheap treatment, social support, staffing of clinical clinics, and burden of the disease. Dietary interventions might not be sufficient to treat all symptoms and some of the existing pharmacotherapies can be linked to limited effectiveness or adverse events. The authors added that a number of novel therapies are under clinical trial to PKU and they pointed out that availability of newborn screening programmes, treatment access and an unwavering dedication to lifelong treatment will translate to better outcomes in individuals with PKU in all geographical locations.

The initial pharmacological therapy that was approved to treat PKU was sapropterin dihydrochloride which is the synthetic form of BH4. Muntau et al., (2019) established international best practice in evaluation of responsiveness to sapropterin in PKU patients. The guidelines suggest 48-hour BH4 loading test or 4 weeks treatment trial to evaluate responsiveness, and further treatment in responders who exhibit clinically significant benefit. It has an estimate prevalence of BH4 responsiveness in 20-50% of patients and greater response rates in the case of milder phenotypes and in patients with specific mutations in PAH. The guidelines reiterate that sapropterin can permit a reduction in dietary Phe restriction or an increase in natural protein intake, which can possibly result in the enhancement of quality of life and nutritional state.

Longo et al., (2015) provided long term safety and efficacy data based on the Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry, a voluntary, Phase 4, observational study that would collect longitudinal data on PKU patients receiving sapropterin dihydrochloride. The PKUDOS group comprised 1,189 individuals with PKU, including 504 who have been continuously exposed since registering in the study. In continuously exposed subjects, a statistically significant mean reduction of 34% in blood phenylalanine level was found, with the baseline level of 591 382 00: 1 decreasing to 392 239 00: 1 after 5 years ($p = 0.0009$) with a concomitant increase in dietary Phe intolerance,

1 Adverse events were drug related in 6% of subjects, and were largely non-serious, and were reported in gastrointestinal, respiratory and nervous systems, with serious drug-related adverse events reported in 0 to 1% of subjects. The authors concluded that long-term sapropterin therapy is tolerably safe and continuous therapy is linked to a substantial and sustained reduction in blood Phe and dietary Phe tolerance, and thus to its continued use as an adjunct to dietary management in BH4-responsive patients.

The pegvaliase enzyme substitution therapy is a significant improvement in adults with severe PKU that lack sufficient metabolic control of dietary therapy. Thomas et al., (2018) published the findings of the pivotal Phase 3 clinical trial programme (PRISM-1 and PRISM-2) assessing pegvaliase in adults with PKU. The trials showed that pegvaliase therapy resulted in significant and long-lasting decreases in Phe levels in the blood, with 60.7% of the participants attaining 360 µmol/L or below at 24 months. Mean decrease in blood Phe at baseline was 62.2%. Nonetheless, pegvaliase was linked with serious adverse events, the most prominent of which was hypersensitivity reactions such as arthralgia and injection site reactions, which happened in most patients. The research reached a conclusion that pegvaliase is a good treatment of adults with PKU who can and want to comply with the monitoring conditions.

Hydery and Coppenrath., (2019) conducted an extensive overview of pegvaliase, including its mechanism of action, clinical trial results, safety, and role in therapy. As noted in the review, pegvaliase is the first non-dietary treatment that can lead to normalisation of blood Phe levels in adults with PKU, possibly without the dietary protein restriction. Nevertheless, the necessity to administer it on a daily basis as a subcutaneous injection, the possibility of immune-mediated adverse events, and strict monitoring routine make it currently applicable only to a few adult patients. The review has highlighted the need to educate patients and engage in shared decision-making when pegvaliase therapy is in view.

The future of PKU research is Gene therapy and other advanced therapeutic modalities. Grisch-Chan et al., (2019) presented a review of the state of the art of gene therapy in PKU, summarizing preclinical reports of adeno-associated virus vectors to deliver functional PAH genes to hepatocytes. It has been shown by animal studies that there is long-term reduction of blood Phe and normalisation of brain monoamine neurotransmitter levels after gene therapy. Nevertheless, there are still issues with regard to vector immunogenicity, transgene expression durability and potential genotoxicity. Clinical trials are in progress at an early-stage to determine the safety and effectiveness of AAV-based gene therapy in humans.

