



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

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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?

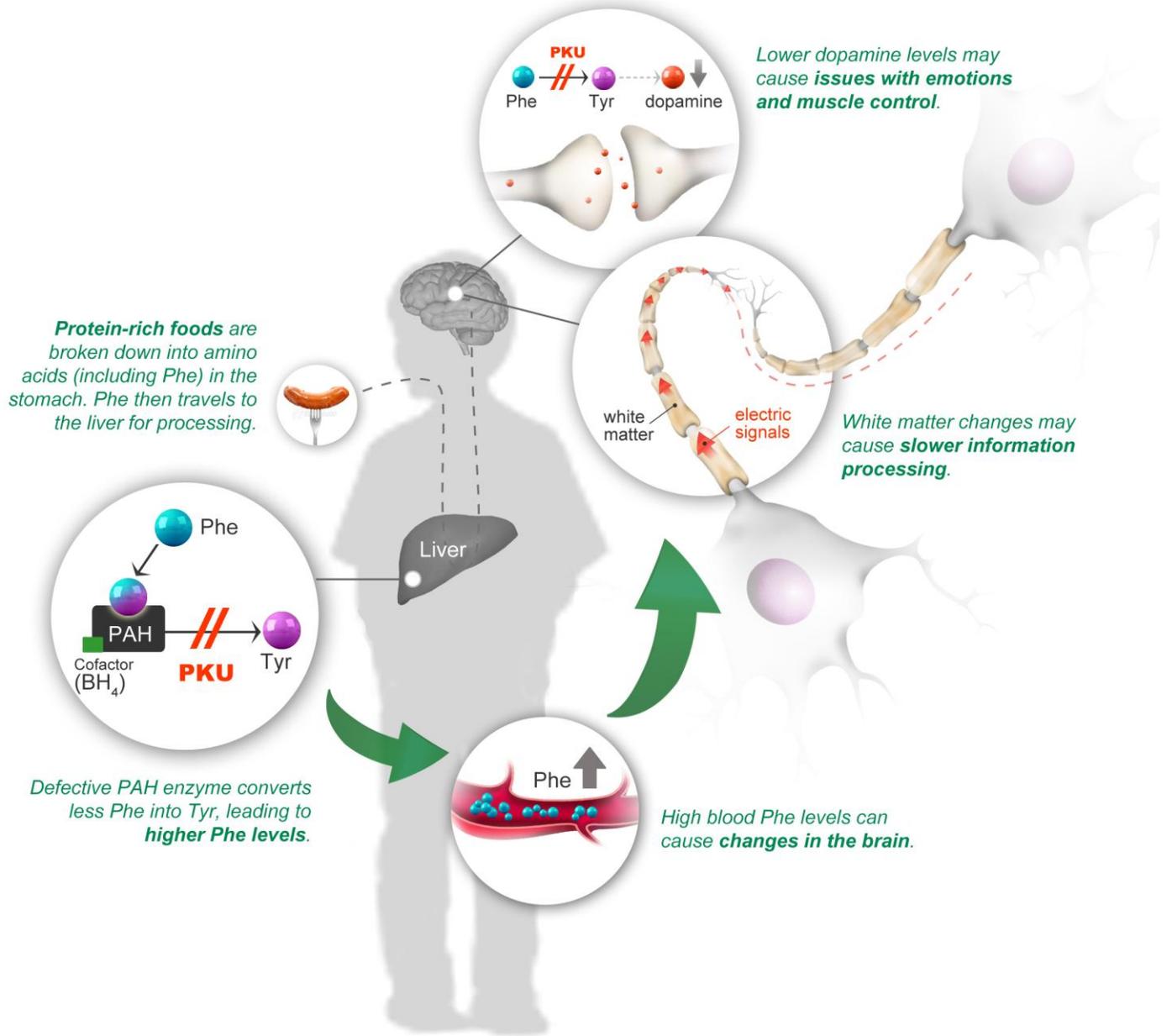
PKU stands for phenylketonuria, a rare disease where your body can't process an **amino acid** called **phenylalanine** (Phe for short). Phe mainly comes from **protein-rich** foods such as meat, eggs, nuts, beans, milk and cheese. Here is some basic information about proteins and amino acids:

- 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** (BH₄) 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).¹ 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.²

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.³ 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.¹

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).⁴ 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:**⁴ Sapropterin is a man-made form of the naturally-occurring cofactor BH₄ 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:**⁴ 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:²

- 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.

