



National  
**PKU**  
Alliance



# PKU and the Brain: New Research and Therapies

A CURRENT REVIEW OF PUBLISHED  
CLINICAL RESEARCH



## Preface

Current medical evidence has led experts on PKU to suspect that current therapy for PKU may leave individuals with an increased risk for subtle deficits in brain function. To address this, a group of PKU experts recently (2010) published a 107-page supplement on current topics surrounding this issue to raise awareness in the PKU scientific community. This supplement, published in the peer-reviewed journal *Molecular Genetics and Metabolism*, is the first collective work on the psychological and neuropathological perspective in PKU. It involved contributions from 50 PKU experts including psychologists, psychiatrists, geneticists, dieticians, neuroscientists, and biologists from countries all over the world. We have taken and summarized key points from this expert supplement that we feel would be of interest to people who have PKU and their family members. In addition, we have included newer relevant research that has become publicly available since the supplement was published in early 2010. The key points are summarized into the following sections:

1. [Introduction: PKU Basics](#)
2. [Physical Evidence for Altered Brain Function in PKU](#)
3. [Cognitive, Psychological and Behavioural Assessment Based Evidence for Altered Brain Function in PKU](#)
4. [Theories for Elevated Phe Levels Altering Brain Function in PKU](#)
5. [Current and Promising PKU Therapies and Assessments](#)

We have also included [References](#) and a [Glossary of Terms](#).

## Acknowledgements

Written by: MediResource, Inc., Toronto, Ontario

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## 1. Introduction: PKU Basics

### Summary

- Routine high blood Phe levels during childhood can cause severe problems in the way the brain develops.
  - Starting a Phe-restricted diet soon after birth keeps blood Phe levels within a safe range.
  - Used in this way, a Phe-restricted diet is a proven powerful therapy that dramatically improves outcomes for people with PKU by preventing severe brain damage. However, a Phe-restricted diet is not a cure for PKU.
- Did you know that despite treatment with the Phe-restricted PKU diet, scientists and physicians are still finding evidence for subtle changes in the brains of some PKU people in all age groups studied?
  - This may be a result of the fact that throughout your entire life, even if you maintain a Phe-restricted diet, your blood Phe levels will still be higher than those of someone without PKU. Additionally, new evidence now shows that even short-term spikes in blood Phe levels can cause some IQ changes. This suggests that stable blood Phe levels are as important as low blood Phe levels.
  - Scientists are looking into whether these higher Phe levels may cause subtle changes in the brain that can affect behavior, mood and thinking, even if the Phe levels are in the target range.