Martinez et al., (2024) have conducted an extensive state-of-the-art review of the field of gene therapy in PKU, outlining the present state and future of the field. The review listed a lengthy list of gene therapeutic experimental strategies that utilized the classical murine model of human PKU comprising recombinant viral (AdV, AAV, and LV) and non-viral (naked DNA or LNP-mRNA) vectors delivery methods, in combination with gene addition, genome editing, gene or base editing, and gene insertion or replacement. The review also contained a list of ongoing and prospective clinical trials of PKU gene therapy, which validated that a few clinical programmes are in active development. The authors, however, warned that there are still huge gaps in long-term safety and durability data and that the most effective serotype of vectors, dose, and administration regimen is yet to be established. The review ended with a conclusion that summarised, compared, and evaluated the different approaches in the interest of scientific understanding and efficacy testing that could one day lead to safe and effective human clinical application.

CRISPR-Cas9 genome editing has the opportunity to introduce the possibility of permanent correction of pathogenic variants of PAH. A study by Richards et al., (2020) using AAV-mediated CRISPR/Cas9 gene editing in a murine model of PKU revealed that the disease phenotype was corrected, and the blood Phe levels returned to normal with the disease avoiding neurological impairment. Although these findings are promising, considerable safety

and ethical issues that should be considered prior to clinical translation are the off-target editing effects, immunogenicity, and long-term effects of genome editing.

Diaz-Trelles and Perez-Garcia (2022) presented a dedicated review of the lipid nanoparticle-mRNA technology to treat phenylketonuria. It is a method that implies the transfer of mRNA that encodes the missing phenylalanine hydroxylase (PAH) enzyme that is encased in lipid nanoparticles, allowing temporary yet repeatable expression of the enzyme in hepatocytes without causing any genomic integration. The review mentioned preclinical experiments that showed viability and efficacy of LNP-mRNA delivery in animal models of metabolic liver disease, and that mRNA therapy has a number of potential benefits such as non-insertional mutagenesis risk, the potential to dose-regulate according to clinical requirement and the generation of a fully functional enzyme with native post-translational modifications. The authors, however, warned that there are still issues with the efficiency of delivery to target hepatocytes, possible immunogenicity of the mRNA and lipid nanoparticle constituents, and the short-term effect that requires repeated administration. The review summarised by examining LNP-mRNA technology in relation to other therapeutic options currently under development in the treatment of PKU, and its potential to treat the underlying cause of disease and to treat patients who fail to respond to currently available pharmacological treatments.

Nulmans et al., (2025) offered a state-of-the-art review of the present treatment environment of phenylketonuria. The review outlined four primary treatment options: (i) a phenylalanine dietary restriction diet that is supplemented with other amino acids and micronutrients using medical mixtures; (ii) large neutral amino acid daily dosing; (iii) tetrahydrobiopterin (BH4) synthetic forms, including sapropterin; and (iv) bacterial phenylalanine ammonia lyase enzym Reducing the level of blood phenylalanine and enhancing the quality of life is the main aim of treatment in all modalities. The authors, however, pointed out that treatment is highly demanding both to the patients and their families and that not all treatment choices can be applied to all patients, suggesting the necessity of personalised choice of treatment.

Elhawary et al., (2022) offered an in-depth overview of the genetic etiology and clinical issues of phenylketonuria with a discussion of the epidemiology, pathophysiology, and management of this autosomal recessive inborn error of phenylalanine metabolism. The authors stressed that a proper diagnosis, prediction of the phenotype, and choice of the proper therapies are impossible without knowing the molecular basis of PKU. The review observed PKU to be genetically heterogeneous and that over 1,000 pathogenic PAH variants have been reported globally and are listed in the locus-specific databases PAHvdb and BioPKU. The system of genotype-phenotype prediction, in which variants are allocated to phenotype classes, such as classic PKU, moderate PKU, mild PKU, and mild hyperphenylalaninaemia, is presented as arbitrary numbers in the paper, but it is emphasized that genotyping can also inform about a patient who might respond to sapropterin (BH4) treatment. The authors addressed the challenge in diagnosis and treatment of this genetic complexity, such as the inability to correlate the genotype and phenotype in compound heterozygotes, and the inter-individual variability of the human brain to hyperphenylalaninemia, and potential emerging treatment therapies, such as enzyme substitution therapy, casein glycomacropeptide, and gene therapy.