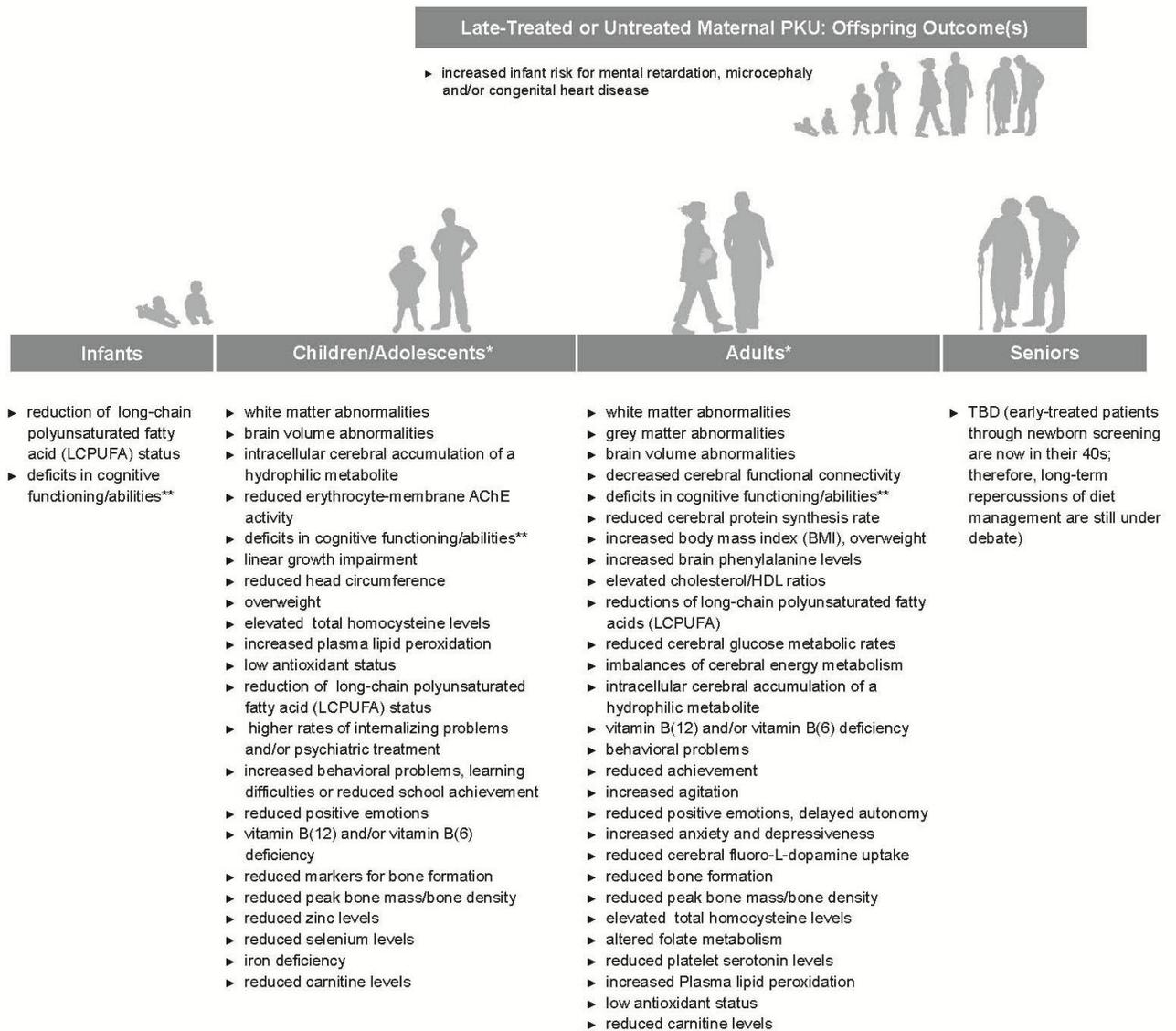
It is important to realize that the authors of this review stated several limitations in their interpretation; one that is of particular significance states:

“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.”²

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](#).*

2. Physical Evidence for Altered Brain Function in PKU

Summary

- Scientists are currently gathering physical evidence to determine whether the current standard therapy involving a Phe-restricted diet and meeting blood Phe targets can still lead to changes in the brain.
 - Some of the physical evidence scientists have gathered involves brain scans. So far, the evidence shows that a large percentage of people with PKU may have some visible brain abnormalities, even when on diet. There is a reasonable correlation between the amount of brain abnormalities and life time Phe levels, the higher the Phe levels the more brain abnormalities.
 - However, it's not yet clear what these changes mean in terms of brain function.
 - Some researchers think that these changes may cause problems in how fast you can process information.
 - However, less than half of the people who have displayed brain abnormalities show any impairment in mental abilities, and these impairments are subtle.
 - The bottom line is that much more research is needed to understand the nature and impact of these brain-scan visual abnormalities in diet-controlled PKU.
 - Another form of physical evidence found that people with PKU may have lower levels of certain brain chemicals called neurotransmitters.
 - **The defective enzyme in PKU, PAH, has the job of changing some of the Phe you eat into a different amino acid called tyrosine (Tyr). Tyr is used to make a brain neurotransmitter (messenger) chemical called dopamine. Evidence suggests that changes in PAH function in PKU can cause lower amounts of dopamine in the brain.**
 - Some symptoms of low dopamine include drastic mood swings, difficulty paying attention and sleep disturbances.
 - Bear in mind that it is hard to do these studies, so there aren't that many documented cases. More physical evidence is needed to draw any conclusions. The jury is still out, but the evidence is piling up.

