

## 5. Current and Promising PKU Therapies and Assessments

### Summary

- The challenge of sticking to the restricted diet is a major reason why scientists and researchers are looking for alternative and/or supporting PKU therapies to the Phe-restricted diet. The goals of these therapies range from improving the taste and variety of low-Phe foods in an effort to improve adherence, to providing a cure for PKU so that diet restrictions would no longer be required. They can be categorized into one of 3 categories; 1) Food and Drug Administration (FDA)-approved drugs that have gone through rigorous testing standards for safety and efficacy; 2) medical foods (which do not require FDA approval); and 3) experimental gene replacement and enzyme substitution therapies that have yet to be approved for use.
  - FDA-approved drugs for PKU
    - **Sapropterin therapy (BH<sub>4</sub>; tetrahydrobiopterin; sapropterin; Kuvan<sup>®</sup>):** Studies have shown that taking daily pills of sapropterin lower and stabilize blood Phe level in some people with PKU. Sapropterin is available by prescription and is meant as an additional therapy to the low-Phe diet. To determine if sapropterin therapy will work, the physician puts the patient on the drug for a trial period and evaluates its effectiveness.
  - Medical foods
    - **Large neutral amino acid (LNAA) therapy (PreKUnil, NeoPhe, PheBLOC):** LNAA therapy aims to decrease the amount of Phe entering the circulation and the brain. Several formulations of LNAA are commercially available. In theory, LNAA therapy might be useful for all people with PKU, but it is only recommended for older teens and adults due to its unknown safety and effectiveness for younger PKU patients.
    - **Glycomacropeptide (GMP):** GMP is a protein derived from goat milk during cheese making that is almost free of Phe. According to those surveyed, it has a better taste than current protein substitutes. Experts believe if more and better-tasting low-Phe protein options become available, patients with PKU are more likely to adhere to the low-Phe diet. Some GMP-containing products are already on the market for PKU, such as Bettermilk<sup>™</sup> with GMP. Experts feel that many more GMP-containing products will be available for PKU in the near future.
  - Not yet approved experimental gene replacement and enzyme substitution therapies
    - **Enzyme substitution therapy (PEG-PAL):** Enzyme substitution therapy substitutes the activity of an enzyme for the deficient PAH enzyme in PKU. The enzyme substitution allows Phe to be broken down, thereby decreasing blood Phe levels. Results of a Phase 1 human clinical trial showed substantial blood Phe reductions with no reported serious safety concerns. Phase 2 studies with a larger population of PKU patients receiving varying doses of PEG-PAL are currently underway.
    - **Hepatocyte transplantation:** PAH, the defective enzyme in PKU, resides in liver cells (hepatocytes). A promising line of research involves replacing some of the defective liver cells with liver cells that have normal PAH activity, causing Phe levels to drop and become normal.
    - **Gene therapy:** Gene therapy would introduce a functional and stable PAH gene into PKU individuals to supplement or replace the defective PAH gene, thereby

providing a cure for PKU. However, the technology required is still experimental and safety issues are substantial. Several laboratories have achieved varying degrees of success in correcting PAH deficiency in PKU mouse models using gene therapy, but there are no existing human trials.

- Psychological issues have been under-diagnosed or insufficiently treated in many metabolic clinics. In addition, patients have limited access to psychologists familiar with metabolic disorders. It is a goal of PKU health practitioners to be able to provide an “early warning” system that would routinely assess psychological and emotional health in PKU patients. Once detected, appropriate and timely therapy can be provided. Experts envision a uniform and routine set of psychological assessments administered at metabolic clinics. This would allow clinics to provide routine and reliable screenings for psychological and emotional problems in people with PKU of all ages.
  - Results from a recent study using this model showed that 29% of patients screened positive for psychiatric distress. More adults than children tested positive (43% vs.17%). In addition, patients who screened positive had significantly higher blood Phe levels.

Newborn screening for **phenylketonuria** (PKU) and the introduction of a **phenylalanine** (Phe)-restricted diet for infants diagnosed with PKU prevent the most serious consequences of untreated PKU. This PKU management strategy is nearly a half century old and is still considered the standard for care of PKU. It is hailed as a success story.