**2.4 Nutritional Supplementation in Long-term management.**

Nutritional supplementation is an inseparable part of the PKU management, to fill the inescapable nutritional deficits that the highly limited diet plan causes. Ahmadzadeh et al., (2022) evaluated the anthropometric and biochemical values of 80 children and adolescents (4-18 years old) with PKU. The researchers have established that a quarter of patients (n = 28) were deficient in 25 hydroxy vitamin D3, 12.5% of the patients were deficient in folic acid, and a high level of vitamin B12 was

common. A more recent systematic review and meta-analysis by Bokayeva et al., (2024) compared the vitamin status of PKU patients with healthy controls, studying 24 studies including 770 individuals with PKU. The meta analyses reported that the folate levels (SMD: 1.378; 95% CI: 0.4362.320; p = 0.004) and 1,25 dihydroxyvitamin D concentrations (SMD: 2.059; 95% CI: 0.2 There were no notable differences in vitamins A, E, B 6, B 12 or 25 hydroxyvitamin D. The research concluded that patients with PKU who were given nutritional advice could reach a similar vitamin status as healthy individuals; yet, they noted that further follow-up and studies were necessary to reaffirm the results and to investigate other factors that could affect the vitamin status in PKU.

Alaninis-Bernal et al., (2025) have carried out a systematic review of 18 studies to determine clinical and biochemical outcomes of the use of docosahexaenoic acid (DHA) supplementation in people with phenylketonuria. The review established that long chain polyunsaturated fatty acid deficiency especially DHA is at risk in persons with PKU because of the highly restricted protein diet. The supplementation of DHA was shown to be safe and effective in raising erythrocyte and plasma DHA levels in all of the involved studies. The improvements in visual evoked potentials were also reported in several trials and it is suggesting that neurophysiological benefit may be present. Nevertheless, the evidence of neurocognitive outcomes improvement was inconsistent. The authors came to the conclusion that DHA supplementation is an effective and safe approach to correct the LC PUFA deficiency in PKU and potentially provides neurophysiological benefit but additional high quality research is required to determine its clinical benefit in the long term neurocognitive development.

The study by Ney et al., (2016) was a 2 stage, randomised, controlled crossover trial comparing glycomacropeptide medical foods (GMP MFs) with traditional amino acid medical foods (AA MFs) in 30 participants with PKU who were early treated (aged 15 to 49 years; 20 with classical and 10 with variant PKU Each type of medical food was taken by the subjects during 3 weeks in random manner with a 3 week washout periods in between. The levels of blood phenylalanine over time did not differ significantly between treatments (AA MFs: 444 ± 34 μmol/L; GMP MFs: 497 ± 34 μmol/L), and showed similar metabolic control even though GMP MFs significantly increased Phe intake (88 ± 6 mg Phe/day, P = 0. The participants who rated GMP MFs as more acceptable than AA MFs, experienced better gastrointestinal symptoms and reduced hunger, and had a higher percentage of medical food intake. There were no significant differences in the results of Behaviour Rating Inventory of Executive Function between treatments. The authors determined that GMP MFs are a safe and acceptable dietary treatment of PKU and that their increased acceptability and reduced side effects have the potential to improve dietary compliance.

Stroup et al., (2017) compared the metabolic impact of amino acid medical foods (AA-MF) and glycomacropeptide medical foods (GMP-MF) in a crossover study of 8 participants with PKU aged 1635 years. The food records and 24 hour urine samples were taken after the participants had consumed a low phenylalanine diet with each type of medical food type in the span of 1-3 weeks. AA MF offered a 1.525-2.5 times greater potential renal acid load (PRAL) and led to 3 times higher renal net acid excretion than GMP MF (p = 0.002). The intake of dietary protein, calcium and magnesium were comparable. But GMP MF lowered urinary excretion of calcium by 40% (p = 0.012) and magnesium by 30% (p = 0.029). Two respondents had low age-adjusted bone mineral density (BMD) and trabecular bone scores, and urinary calcium with AA MF was found to be negatively correlated with L1-L4 BMD. The authors concluded that, relative to GMO MF, AA MF augment dietary acid load, which in turn elevates urinary calcium and magnesium release, and presumably plays a role in skeletal fragility in PKU.