Altered brain white matter: Sophisticated imaging technology such as **magnetic resonance imaging (MRI)** has allowed scientists to take a peek at the brains of PKU patients. A recent review of MRI evidence in PKU has shown that 93% of the 312 brains of PKU patients investigated by MRI, 107 of which were still on a PKU diet*, showed abnormal **white matter**.⁵ The white matter is mostly made up nerve fibers in your brain that send electrical signals to process information. It is called white matter because it appears white, mainly because of a white-colored insulating layer on your nerve fibers called the **myelin sheath**.

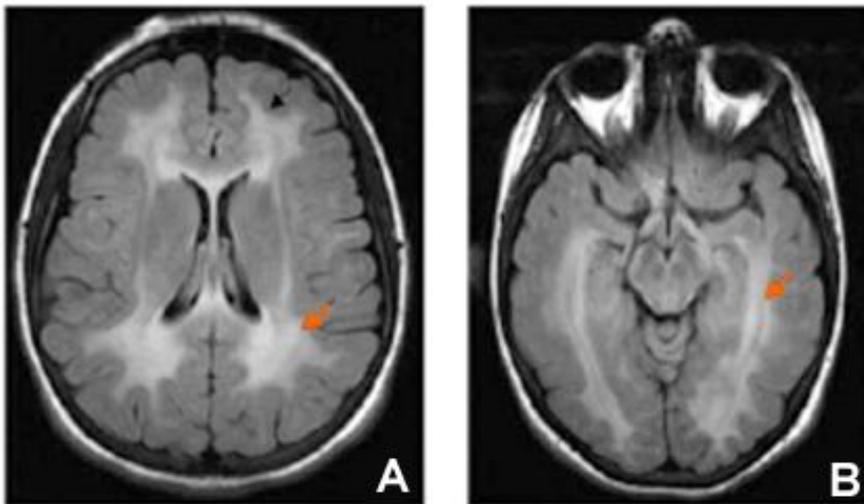
It's not yet clear what these changes mean in terms of brain function, but changes in white matter may cause information to be sent more slowly, causing thinking problems and slower information processing. It is worth mentioning that even though nearly all of the PKU patients studied thus far have been seen to have white matter abnormalities, only 38% of those studied showed any impairment of mental abilities, most of which were

subtle in nature.⁵ Thus, much more research is required to understand the nature and impact of white matter pathology in PKU.

What is sure is that there is a reasonable association between the lifetime blood Phe levels and the amount of white matter abnormalities observed (the higher the Phe, the more abnormalities observed).⁵ There is also preliminary evidence suggesting that a certain degree of white matter abnormality can be reversed if a stricter control of blood Phe levels is obtained for a prolonged period of time.⁵

Here is an example of an MRI showing white matter abnormalities in a 15-year-old girl early-treated and still on diet* who, despite having white matter abnormalities, presented normal mental and neurological development:⁶

*Authors of the publications only stated that the subjects were on a PKU diet; they did not report their lifetime blood Phe averages. It is assumed that these individuals were in metabolic control of their PKU.



Orange arrows show the “lighter area” of white matter abnormality in a diet-treated 15-year-old girl with PKU and normal mental and neurological development.⁶

A) represents white matter abnormalities in the frontal lobe of the brain.

B) represents white matter abnormalities in the temporal lobe of the brain.

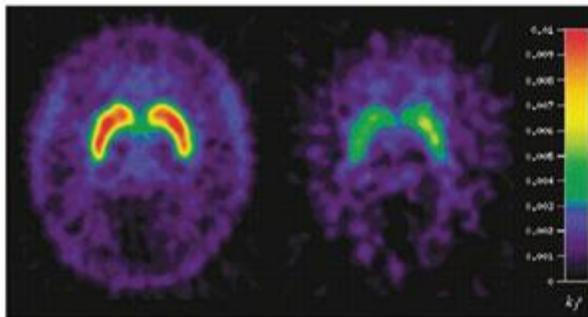
Reduced levels of brain neurotransmitters: Scientific evidence suggests that higher-than-normal blood **phenylalanine** (Phe) levels can reduce neurotransmitter levels in the brain of a person with PKU.⁷ The defective enzyme in PKU, **phenylalanine hydroxylase** (PAH), has the job of changing some of the Phe you eat into a different amino acid called **tyrosine** (Tyr). Tyr is used to make a brain neurotransmitter (messenger) chemical called **dopamine**. Evidence suggests that changes in PAH function in PKU can cause lower amounts of dopamine in the brain.