However, cognitive and social-emotional problems occur more commonly among people with PKU than in the general population, even in early-and-continuously-treated PKU individuals. For this reason, researchers have continued to:

- examine best practices for the early identification of cognitive and social-emotional problems in individuals with PKU so that appropriate and timely therapy can be provided
- look for supplemental or alternative PKU therapies to the Phe-restricted diet in hopes of reducing the risk of cognitive and social-emotional problems

It is known that it can be hard for people with PKU to adhere to the Phe-restricted diet. A recent study examined blood Phe levels of 1,921 patients across 10 European centers and found that all age groups had a large number of blood Phe sample readings above recommended levels: 12% of patients less than 1 year old, 26% of patients 1–10 years old, 11% of patients 11–16 years old, and 35% of patients older than 16 years of age.<sup>34</sup>

The challenge of sticking to the restricted diet is another major reason why scientists and researchers are looking for alternative and/or supporting PKU therapies to the Phe-restricted diet. Several of these therapies are described below in “Supplemental or alternative PKU therapies to the low-Phe diet.” The goals of these therapies range from improving the taste and variety of low-Phe foods in an effort to improve adherence, to providing a cure for PKU so that diet restrictions would no longer be required.

### Uniform Assessment Method to identify cognitive and social-emotional problems in people with PKU<sup>16,35</sup>

Historically, cognitive and social-emotional problems have been under-diagnosed or insufficiently treated in many metabolic clinics.<sup>16</sup> In addition, patients have limited access to psychologists familiar with metabolic disorders. A group of 10 psychologists and a psychiatrist in the United States with expertise in PKU recently addressed this shortcoming in routine PKU management and have offered a solution.

The solution is for all metabolic clinics to adopt a uniform set of psychological assessments and tests that could be administered by non-psychologists as well as by psychologists. This Uniform Assessment Method would allow clinics to provide routine and reliable screenings for cognitive and social-emotional problems in people with PKU of all ages. The concept is to use the information obtained from each individual's assessments to tailor treatment based on blood Phe measurements and to provide psychological intervention if required.

The group realizes that not all people with PKU are the same. For example, two people with PKU can have the exact same blood Phe levels in the recommended range for their age, but one of them can be more sensitive to the effects of Phe and suffer mild cognitive impairments. Without routine assessment of their cognitive and social-emotional function, this individual would not get the psychological help needed. Nor would the clinician be prompted to try to reduce this individual's blood Phe levels in an attempt to manage the cognitive symptoms.

A non-psychologist or a psychologist can administer the Uniform Assessment Method for PKU (Table 3) every time a PKU patient visits a metabolic clinic to assess changes in function that may be related to treatment strategies or Phe levels. Routine assessment will also allow clinicians to detect modest changes in cognitive and/or social-emotional function in each individual over time, so that potential issues can be “nipped in the bud.” Table 3 describes the age-appropriate assessments that are suggested to be included in the Uniform Assessment Method.

**Table 3: Uniform assessment method for PKU**

Psychological domain	Infants (0–2 years)	Children (3–17 years)	Adults (≥18 years)
Adaptive behavior	ABAS-II	—	—
Executive functioning	—	BRIEF-P or BRIEF	BRIEF-A
Social/emotional functioning	—	BASC-II	BAI, BDI-II

ABAS- II: Adaptive Behavior Assessment System – Second Edition; BRIEF: Behavior Rating Inventory of Executive Function; BRIEF-P: Behavior Rating Inventory of Executive Function Preschool Version; BRIEF-A: Behavior Rating Inventory of Executive Function Adult Version; BASC-II: Behavior

Assessment System for Children – Second Edition; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory – Second Edition.