Rocha et al., (2024) performed a meta-analysis to measure the degree of bone mineral density (BMD) impairment in adults with phenylketonuria, synthesising information on

4097 patients in 10 studies. The statistically significant mean bone Minerals Density Z scores were lower than the reference non PKU population at all skeletal sites measured that is lumbar spine is -0.63, femoral neck -0.74, radius -0.77 and total body -0.61. Nevertheless, the mean Z scores were within the age-specific range (> –2.0) in all bones. The prevalence of BMD Z scores of -2.0 and below was estimated at 8% (95% CI: 5%, 13%), which means that less than 1 in 10 adults with PKU was below the normal range of age. and came to the conclusion that the incidence of BMD Z scores less than -1.0 was 42%. The authors concluded that adults with PKU experience decreased BMD compared to the general population but that the majority of them stay within the age expected range and that the number of available studies is too low to determine which population characteristics have the strongest impact on the BMD results.

## 4. Methodology

The literature available on PKU was very diverse, so a narrative review approach was chosen. This allowed integrating epidemiological, clinical, therapeutic and nutritional evidence comprehensively. It also provided flexibility to deal with more complex questions and to contextualise findings (Green et al., 2006; Ferrari, 2015; Baethge et al., 2019). The research objectives allow this narrative review design to incorporate a variety of types of evidence. These include epidemiological studies, clinical trials, systematic reviews, guidelines and qualitative studies (Grant and Booth, 2009; Pautasso, 2013). Narrative reviews are less structured than a systematic review, but a systematic literature search, selection and appraisal was undertaken with the aim of minimising bias (Green et al., 2006; Ferrari, 2015).

The literature search was carried out from January 2026 to March 2026 in PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library and Google Scholar with the use of MeSH terms and free text keywords. The studies included met the following criteria: They were written in English and published between January 2015 and March 2026. Those included were peer reviewed original research, systematic reviews, meta-analyses, narrative reviews, clinical guidelines, consensus statements and relevant grey literature. Other inclusion criteria included human studies of all ages with PKU, studies directly relevant to the care of PKU and studies with a clear methodology and reliable data. Exclusion criteria were: non-English publications, editorials, letters, and case reports. Animal or in vitro studies and studies on other metabolic conditions or maternal PKU that is not relevant to the core questions were not included. Publications with severe methodological issues, or retracted publications, were also not included.

The study was selected according to PRISMA (Page et al., 2021). A total of 128 records were found. Of these 102 were unique after deduplication. Of the 62 excluded at title/abstract screening, 40 full-text articles were evaluated for eligibility. Seven were excluded because they did not have relevant outcomes, inappropriate design, inadequate data, or were redundant. This led to a total of 32 studies being included. A standardised form was created and used in 5 studies for data extraction. The following specific information was captured for each study included: author, year of publication, title, participant characteristics (sample size, age, demographics), methodology (study design, setting, interventions, outcome measures), and key findings (prevalence estimates, dietary adherence rates, treatment responses, nutritional status indicators, adverse events). The extraction process was conducted following the procedure for narrative reviews (Green et al., 2006; Ferrari, 2015; Popay et al., 2006). One reviewer extracted the data which was then checked with the original articles. Study-type appropriate tools were used for quality assessment with results used for interpretation, not exclusion.

Thematic analysis was then carried out based on the framework of Popay et al. (2006) and Ferrari (2015). Data collected were classified into themes related to the research goals, namely: global epidemiology, dietary management, emerging therapies, and nutritional supplementation. Comparative analyses along with critical interpretation were conducted. No ethical

approval was necessary as only published literature was used. The study followed the guidelines for research integrity (National Institute of Environmental Health Sciences, 2024).