Decreased dopamine levels may cause problems with motor function (controlling your muscles) and emotional state. Symptoms of low dopamine include drastic mood swings,

decreased libido (sex drive), difficulty paying attention and sleep disturbances. Illnesses such as Parkinson's disease and attention deficit/hyperactivity disorder (ADHD) have been linked to low dopamine levels in the general population. Although there is no evidence suggesting a higher incidence of Parkinson's disease in the PKU population, there is evidence of a higher frequency of ADHD-like symptoms in PKU.⁸

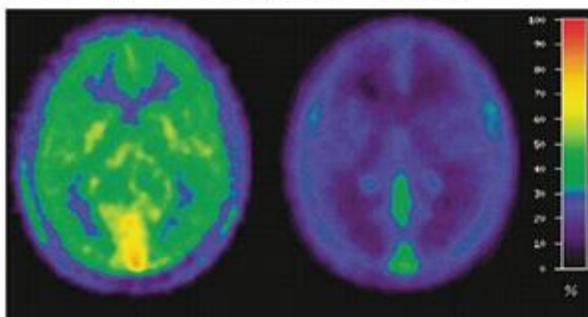
The following image shows that FDOPA (a fluorescent version of a chemical that is turned into dopamine in the brain) is not transported into or used by the brain of a person with PKU in the same way as by unaffected individuals. The fluorescent version was used so that it could easily be seen in the images.⁹ The image of the PKU brain is an overall average obtained from imaging 7 patients with PKU (2 males, 5 females; age 21 to 27 years) selected to have no impairment in intellectual or neurologic function. The PKU patients imaged had adhered to a Phe-restricted diet until the age of 15 to 18 years, then abandoned the diet afterwards. The normal control group image was obtained from the average of 7 age-matched, healthy male volunteers (age 23 to 34 years).

FDOPA levels in the brain



In people with PKU, less FDOPA is taken up into the brain compared with unaffected people.

Use of FDOPA in the brain



Unaffected people

PKU

In people with PKU, less FDOPA is used in the brain compared with unaffected people.

3. Cognitive, Psychological and Behavioral Assessment Based Evidence for Altered Brain Function in PKU

Summary

- Some researchers gather physical evidence using sophisticated brain imaging machines. There are also other researchers such as psychologists, psychiatrists, and sociologists gathering psychological evidence to determine whether the current PKU standard therapy involving a Phe-restricted diet and meeting blood Phe targets can still lead to changes in the brain.
 - In fact, psychological evidence in the form of IQ testing was the main evidence to show the dramatic improvements in PKU patients who were treated with the Phe-restricted diet shortly after birth. Prior to current standard PKU therapy, IQ in PKU was dramatically lower in untreated individuals.
 - Although a recent study suggests that short-term spikes in blood Phe levels can cause lower IQ, the vast majority of studies indicate that maintaining a Phe-restricted diet and blood Phe levels within range result in normal IQ.
 - The research focus has shifted away from IQ to determining if more subtle psychological/emotional changes occur in PKU patients adhering to diet therapy.
 - One area of research involves something called **executive function** (EF) which is deliberate, conscious control over your own thoughts, actions and emotions. Some of the many characteristics of people with EF difficulties include disorganization, being easily frustrated, and poor judgment. The evidence for EF problems in diet-controlled PKU is a mixed bag, with some studies finding problems and some finding none. Researchers are looking to do a large-scale long-term study on EF in PKU in hope of getting a more accurate picture of what is going on.
 - Another area of research is how quickly you can react to incoming information, process it, understand it and use it. This is known as **information processing speed** and can be measured by a variety of tasks with time limits. People who suffer from problems in information processing speed might take longer to start/complete complex tasks and appear to struggle. More evidence is required to determine if information processing is affected in diet controlled PKU. However, one strong piece of evidence suggests that if one stays within the current blood Phe range for their age group then information processing will not be affected.
 - The chemical brain imbalances found in PKU are similar to those found in children with **attention deficit hyperactivity disorder** (ADHD). For this reason researchers are interested in knowing if ADHD or ADHD symptoms are more common in people with PKU. Symptoms of ADHD fall into one of three large categories: inattention (inability to concentrate), hyperactivity and impulsivity. Using standardized criteria for diagnosing ADHD, researchers have found that people with PKU are more likely to have ADHD or symptoms of ADHD. Surprisingly, only a handful of studies have been done and more research is required to strengthen the possible link between PKU and ADHD.
 - Researchers have also looked for **learning disabilities** and problems in **academic performance** in people with PKU. Of the studies done to date, it appears that math skills may be affected in some individuals with PKU. These are small studies and not conclusive by any means.

- Studies looking at whether **psychiatric disorders** occur more frequently in PKU showed no significantly different overall rate than the general population. However, psychiatric symptoms have been uncovered in some PKU patients that include, but are not limited to, anxiety, depressed moods and phobias. Most convincingly was a recent study done in adults that showed that higher blood Phe levels were associated with increased self-reported incidences of depression and fatigue.
- More psychological evidence is needed to determine the nature and frequency of any problems that may be occurring at higher rates in PKU individuals who adhere to their recommended blood Phe targets. However, it is clear that higher blood Phe levels do strongly correlate with many of the psychological and behavioral symptoms observed.