- **Adaptive Behavior Assessment System – Second Edition (ABAS-II):** The ABAS-II is the only assessment the group selected for infants 0–2 years of age. There are 193 items that can be completed in about 20 minutes.
- **Behavior Assessment System for Children – Second Edition (BASC-II):** The BASC-II is designed to evaluate the behavior and self-perceptions of children and young adults aged 2–25 years. Parents and teachers can use a self-reporting form (the Parent Rating Scale), which contains 134 items for the Preschool Form (ages 2–5 years), 160 items for the Child Form (ages 6–11 years), and 150 items for the Adolescent Form (ages 12–21). The BASC-II can be completed in about 20 minutes. The Uniform Assessment Method recommends using this assessment for children 2–17 years of age.
- **Behavior Rating Inventory of Executive Function (BRIEF):** The BRIEF-P (BRIEF Preschool Version) is designed for children aged 2 years to 5 years and 11 months, and it is completed by parents/guardians or teachers. This questionnaire contains 63 items. The BRIEF for School-Aged Children is for children aged 5–18 years and contains 86 items. The BRIEF-A (BRIEF Adult Version) assesses patients aged 18–90 years with a minimum fifth-grade reading level and contains 75 items. BRIEF-P, BRIEF, or BRIEF-A can be completed in 10–15 minutes. The Uniform Assessment Method recommends using the BRIEF-P or BRIEF for children 3–17 years, and the BRIEF-A for adults 18 years of age or older.
- **Beck Anxiety Inventory (BAI):** The BAI is a 21-item scale measuring anxiety in adults and adolescents and requires 5–10 minutes to complete.
- **Beck Depression Inventory – Second Edition (BDI-II):** The BDI-II is a 21-item self-report measure of depression in adults and adolescents aged 13 years and older. This questionnaire requires 5–10 minutes to complete.

Preliminary results of using an assessment method similar, but not identical, to the one described above were recently made available from a clinical study.<sup>35</sup> This study involved 89 patients (42 adults and 47 children) over 5 years of age with a confirmed PKU diagnosis. These patients were screened for psychiatric distress and cognitive impairment as part of their standard of care over a 10-month period. Standardized self- and parent-reported questionnaires were used as screening tools, including a Psychiatric Distress Assessment for patients 5–17 years of age (Pediatric Symptom Checklist) and adults (Brief Symptom Inventory), and a Cognitive Impairment Assessment (child or adult versions of the BRIEF).

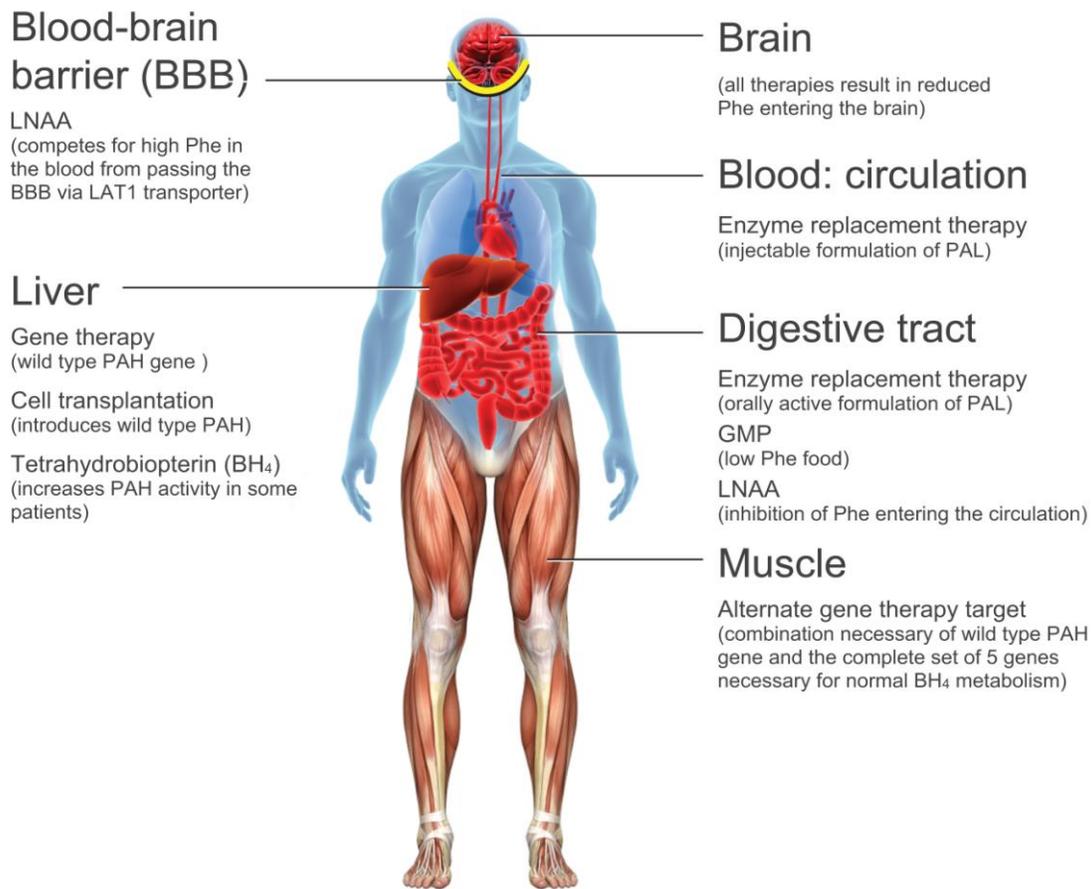
Results from this study show that 29% of patients screened positive for psychiatric distress (26 out of 89 patients). More adults than children tested positive (43% vs.17%). In addition, patients who screened positive had significantly higher mean blood Phe levels ( $749 \pm 575 \mu\text{mol/L}$ , or  $12.37 \pm 9.5 \text{ mg/dL}$ ) than did those who screened negative ( $468 \pm 351 \mu\text{mol/L}$ , or  $7.73 \pm 5.8 \text{ mg/dL}$ ).