Limitations of the methodology are the subjectivity and selection bias that can occur in narrative reviews (Ferrari, 2015; Byrne, 2016). There are other issues, such as English-only language bias, publication bias (Dalton et al., 2016), and single reviewer extraction (only 10% was independently verified). Additionally, quantitative synthesis was constrained by heterogeneity and the dynamic nature of PKU research makes findings only applicable as of March 2026. Despite the limitations, the methodology offers a structured and transparent synthesis of the existing evidence on PKU.

## 5. Discussion and Findings

This narrative review aimed to provide a synthesis of 32 studies from four thematic areas of phenylketonuria (PKU) that are global epidemiology, dietary management, emerging therapies, and nutritional supplementation. As far as prevalence is concerned, the literature indicates that the prevalence of classic PKU is about 6.002 per 100,000 births, and the number of patients in the world is estimated at 450,000 (Shoraka et al., 2020; Hillert et al., 2020). The variation is very high between regions, with the highest prevalence in Turkey (38.13 per 100,000) and the lowest in Thailand (0.3 per 100,000), a 130 fold difference (Shoraka et al., 2020). There is a clear gradient from east to west in Europe with classic PKU more common in Eastern Europe, and more mild variants in the south west (Hillert et al., 2020). There is a strong association between prevalence and rates of consanguinity, with high rates in the Middle East and North Africa (MENA) and low rates in Southeast Asia (Dóczi et al., 2026; de Oliveira and Bjoraker, 2021). The prevalence of 16.7 per 100,000 in Iran is higher than the global prevalence (Faraji et al., 2026). This relationship is confirmed by direct molecular evidence in Iran, 86.6% of PKU patients had consanguineous parents, which is much higher than the background population (Senemar et al., 2009). The study was also retrospective NGS study in Turkey, with a population carrier frequency of 3.2% (1 in 31 individuals), which is a high carrier frequency, further compounded by consanguineous marriages. The clinical implication is straightforward as in societies with a high rate of consanguinity. it is cost effective to screen PAH variants universally in the preconception period to allow prenatal testing and early neonatal surveillance (El Metwally et al., 2018; Dababneh et al., 2022). In most low and middle income countries, however, universal newborn screening (NBS) is still missing, resulting in substantial under ascertainment and late diagnosis. Another international survey revealed that 20% of the patients were diagnosed late and 55% were born before NBS was implemented or in unscreened areas (van Wegberg et al., 2021). In the world, over half of all babies are born in nations with incomplete NBS (IndoUSrare, 2026). Pilot screening is available in some states in India and awareness and financial barriers exist in Bangladesh (Al Bari, 2022). In high income countries, it takes an average of 9.5 years (Brower et al., 2022) to add a new condition to NBS panels. According to WHO, NBS is not definitive and should be confirmed by further testing (Herbst, 2024). There are considerable methodological limitations in prevalence information, with the majority of estimates based on NBS programmes which only register the births that occur in health facilities, and births at home continue to be common in many countries. Shoraka et al. (2020) reported high statistical heterogeneity ($I^2$=99), which could be attributed to differences in consanguinity, methods of study, diagnostic cut offs, and screened populations. Future studies should use modelled estimates which incorporating consanguinity prevalence and regionally representative allele frequencies (Hillert et al., 2020; Dóczi et al., 2026).

In the field of dietetic management the literature reports that diet therapy is still the primary method of treatment for PKU. According to the European guidelines, the target Phe level is 120 360 µmol/L for children younger than 12 years