Executive function

What is executive function (EF)? One of the most studied cognitive abilities in PKU is known as **executive function (EF)**.¹⁰ EF is a complex concept. Scientists and psychologists have defined EF as “*the higher-order cognitive abilities that facilitate the flexible modification of thought and behavior in response to changing cognitive or environmental demands.*”¹¹ **In basic terms EF can be thought of as deliberate, conscious control over your own thoughts, actions and emotions.**¹⁰

There is no clear-cut agreement among experts on exactly what factors make up EF, but many experts include the following “higher-order cognitive abilities” or “domains” under the umbrella of EF:^{11,12}

- planning
- organization
- **conceptual reasoning**
- **mental/cognitive flexibility**
- **impulse/inhibitory control**
- **selective and sustained attention**
- **working memory**

It is important to know that problems with EF have been found in many different developmental disorders (such as autism and attention deficit/hyperactivity disorder). However, EF is an umbrella of many “cognitive domains.” Because of this, different development disorders may share common EF impairments but may also have unique EF impairments. This complexity has made it difficult for experts to define and come up with a single statement to describe EF disorders. Some impairments in EF may result in obvious behavioral or learning disorders, while some will result in behaviors that are subtle in nature and not easily caught by the untrained observer.

As already stated, EF is a complex topic. An expert in the field, Dr. Philip David Zelazo, has written a series of comprehensive and easy-to-understand articles that make EF easier to understand.¹⁰ In his articles, he refers to the analogy of a business executive to describe EF. “An executive is someone *who decides upon a course of action, issues commands by*

virtue of rank in a hierarchy, and ensures that the commands are implemented. Executive function, therefore, refers to the business of making decisions and carrying them out, as when one is deliberately trying to solve a problem.” He further explains that, in the context of problem solving, EF can be broken down into subfunctions. In order to deliberately solve a problem, it is necessary to do several smaller things, in a specific sequence:^{10,13}

1. Identify the goal and the barriers to achieving it: **Represent** the problem by asking, “What do I need to accomplish? What is preventing me from accomplishing it?”
2. Create an action plan: Come up with a **plan** for a solving the problem.
3. Take action: Actually **execute** or carry out that plan.
4. See if the goal was reached: **Evaluate** the adequacy of the attempted solution.



Individuals with difficulties in EF may present some of the following characteristics¹⁴:

- **poor frustration tolerance:** not persisting in completing a task that is the least bit difficult. This can result in angry outbursts, including yelling and throwing things.
- **disorganization:** not being able to obtain necessary information, make it accessible, and then use it for decision making. A disorganized person may lose things frequently, be messy, and have difficulty in putting their thoughts together in writing.
- **difficulty coping with change:** not liking their daily routine altered. This may manifest in anxiety when their daily routine is altered.
- **poor judgment:** frequently choosing courses of action that have negative consequences either to themselves or to others.
- **emotional instability:** having frequent mood swings.
- **disinhibition:** being impulsive and appearing to lack control of their own behavior. This may manifest as interrupting others in a conversation, talking out of turn, or laughing or crying too easily.
- **forgetfulness:** making mental errors or getting distracted when performing a task.
- **apathy:** lacking motivation. They may start something but fail to finish it.
- **not following rules in spite of knowing the rules:** not following authority.
- **difficulty in understanding consequences and cause-and-effect relationships:** see poor judgment.
- **inefficiency:** taking longer to complete tasks (e.g., homework) than warranted under the circumstances.
- **difficulties learning from past experience:** see poor judgment.

Why people with PKU may have EF difficulties:^{11,15} There are two main reasons why psychologists and researchers have focused on EF as a potential problem area in people with PKU.

1. EF has been linked to the frontal lobes of the brain, specifically an area of the frontal lobe called the *prefrontal cortex*, which is one of the very last regions of the brain to fully mature (typically in early adulthood). There is strong evidence that the **neurotransmitter dopamine** (one of several chemical messengers in the brain) is involved with normal functioning of the prefrontal cortex, and there is evidence that dopamine levels may be lower in individuals with PKU.
2. Clinicians have noticed that diet-treated PKU patients have certain behavioral, learning and cognitive problems despite having normal-range intelligence. Many of these behavioral problems appear to fall under the big umbrella of EF.

How EF is measured: Researchers have devised “tasks” or “tests” that measure different aspects (domains) of EF. Extensive research and testing have helped them understand what the “normal range” is for each test/task for healthy individuals at different ages. Scores below the normal range may indicate a potential problem in EF. This is similar to IQ testing, where scores below the normal range indicate a deficit in intelligence. However, it is important to remember that IQ testing and EF testing do not measure the same abilities. An individual can have normal or high-range IQ and still have EF difficulties.