### What is PKU?

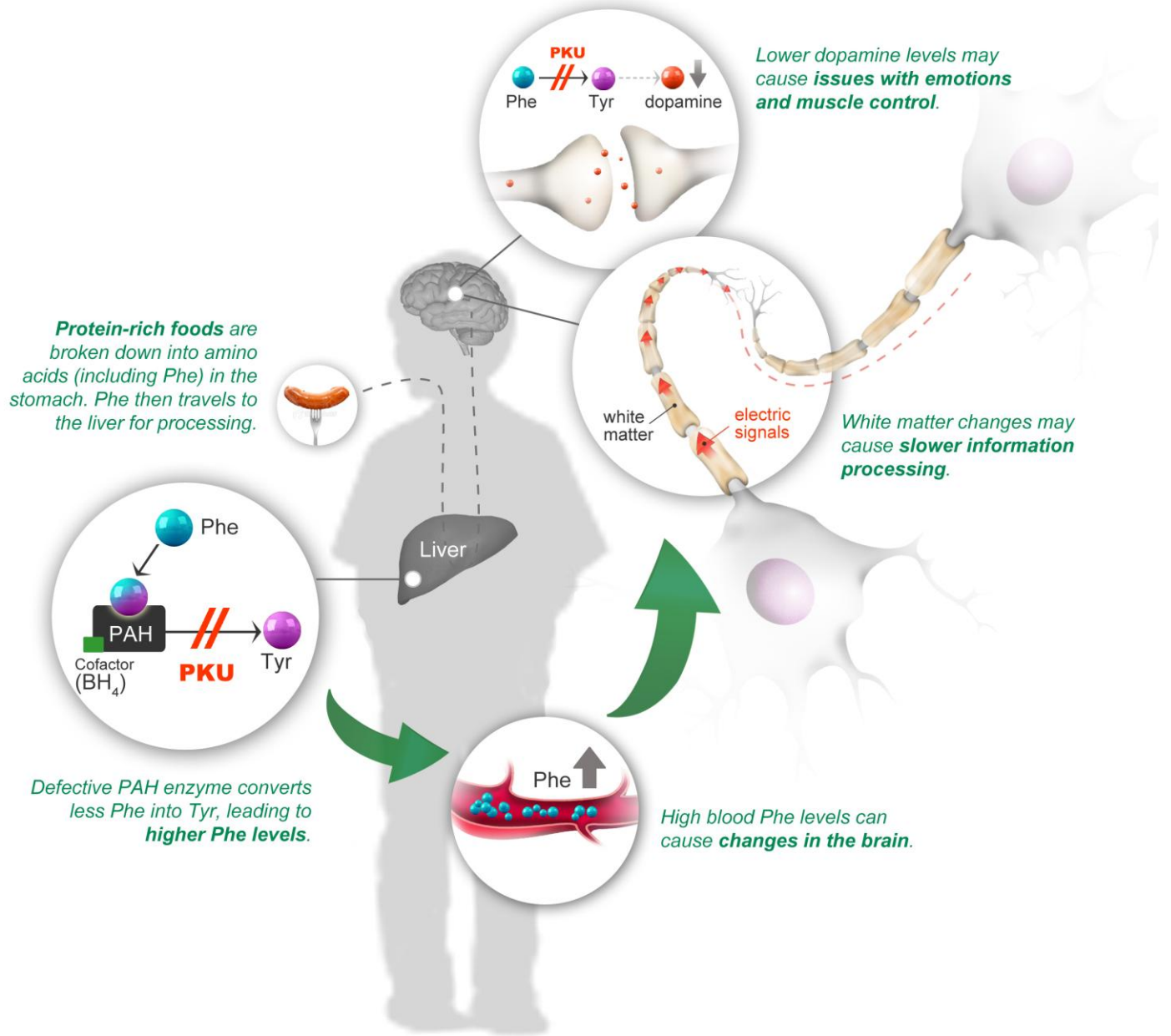
**PKU stands for phenylketonuria**, a rare disease where your body can't process an **amino acid** called **phenylalanine** (Phe for short). Phe mainly comes from **protein-rich** foods such as meat, eggs, nuts, beans, milk and cheese. Here is some basic information about proteins and amino acids:

- Protein is made of long chains of amino acids. There are 20 different amino acids found in protein. These amino acids can combine together in thousands of different ways to form different types of protein. An analogy is to think of each amino acid as a pearl and a protein as a string of pearls.
- When you eat protein, your body breaks it down into amino acids, which it then “recycles” to build its own proteins. Proteins help maintain the cells in your body. Your body can make 12 of the 20 amino acids by itself. The other 8 are called **essential amino acids** because your body cannot make them and must get them from food.
- Phenylalanine is one of the essential amino acids. The liver uses an **enzyme** called **phenylalanine hydroxylase** (PAH) together with a helper known as a **cofactor** (BH<sub>4</sub>) to change some of the Phe to a non-essential amino acid called **tyrosine** (Tyr). Tyr is not only used to build your own proteins but is also used to make a brain **neurotransmitter** (chemical messenger) called **dopamine**.

Having **PKU** means your body does not have enough **PAH** enzyme and cannot convert the same amount of Phe into Tyr that someone without PKU is able to. This means that

your Phe levels build up to higher levels compared to unaffected people when you eat the same amount of protein as they do. It also means that Tyr becomes an essential amino acid because your body can't make Tyr from Phe due to the defect in your PAH enzyme.

**Figure 1: How PKU can affect the brain**



## How is PKU detected and treated?

Every newborn baby is tested for PKU by taking a blood sample and measuring the amount of Phe.

- Normal levels of blood Phe average about 1 mg/dL (milligram per deciliter), with an upper normal range of 2 mg/dL.
- Blood Phe levels in PKU range from 6 to 80 times as much as the normal average of 1 mg/dL (6–80 mg/dL).

If your baby’s blood Phe is in the PKU range they will be retested for confirmation and then immediately put on the “gold standard” treatment for PKU: a life-long Phe-restricted diet.

## What are the target Phe levels?

The younger you are, the lower the target. This is because young, rapidly developing brains are most sensitive to the effects of Phe.