and 120 600 μmol/L for children older than 12 years (van Wegberg et al., 2017). Protein substitutes can supply 75 85% of the total protein requirement (MacDonald et al., 2020). A pioneering meta-analysis by Romani et al. (2025) showed that, in early treated patients with PKU, a cognitive deficit of 0.46 SD was identified in all domains, with the greatest deficit being in processing speed (−0.74 SD). Importantly, there is a dose response relationship; with each 100 μmol/L increase in lifetime blood Phe, the cognitive performance decreases by 0.04 SD. This corresponds to an IQ 7 8 points lower than untreated controls, and 10 15% of early treated children in the borderline intellectual functioning range. Overall, the results are consistent with previous meta-analyses (Romani et al., 2022; Thomas et al., 2023). This dissociation between processing speed and crystallised intelligence has real world implications: adults with well controlled PKU can learn normally, but have difficulties with tasks that are time sensitive, like working on challenging tasks or when they are presented with many stimuli in short succession, like in social interactions (Hofman et al., 2018). Rates of adherence are significantly lower with age; for adults, 40 60% keep target Phe levels (Jurecki et al., 2017). A survey of the compliance rates of protein replacements was conducted in the USA with 527 patients who suffer from PKU; the results revealed that adherence to protein replacements decreased from 88% among children aged 0-4 years to 33% of adults older than 30 years. In a UK study, 80% of adolescents and adults had levels of Phe above the recommended levels, and 43% were non adherent (Green et al., 2019). The barriers include poor palatability, taste aversion, psychosocial distress, cost and social pressure (Ford et al., 2018; Yagudina et al., 2024). The annual costs of protein substitutes in the US are more than $10,000, and adults who lose paediatric coverage frequently stop using protein substitutes (Belanger Quintana et al., 2012). Nutritional problems are prevalent, with vitamin D deficiency up to 35% and bone mineral density is also significantly diminished. Ten studies were included in the meta-analysis (4,097 participants) with mean BMD Z scores below the reference population at all skeletal sites: lumbar spine, −0.63 SD; femoral neck, −0.74 SD; radius, −0.77 SD; and total body, −0.61 SD (Rocha et al., 2024). Z scores ≤ −2.0 were found in 8% of adults (1 out of 12) compared with the expected 2.5% in a normal population. The prevalence of osteopenia is 23 48% and osteoporosis is 9 14% in adult PKU patients (de Castro et al., 2020). Pathophysiology is multifactorial such as low calcium and vitamin D, secondary hyperparathyroidism, excessive acid load from amino acid formulas, and possible direct Phe effects on bone metabolism (Rocha et al., 2024). The findings of comparison to BMI of healthy controls are ambiguous: Rodrigues et al. (2021) did not find any significant difference, while Tankeu et al. (2023) did report a higher prevalence of obesity. Nutritional biomarkers should be proactively monitored in clinical practice.

With respect to new therapies, there has been a vast evolution of therapy beyond diet for PKU. Synthetic BH4 (sapropterin dihydrochloride) is effective in 20% to 50% of patients and has a higher response rate in milder phenotypes (Muntau et al., 2019; Elhawary et al., 2022). The mean reduction of blood Phe after 5 years of PKUDOS registry data is 34% and dietary Phe tolerance has increased from 1,000 to 1,539 mg/day after 6 years in the same registry data (Longo et al., 2015). The incidence of adverse events was 6%, mostly non serious. Sapropterin is costly (≈$100,000/year) and access is limited (Rose et al., 2019). Inconsistent evidence of executive function improvements has been found in a systematic review in 2025 (Lin, 2025). Pegvaliase is the first non-dietary treatment for adults with PKU, which is a pegylated recombinant phenylalanine ammonia lyase. Final Phase 3 PRISM data on 261 participants showed 71.3%, 65.1%, and 59.4% reached blood Phe ≤600, ≤360, and ≤120 μmol/L, respectively, after a mean of 36.6 months (Harding et al., 2024). Mean blood Phe fell from 1,233 μmol/L at baseline to 311 μmol/L (68.7% reduction) at 24 months (Thomas et al., 2018). But treatment is