If a clinician thinks a person may have problems with EF, they might refer that person to a psychologist. The psychologist will conduct an interview and may decide to administer a “battery” of EF tests, which simply means a bunch of tests that measure many “domains” of EF. One example of a “battery” EF test for children aged 5–18 years is called the Behavior Rating Inventory of Executive Function (BRIEF).^{16,17} This 10- to 15-minute test measures 8 domains of executive function.

Alternatively, the psychologist may have an idea of what EF domain(s) are affected after conducting the initial interview and decide on administering EF domain-focused tasks/tests. One such test is called the Go-NoGo Task. For this task, children are required to respond to one cue, called the “Go stimulus,” while refraining from responding to another stimulus, called the “NoGo stimulus.” This task provides a measure of the EF domains of mental flexibility, selective and sustained attention and inhibitory control.¹⁰

Evidence of EF difficulties in people with PKU: Recently, a group of experts published a review of studies done on EF in people with PKU. The authors concluded that there are mixed results from studies of EF in diet-treated PKU.¹¹ Some studies found EF deficits in diet-treated PKU patients and some did not; some studies found a relationship between blood phenylalanine (Phe) levels and difficulties in EF and some did not. The authors found that the domains most commonly associated with EF deficits in diet-treated PKU were working memory and inhibitory control. The authors concluded that it was hard to compare different studies because they used different measures of EF. Another criticism

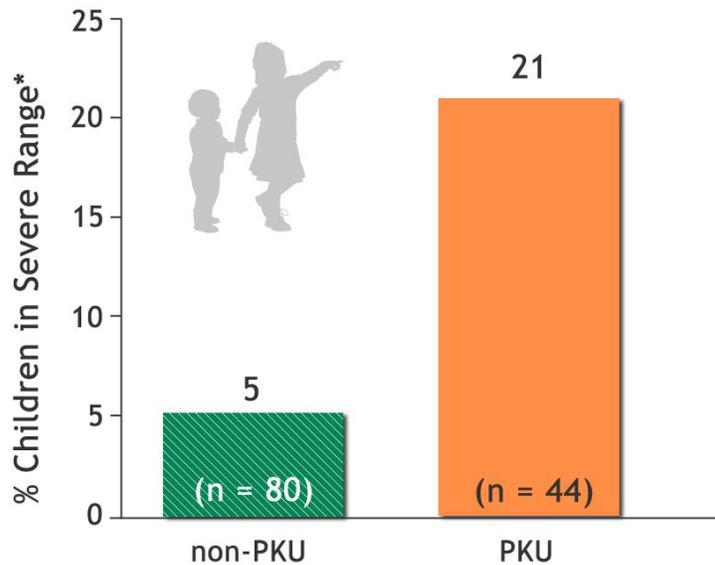
they made was that it was not known how EF scores relate to “day-to-day” functioning (i.e., classroom, home, social and work environments).

The authors call for large-scale and long-term studies of the EF of people with PKU using standardized measures of EF (i.e., everyone uses the same tests to evaluate EF) and assessing if these EF scores are related to day-to-day functioning in different environments. One such tool that should be considered is the BRIEF questionnaire for parents and teachers of school-age children, which provides a profile of behaviors associated with EF at home and in school.¹⁶

One recent study that used the BRIEF questionnaire and showed day-to-day EF deficits in children with PKU is shown below.¹⁷ Clinicians administered the BRIEF questionnaire to 189 children aged 5–18 years, who were divided into 4 groups:

- 44 with early-treated PKU (treatment started in the first month of life, no elevated Phe levels reported)
- 45 with early-treated hydrocephalus (a condition where treatment involves inserting a shunt in the first 12 months of life to relieve “water on the brain”); these subjects were included because “water on the brain” can affect EF functioning
- 20 with focal frontal-lobe lesions (documented with MRI scan); these subjects were included because many EF attributes exist in the frontal lobe of the brain and damage (i.e. lesions) in the frontal lobe can affect EF
- 80 unaffected controls (healthy siblings of other group members or recruited from local schools); these were included as “normal controls”

The overall scores of the BRIEF questionnaire showed a significant difference in the percentage of children with severe EF deficits in the hydrocephalus, frontal-lobe lesion and PKU groups compared to the “normal controls.” In the frontal-lobe lesions group, 55% had severe EF deficits. In the PKU group, 21% had severe EF deficits. In the hydrocephalus group, 18% had severe EF deficits. Only 5% of the normal control group had severe EF deficits.



*Based on Behavior Rating Inventory of EF (BRIEF) global executive composite score

Information processing speed

What is information processing speed? Your **information processing speed** is how quickly you can react to incoming information, process it, understand it and use it.¹⁸ This is not the same as intelligence. Someone can have high intelligence but process information more slowly.