In 2000, the National Institutes of Health (NIH), on the basis of data available at the time, recommended blood Phe targets for people with PKU to allow for the development of normal-range intelligence (see Table 1).<sup>1</sup> Since that time, new evidence has become available on subtle risks to brain health and intellectual function still faced by people with PKU who adhere to the 2000 recommended targets.

As a result of this new evidence, the NIH has reconvened (and is still convening) to address the possibility of releasing new evidence-based blood Phe targets. For example, many US clinics believe the upper range of blood Phe levels for adults with PKU should be considerably less than the 15 mg/dL threshold reported in the 2001 NIH guidelines.

**Table 1: 2000 Published NIH Blood Phe Targets**

| Age                                | Blood Phe target  |
|------------------------------------|---|
| Birth to less than 12 years of age | 2–6 mg/dL (2–6 times the normal average for unaffected children)  |
| 12 to less than 18 years of age    | 2–10 mg/dL (2–10 times the normal average for unaffected adolescents)   |
| Adults* (18 years of age or older) | 2–15 mg/dL* (2–15 times the normal average for unaffected adults)   |
| Expectant mothers with PKU         | It is recommended that Phe levels below 6 mg/dL be achieved at least 3 months before conception; levels should be kept at 2–6 mg/dL during pregnancy. |

\* Many US clinics believe this older recommendation to be outdated and target a range considerably less for adults living with PKU.

The general PKU treatment concept is “**the lower the Phe, the better.**” However, it is important to understand that blood Phe targets in PKU should never go below 2 mg/dL

using current dietary therapy. The reason being is the PKU individual becomes at risk for protein catabolism, which means they may start breaking down their own bodily proteins.

### What happens if PKU is not treated?

Without early and continuous treatment to control blood Phe levels, sustained high levels of Phe can cause severe mental retardation. Mental retardation can be prevented by controlling blood Phe through diet, starting in the weeks after birth and continuing throughout childhood.

Even though the risk for developing mental retardation caused by high Phe levels goes down from about 12 years of age onward, experts strongly recommend controlling blood Phe levels for the rest of a person's life – there are increasing amounts of scientific evidence suggesting that sustained high levels of Phe during adolescence and adulthood can still negatively impact intelligence and normal brain functioning.<sup>2</sup>

There is also new evidence suggesting that short-term spikes in blood Phe levels caused by “diet holidays,” in otherwise well-controlled PKU, can result in long-term impairment of mental function as measured by IQ.<sup>3</sup> Thus, the concept of “**the lower the Phe levels the better**” should include the concept of **stable and low blood Phe levels for a lifetime**.

Expectant mothers with PKU have an additional special situation. High Phe levels during pregnancy can cross into the placenta and cause high Phe levels in the developing child, even if the child does not have PKU. Experts recommend that woman with PKU who are capable of becoming pregnant should carefully control their blood Phe levels before and during pregnancy (see Table 1). Otherwise, high uncontrolled Phe levels during pregnancy can cause what is known as **maternal PKU syndrome** in the child and lead to a high rate of birth defects, including ones affecting the brain and heart.<sup>1</sup>

Although a Phe-restricted diet is a proven powerful therapy that leads to dramatic improvements in the outcomes of PKU individuals, the unfortunate truth is that it requires a compromise. On one hand, you need to keep the amount of Phe low to prevent a toxic build-up that can lead to mental retardation when occurring in childhood and impaired brain functioning when occurring in adolescence and adulthood. But on the other hand, you need enough Phe and other amino acids to allow your body to make its own proteins. Because of this, a Phe-restricted PKU diet is rarely able to bring your Phe levels down to those of unaffected individuals. This may lead to problems:

- Scientists think having routine blood Phe levels above the normal range of unaffected individuals (more than 1 mg/dL, while remembering that diet treatment of PKU should never target below 2 mg/dL due to the risk of protein catabolism) may cause subtle changes in the brain that can affect behavior, mood and thinking.
- At higher blood levels, Phe reduces the transport of other amino acids into the brain, leading to lower amino acid levels in the brain. This is thought to interfere with the brain's ability to make proteins and neurotransmitters (chemical messengers).

Because of these problems, scientists are working hard to find new treatments such as **enzyme substitution** and **gene therapies** to do what diet therapy alone cannot routinely do: bring Phe levels down to those observed in unaffected individuals (1 mg/dL) while still promoting healthy normal body function (i.e. not increasing the risk of protein catabolism observed at less than 2 mg/dL in those treated by dietary therapy).<sup>4</sup> Although the “holy grail” of PKU therapy has not yet been discovered to return body function to normal, there are newer therapies available that can be used as “add-ons” to the low-Phe PKU diet to help reduce and stabilize the amount of Phe that gets into the brain.