hard work, with median time to first attainment of ≤360 µmol/L being 8.0 months. Adverse events reported were arthralgia (70.5%), injection site reactions (62.1%), headache (47.1%) and anaphylaxis (17 events in 12 participants) which were all without sequelae. A tight monitoring and risk mitigation process is crucial. Animal models of gene therapy with AAV vectors for delivery of functional PAH genes have demonstrated sustained Phe reduction, and CRISPR Cas9 genome editing has corrected the disease phenotype in murine models (Grisch Chan et al., 2019; Richards et al., 2020). There are several clinical programmes in progress, but there is no long term safety and durability information (Martinez et al., 2024). Temporary and repeatable PAH expression without genomic integration has been obtained by mRNA based therapy with lipid nanoparticles (Diaz Trelles and Perez Garcia, 2022). Using transient prime editing in mice, a recent study obtained a range of gene correction rates between 4.3 20.7%, which allowed for a reduction of blood Phe from >1,500 µmol/L to <360 µmol/L (Rothgangl et al., 2025). But, only lasts for days to weeks, and needs to be repeated. There are limited comparisons, and pegvaliase is shown to be more effective than sapropterin and medical nutrition therapy (MNT) alone (Burton et al., 2024). There are still major disparities in access to these advanced treatments, with the majority of low and middle income countries unable to afford any of these treatments.

As for nutritional supplements, protein substitutes have progressed from casein hydrolysates to L amino acid blends, glycomacropeptides (GMP) based formulas, and physiomimic technology (Daly et al., 2021). GMP formulas provide metabolic control comparable to that of conventional amino acid formulas (blood Phe 497 vs 444 µmol/L) and superior palatability, satiety and gastrointestinal tolerance (Ney et al., 2016). GMP is also known to decrease urinary calcium loss by 40% and magnesium by 30%, which may have beneficial effects on bone health (Stroup et al., 2017). A three year longitudinal paediatric study, however, showed no statistically significant bone benefit of GMP when compared to L amino acids (Daly et al., 2021). As far as vitamin status concerns, the results of a meta-analysis of 24 studies including 770 PKU patients showed that well-nourished PKU patients had an equivalent level of most vitamins compared to healthy controls, and higher level of folate and 1,25 dihydroxyvitamin D as a result of fortification (Bokayeva et al., 2024). Non adherent subsets, however, have high prevalence of vitamin D deficiency (35%), sub-optimal B12, iron, zinc and selenium (Ahmadzadeh et al., 2022). Supplementation with DHA has been shown to increase blood DHA levels and enhance visual evoked potentials (VEPs), but a consistent improvement in functional neurocognitive outcomes has not been seen (Alanís Bernal et al., 2025; Demmelmair et al., 2019). Nevertheless, clinical guidelines suggest DHA supplementation because of its good safety profile (van Wegberg et al., 2017). Poor palatability, high cost of these foods, and limited access to low phenylalanine foods directly influence nutritional supplement consumption (Ford et al., 2018). Access to NBS is very unequal, with a survey of 16 countries demonstrating that many countries do not have NBS programmes, and immigrants being late diagnosed (Jurecki et al., 2019).

## 6. Conclusion

This narrative review validates that phenylketonuria (PKU) is a worldwide important inherited metabolic disorder, which exhibits a high regional variation in incidence. The prevalence of classic PKU is about 6/100,000 neonates and the estimated number of affected people worldwide is 450,000. The highest prevalence is seen in high consanguinity regions such as Turkey and the lowest rates are seen in Southeast Asian countries. Most importantly, there is significant under-ascertainment and the potential for preventable neurological damage due to the lack of universal newborn screening (NBS) in most LMICs. Dietary management is the backbone of treatment of PKU but it is severely restricted. The cognitive deficit of about 0.46 SD for early treated patients is also seen in more severely affected patients, and processing speed is most affected. Adherence decreases with age, with only 40 to 60% of adults having target

levels of blood phenylalanine. Long-term dietary monotherapy is unsustainable due to a number of barriers including diet restrictions, poor palatability of medical foods, social isolation, and cost. New treatments are available for additional possibilities. Sapropterin provides metabolic control for 20–50% of patients, and pegvaliase offers transformative metabolic control in adults with severe PKU with >60% having blood Phe <360 µmol/L at 24 months; however, hypersensitivity reactions must be monitored closely. Although there are exciting pre-clinical developments in gene therapy and mRNA-based therapies, they do not have long-term safety and efficacy data and there are significant global disparities of access. Comprehensive management includes nutritional supplementation. Glycomacropeptide (GMP) based formulas are newer, are more palatable and may have bone benefits. Well-nourished patients can obtain vitamin status similar to healthy individuals, whereas non-adherent patients are at risk for vitamin D, B12, iron, zinc and selenium deficiency. All skeletal sites have reduced bone mineral density, but most adults are within normal age ranges.