Speed of information processing is influenced by a variety of factors, including:¹⁸

- the balance of **neurotransmitters** in the brain
- the amount of electrical insulation on the nerves, which is called myelin or “white matter”^{18,19}
- the organization of the networks in the brain that allow communication and information flow
- the size of synaptic spaces in the brain, which is the distance between the nerves.
- the efficiency of the frontal lobes (the front part of the brain) in organizing and directing the flow of information
- knowledge and experience (e.g., the more a person knows about a topic, the quicker it is for the person to process new information about that topic)

Individuals with slow information processing speed may be affected throughout life in varied settings such as school, home or work. Some of the following characteristics have been observed in people with slow information processing speeds in terms of thinking:¹⁹

- struggling with complex tasks or tasks that require multiple steps
- taking more time to do complex tasks
- taking longer to begin tasks
- working less efficiently under time constraints than their peers

Why people with PKU may have slow information processing difficulties:^{19,20,21}

There are 3 main reasons why psychologists and researchers have focused on information processing as a potential problem area in people with PKU:

1. Information processing speed has been linked to neurotransmitter levels and there is evidence suggesting that the levels of the neurotransmitter called dopamine may be lower in individuals with PKU.
2. Information processing speed has been linked to the amount and integrity of the insulation (myelin or “white matter”) on nerves. There is evidence showing that there are abnormalities in this insulation in some diet-treated individuals with PKU.
3. Clinicians have noticed that diet-treated PKU patients may have certain behavioral and learning problems despite having normal range intelligence. Studies have shown that many of these behavioral problems may be associated with slow information processing speed.

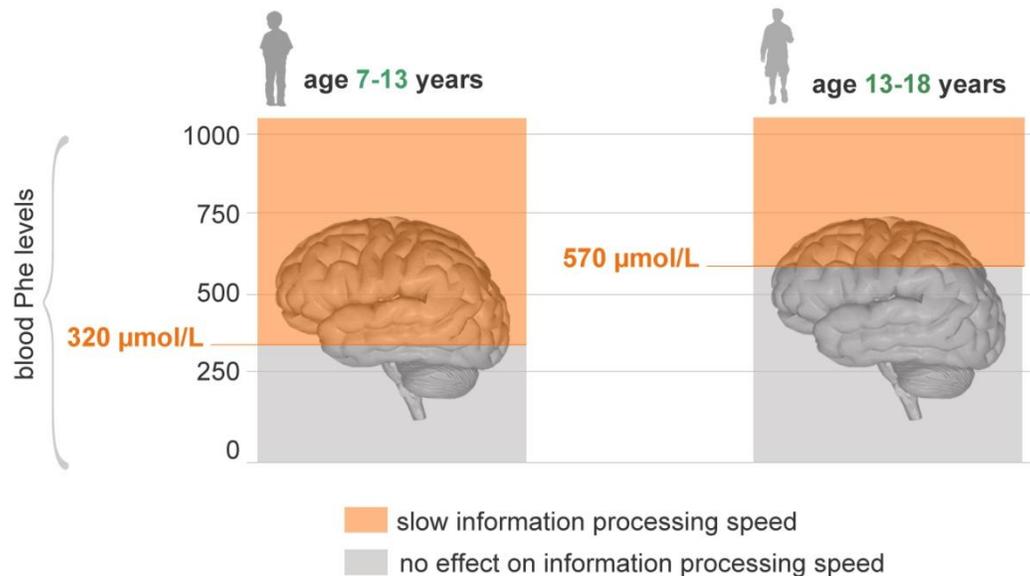
How information processing speed is measured: Researchers have devised “timed tasks” to measure information processing speed. Extensive research and testing have helped establish what the “normal-range time” is for each task for healthy individuals at different ages. Times above the normal range may indicate slow information processing speeds.

One test that measures speed of processing is called choice reaction time.^{19,20,21,22} In the choice reaction time test, a person might be asked to sit in front of a computer monitor where an arrow (the stimulus) is displayed on either the left or the right side of the screen.²² The subject must press the left hand button on the press pad if the stimulus is displayed on the left side of the screen, and the right hand button on the press pad if the stimulus is displayed on the right side of the screen. This task will go on for several minutes. At the end of the test, researchers assess the number of correct and incorrect responses, the number of late or early responses, and the average response speed. The scores are compared against those of a “normal range.”

Evidence of slow information processing speed in people with PKU: A number of studies using a variety of different tests and parameters have found that people with PKU tended to have slower information processing than “control” (non-PKU) subjects.^{19,20,21} One “study of studies” (known as a meta-analysis – looking at a variety of results from multiple PKU studies) examined many different outcomes including information processing speed.²⁰ Using sophisticated math techniques, the authors concluded that of all the different cognitive difficulties found in people with PKU, slow information processing was the most likely to be present compared to impairments in other cognitive domains.