The results of the study prompted one of the investigators of this study, the prominent PKU expert Dr. Barbara Burton, MD, Professor of Pediatrics, Northwestern University Feinberg School of Medicine, and Director, PKU Clinic, Children's Memorial Hospital, to state, *"The interim results [from this study] are important to clinicians, patients and patients' families because neuropsychiatric impairment can have a devastating impact on the success of overall PKU treatment; yet, mental health screening is not a part of standard PKU treatment practice... By adding simple questionnaires to a routine PKU clinic visit, treating clinicians have the potential to assess psychiatric symptoms and neurocognitive function and, if appropriate, refer patients to a mental health professional. This new standard of care could improve not only the care and quality of life of patients but also adherence to a PKU treatment plan."*<sup>35</sup>

#### **Supplemental or alternative PKU therapies to the low-Phe diet<sup>4</sup>**

- Evidence has shown that dietary PKU therapy alone is not enough to help individuals with PKU have normal cognitive and social-emotional functioning. In addition, it's not easy for many patients to stick with the PKU the diet. Because of these facts, researchers have investigated additional therapeutic possibilities for the treatment of individuals with PKU. During the past few years, several ideas for new treatment strategies have emerged. Experts in the field recently reviewed and summarized these treatment strategies and potential cures based on where in the body they would act (see Figure 7). They can be categorized into one of three categories: 1) FDA-approved drugs that have gone through rigorous testing standards for safety and efficacy; 2) medical foods (which do not require FDA approval); and 3) experimental gene replacement and enzyme substitution therapies that have yet to be approved for use.

**Figure 7: Treatment options for PKU**



- Medical foods, which are not subjected to rigorous clinical safety and efficacy standards, do not require FDA approval.
  - **Glycomacropeptide (GMP)**: GMP is a **protein** derived from goat milk during cheese making that is almost free of Phe (2.5–5 mg of Phe per gram of GMP protein compared to 50 mg of Phe per gram of natural protein). It has a better taste than current protein substitutes. Although GMP has to be supplemented with other amino acids (**tyrosine** and **tryptophan**), research has shown that it may be a good palatable addition to the current low-Phe diet treatment.

Experts believe if more and better-tasting low-Phe protein options become available, patients with PKU are more likely to adhere to the low-Phe diet. Some GMP-containing products are already on the market for PKU, such as Bettermilk™ with GMP.<sup>36</sup> Experts feel that many more GMP-containing products will be available for PKU in the near future.

- **Large neutral amino acid (LNAA) therapy** (PreKUnil, NeoPhe, PheBLOC): LNAA therapy aims to decrease the amount of Phe entering

the circulation and the brain. LNAs and Phe share a common transport mechanism. The theory is that high levels of these other amino acids compete with the high Phe levels for “seats on the bus” (the transporter). This competition for the transporter reduces the amount of Phe that gets transported across the gut into the blood circulation and across the **blood-brain barrier** (BBB) into the brain. Several formulations of LNA are commercially available. In theory, LNA therapy might be useful for all people with PKU, but it is only recommended for older teens and adults due to its unknown safety and effectiveness for younger PKU patients.