The following recommendations can be made for clinical practice based upon these findings. The adoption of NBS should take place right away in all regions, where it is not yet being used, with strong follow-up. The desirable range for blood Phe is 120-360 µmol/L for children below 12 years and 120-600 µmol/L for older children and adults, except for pregnant women, for whom the blood Phe level should be more tightly controlled. Protein substitutes that supply 75–85% of protein requirements should be provided and GMP based formulas are preferred for patients who report poor palatability or gastrointestinal symptoms. Vitamin D, B12, folate, ferritin, zinc, selenium and calcium should be assessed annually, and supplemented when indicated. Bone mineral density should be evaluated in all adults and at-risk children. The recommended dosage of DHA is 10-20 mg/kg/day, particularly during childhood, adolescence and pregnancy. All patients should be considered for a trial of sapropterin, and pegvaliase is recommended for adults with severe PKU with poor metabolic control who are able to meet monitoring requirements. Standard of care includes regular neurocognitive assessments, structured transition programmes and multidisciplinary teams. The need of health policy in LMICs is to put into focus universal NBS with international assistance. The cost of low protein foods and protein substitute for PKU should be considered an essential medical product and fully reimbursed or subsidized, which removes the "out of pocket" expense. Sapropterin and pegvaliase should be listed on essential medicines lists; price negotiation and voluntary licensing to lower prices. Care should be taken in setting up national and regional PKU registers to monitor prevalence, treatment pattern and outcome. The medical curriculum should include PKU training and patient organisations should be funded for education and advocacy. It is essential for patients and families to stick with a treatment plan for life. Home blood Phe monitoring can also be used if available. Protein substitutes and micronutrient supplements are to be used on a regular basis. It is important that there is a strong partnership between paediatric and adult services. Eating distress should be addressed with psychological support and peer relationships. For women who are planning pregnancy, blood Phe should be less than 360 µmol/L before they become pregnant and be carefully controlled thereafter.

Looking ahead, comparative effectiveness trials of GMP-based versus amino acid-based protein substitutes are research priorities. Pragmatic trials of integration of pegvaliase and cost-effectiveness studies are required, as are long-term follow-up studies of 10-year outcomes for pegvaliase and gene therapy. There is also a need for development of validated patient-reported outcome measures and assessment of behavioural interventions to improve adherence, and for optimisation of nutritional monitoring guidelines. Implementation science studies should seek to define the challenges to NBS in low-resource communities and evaluate point-of-care low-cost Phe monitoring devices. There is a need to explore further the design of vectors,

immune mitigation and non-viral delivery methods for gene therapy. Emerging strategies being explored include gut microbiome modulation, next generation low immunogenicity Phe-degrading enzymes, liver transplantation and artificial intelligence for personalised dietary management. The advocacy priorities are a global programme for NBS with universal screening by 2035, an official petition to add PKU protein substitutes to the WHO Model List of Essential Medicines, a 'fair access model' for gene therapies and a global patient registry standard. For the first time in the history of medicine, PKU has been proven to be the first disorder for which NBS has prevented severe intellectual disability, the first inborn error with a specific dietary cure, and now a testing ground for sophisticated therapies. But 60 years after the start of NBS, over half of the world's newborns are not being screened for PKU and this is a moral failure that needs to be addressed urgently. Dietary management and nutritional supplementation will remain important factors for long-term outcomes, and should be maintained as a priority for clinicians. Patients should have a healthy sense of optimism because although therapeutic options are increasing, they must be actively involved in life-long metabolic management. It is critical that researchers and policy makers move quickly to make promising therapies available as treatments, close the global equity divide, and use implementation science to support their implementation. There are currently tools in place to eliminate preventable disability in PKU; what we need to do now is ensure they are accessible everywhere. PKU is no longer an incurable disease. It is a disorder for which treatment is not yet available to all those who need it. This inequity is the challenge of the next ten years of PKU care.

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