They fall into 2 separate categories:

- **Sapropterin therapy:**<sup>4</sup> Sapropterin is a man-made form of the naturally-occurring cofactor BH<sub>4</sub> required for PAH activity (the enzyme in PKU that does not work properly). Studies have shown that daily ingestion (taking pills) of sapropterin can restore some of the lost activity of PAH in PKU and lead to lower and more stable blood Phe levels. Studies have also shown that sapropterin therapy will not work on everyone with PKU. To determine if sapropterin therapy will work for you, a trial period on the drug with evaluation by a physician is necessary. Sapropterin is a drug that has undergone rigorous clinical testing for efficacy in lowering blood Phe levels and safety over the long term and has been approved by the FDA (Food and Drug Administration) for use in PKU.
- **Large neutral amino acid (LNAA) therapy:**<sup>4</sup> LNAAs are considered “medical food.” Taking oral supplements of certain amino acids called large neutral amino acids (LNAAs) can lower the amount of Phe absorbed from food into the bloodstream, thereby lowering blood Phe levels. It is thought that decreased amounts of Phe in the brain are the result of having higher amounts of these amino acids in the bloodstream. The concept is that higher levels of these amino acids would slow Phe from entering the brain, as they share a common transporter (think seats on a bus: these amino acids take up seats that Phe would normally be sitting in as it waits to get into the brain). In theory, LNAA therapy might be useful for all people with PKU, but it is only recommended for older teens and adults due to the unknown safety and efficacy for younger PKU patients. It is important to remember that because LNAA is a medical food, it does not require approval by the FDA and does not go through the same rigorous safety and efficacy testing as a drug.

In support of the need for improved therapies in PKU, a recent review looked at the evidence of outcomes in diet-treated PKU in the period from 2000 to 2010 and found:<sup>2</sup>

- Of the 771 scientific papers published on PKU during that time period, 150 reported data on the outcomes of individuals with PKU who were treated with diet alone.
- Of these 150 scientific publications, the majority (92) of the research publications focused on cognitive brain functions/psychosocial outcomes and brain pathology, followed by growth/nutrition (34), maternal PKU (19), bone pathology (9), and overall quality of life (6). The following is a breakdown on how many of these publications reported suboptimal (poorer-than-desired) outcomes in diet-treated PKU:

- Cognitive brain function and psychosocial outcomes (60): 58 of the 60 research studies reported suboptimal outcomes. Altered brain pathology and brain chemistry (32): 30 of the 32 research studies reported suboptimal outcomes. Growth/nutrition (34): 29 of the 34 research studies reported suboptimal outcomes. Maternal PKU (19): All 19 of the research studies reported suboptimal outcomes.
- Bone pathology (9): All 9 of the research studies reported suboptimal outcomes.
- Overall quality of life (6): 4 of the 6 research studies reported suboptimal outcomes.