- Drugs that are clinically proven and FDA-approved for safety and efficacy.
  - **Sapropterin therapy** (BH<sub>4</sub>; tetrahydrobiopterin; sapropterin; Kuvan<sup>®</sup>): Sapropterin is a man-made form of the **cofactor** BH<sub>4</sub>, which is required for **phenylalanine hydroxylase** (PAH) activity. PAH is the **enzyme** in PKU that does not work properly, causing high blood Phe levels. Studies have shown that taking daily pills of sapropterin can restore some of the lost PAH activity in PKU and lead to lower and more stable blood Phe levels. Studies have also shown that sapropterin therapy will not work for everyone with PKU. Sapropterin is available by prescription and is meant as an additional therapy to the low-Phe diet. To determine if sapropterin therapy will work, the physician puts the patient on the drug for a trial period and evaluates its effectiveness.
- Experimental gene replacement and enzyme substitution therapies, which are not yet approved.
  - **Enzyme substitution therapy** (PEG-PAL): **Enzyme substitution therapy** substitutes the activity of the deficient PAH enzyme in PKU with another enzyme. The enzyme substitution allows Phe to be broken down, thereby decreasing blood Phe levels. Phenylalanine ammonia lyase (PAL) is the enzyme substitute joined with polyethylene glycol (PEG) for an increased therapeutic affect. PEG-PAL converts Phe into transcinnamic acid (TCA) and ammonia, which break down into non-toxic compounds that are easily handled by the body.

Investigators are looking into PEG-PAL as a therapy injected under the skin like insulin (where the drug is directly introduced into the blood stream) for PKU because PAL, a protein, is broken down as food when taken by mouth. Successful preclinical studies in PKU mice have been completed, and subsequent trials in humans receiving PEG-PAL as an injection are ongoing. Results of a Phase 1 human clinical trial showed substantial blood Phe reductions with no reported serious safety concerns.<sup>37</sup> Phase 2 studies with a larger population of PKU patients receiving varying doses of PEG-PAL are currently underway.<sup>38</sup>

- **Hepatocyte transplantation:**<sup>39</sup> PAH, the defective enzyme in PKU, resides in liver cells (**hepatocytes**). A promising line of research involves

replacing some of the defective liver cells with liver cells that have normal PAH activity, causing Phe levels to drop and become normal. Liver transplantation is not an option for an otherwise healthy PKU individual because the low-Phe diet corrects for the most severe symptoms of PKU (i.e., PKU is not life-threatening, and liver transplantation is reserved for life-threatening situations). Because of this, **hepatocyte** (liver cell) transplantation in PKU is under investigation.

This technique involves removing part of the PKU liver and replenishing (“seeding” it) with hepatocytes containing a fully functional PAH gene. These hepatocytes with normal PAH activity can come from another person (donor), or they might come from the original PKU individual and be modified in the lab to have normal PAH activity. There is a catch that is still being worked out: the donor cells need to grow better than your own liver cells.

Hepatocyte transplantation has been attempted in humans for certain diseases with encouraging results. However, studies involving hepatocyte transplantation in PKU have only been done with animals so far. These animal studies suggest that even if just enough hepatocytes were transplanted so that 10–20% of the liver cells contained functional PAH, blood Phe levels would likely be completely corrected in PKU individuals. Researchers are currently investigating clinically acceptable methods of obtaining these transplantation levels in humans.<sup>39</sup> Other researchers are looking at using stem cells (cells that can turn into many other cell types) for transplantation instead of directly using hepatocyte cells. Again, stem cell transplantation in PKU has so far only been done with animals, but both cell transplantation techniques (stem and hepatocyte) hold promise.

- **Gene therapy:** **Gene therapy** would introduce a functional and stable PAH gene into PKU individuals to supplement or replace the defective PAH gene, thereby providing a cure for PKU. However, the technology required is still experimental and safety issues are substantial. Several laboratories have achieved varying degrees of success in correcting PAH deficiency in PKU mouse models using gene therapy, but there are no existing human trials.