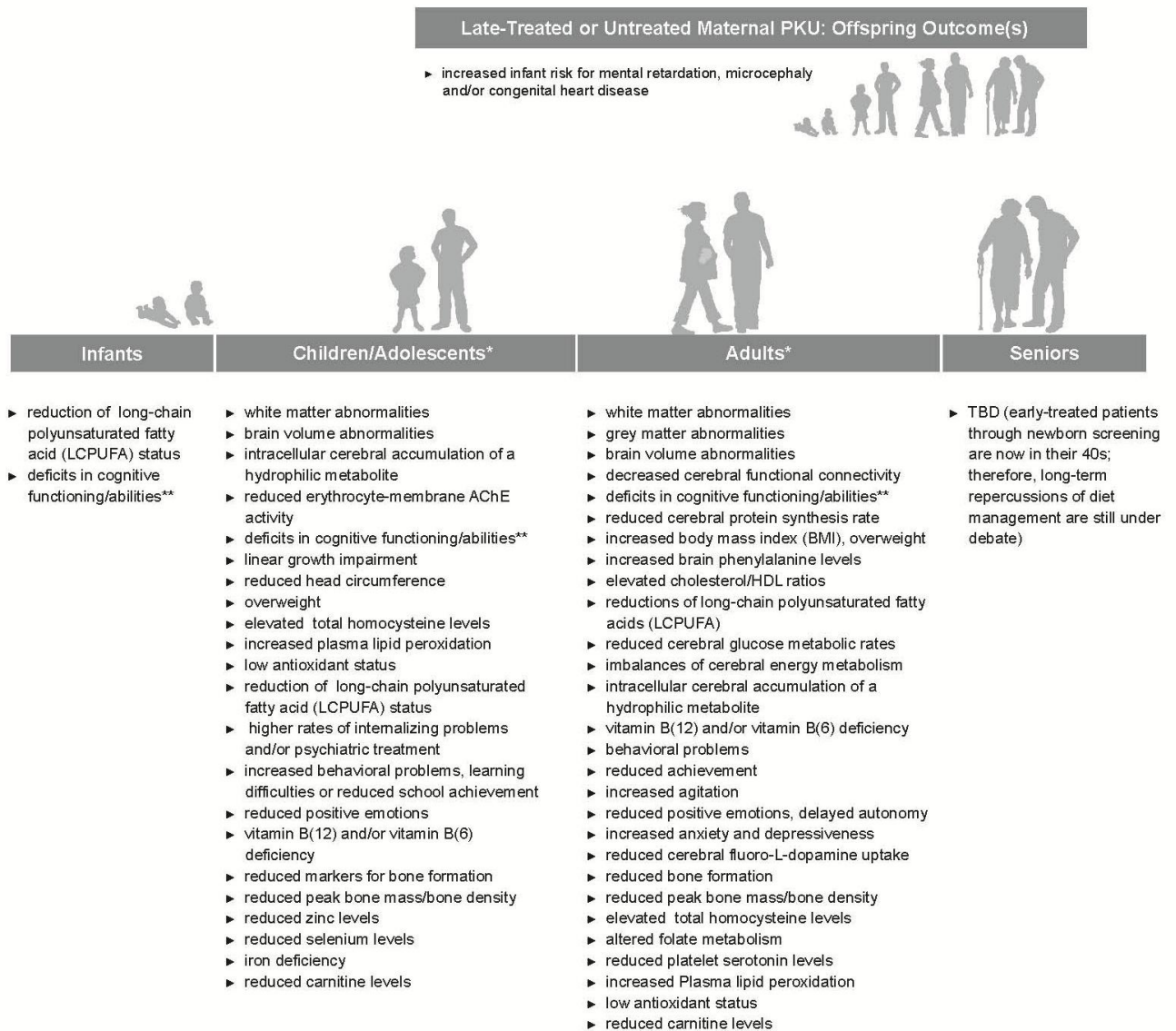
It is important to realize that the authors of this review stated several limitations in their interpretation; one that is of particular significance states:

*“The assignment of suboptimal outcomes to diet-alone therapy may be perceived as misleading as many suboptimal outcomes were related to higher blood Phe levels potentially indicating lack of dietary control in these patients. However, lack of adherence to the onerous regimen of the diet may also be a suboptimal outcome of diet-alone therapy: a sentiment echoed in the 2000 NIH guidance document recommending alternative therapies to the diet.*

*Additionally, the majority of the literature reports comparisons between PKU patients and healthy control subjects but not between PKU patients on- and off-diet; thus in many instances the distinction cannot be easily made as to whether suboptimal outcomes are due to the stress and burden of the disease or due to lack of metabolic control of the disease.”<sup>2</sup>*

In addition to the fact that, in many cases, suboptimal results may be linked to the patients’ failure to follow the diet properly, it is also important to realize that the negative effects are typically subtle. This means that diet-treated PKU individuals can grow up to be as successful as any non-PKU individuals as measured by intelligence, education, employment and the forming of relationships. The point researchers and health professionals want to make is that dietary treatment of PKU, while successful in many measures, still has room for improvement, as is indicated by the evidence of suboptimal outcomes in all age ranges (see Figure 2).

**Figure 2: Suboptimal outcomes exist in all age groups of diet-treated PKU\***



\* Includes early-treated PKU patients who may or may not be adhering to dietary treatment.

\*\* Measures of deficits in cognitive functioning/abilities in PKU were too many to list in entirety; examples include but are not limited to measures of IQ, executive functioning, information processing speed, visual evoked or event-related potentials, selective and sustained attention, flexible attention, inhibition, verbal memory, recognition memory, and/or expressive naming verbal fluency.

*\*Adapted from Figure 4 within [Enns et al 2010](#).*