Another research group came along after that to try to determine if slow information processing speed observed in PKU was related to blood phenylalanine (Phe) levels.²¹ They did their own meta-analysis on information processing speed PKU studies that reported blood Phe levels and age of their participants. Using sophisticated math to analyze the data, these authors then suggested that information processing speed is

affected by blood Phe levels depending on age. Their results recommend upper thresholds (the maximum level before there is an effect on information processing speed) for blood Phe concentrations of about 320 $\mu\text{mol/L}$ (5.3 mg/dL) for children between 7 and 13 years of age and about 570 $\mu\text{mol/L}$ (9.5 mg/dL) for adolescents between 13 and 18 years of age. Adults showed no blood Phe concentration effect on information processing speed; the authors suggested that there still might be an effect, but more studies need to be done to determine the effect.



Attention deficit hyperactivity disorder (ADHD)

What is attention deficit hyper activity disorder (ADHD)?²³ Attention deficit hyperactivity disorder (ADHD) is a disorder that may be characterized by a pattern of inattention (inability to concentrate) sometimes combined with hyperactivity and impulsivity. This pattern is persistent and developmentally inappropriate, and occurs in at least two different contexts.

Many people think ADHD and ADD (attention deficit disorder) are two different conditions, but they are in fact two names for the same condition. Other names no longer in use are minimal brain dysfunction (MBD) and hyperactivity.

ADHD affects 5–15% of school-aged children, occurring more frequently in boys than girls. ADHD may persist into adulthood in many cases. An inability to integrate in social, academic, or work-related settings is a pattern seen in people with a history of ADHD. In childhood, a person with ADHD may have academic problems, as the condition affects a person's ability to concentrate and focus on tasks. Because they are unable to organize their work or pay attention to their studies, children with ADHD may try to distract other children in class.

People with ADHD are especially sensitive to sensory stimuli such as noise, touch and visual cues. They can easily be overstimulated, leading to changes in behavior that may include aggressiveness.

Symptoms of a child with ADHD fall into three large categories: inattention, hyperactivity, and impulsivity. They may include:

- fidgeting or squirming excessively
- having difficulty remaining seated
- being easily distracted
- not paying attention to details
- having difficulty organizing tasks
- being forgetful
- having difficulty awaiting their turn in games
- blurting out answers to questions
- having difficulty following instructions
- having difficulty sustaining attention
- shifting from one activity to another
- having difficulty playing quietly
- often talking excessively
- often interrupting
- often not listening to what is said
- often losing things
- often engaging in dangerous activities

There's no official symptom list for adults, but symptoms are similar to those listed above.

Why people with PKU may have ADHD:^{23,8} There are two main reasons why psychologists and researchers have focused on ADHD as a potential problem area in people with PKU:

1. ADHD has been linked to lower levels of the neurotransmitter dopamine, and there is evidence suggesting that dopamine levels may be lower in individuals with PKU.
2. Clinicians have noticed that there are certain behavioral and learning problems in diet-treated PKU patients despite having normal-range intelligence. Studies have shown that many of these symptoms are similar to those found in individuals diagnosed with ADHD.

How ADHD is diagnosed:^{24,25} Psychologists use a comprehensive manual to diagnose mental disorders, called the Diagnostic and Statistical Manual for Mental Disorders (DSM), which includes criteria for diagnosing ADHD. The following simplified diagnostic information should only be used by a trained health care provider to accurately diagnose or treat ADHD. This information is taken from the most recent version of the DSM, known as DSM-IV.

Based on the criteria below, three types of ADHD are identified:

Type of ADHD	Presence of Criteria IA for the past 6 months	Presence of Criteria IB for the past 6 months	Presence of Criteria II, III, IV and V
Combined	Yes	Yes	Yes
Predominantly inattentive	Yes	No	Yes
Predominantly hyperactive-impulsive	No	Yes	Yes

- IA** Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:
1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
 2. Often has trouble keeping attention on tasks or play activities.
 3. Often does not seem to listen when spoken to directly.
 4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
 5. Often has trouble organizing activities.
 6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
 7. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
 8. Is often easily distracted.
 9. Is often forgetful in daily activities.

OR

- IB** Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:
- Hyperactivity**
1. Often fidgets with hands or feet or squirms in seat.
 2. Often gets up from seat when remaining in seat is expected.
 3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
 4. Often has trouble playing or enjoying leisure activities quietly.
 5. Is often "on the go" or often acts as if "driven by a motor."
 6. Often talks excessively.
- Impulsivity**
1. Often blurts out answers before questions have been finished.
 2. Often has trouble waiting one's turn.
 3. Often interrupts or intrudes on others e.g., butts into conversations or games.

+

II Some symptoms that cause impairment were present before age 7 years.

+

III Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).

+

IV There must be clear evidence of significant impairment in social, school, or work functioning.

+

V The symptoms do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder. The symptoms are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Evidence of ADHD in people with PKU:⁸ The author of a recent review found it surprising that there are only a handful of studies investigating the correlation of ADHD with PKU, given the fact that ADHD and PKU have similar underlying potentials for neurotransmitter deficiencies in the brain. However, of the studies performed to date, it is not surprising that the authors found that people with PKU are more likely to have ADHD.

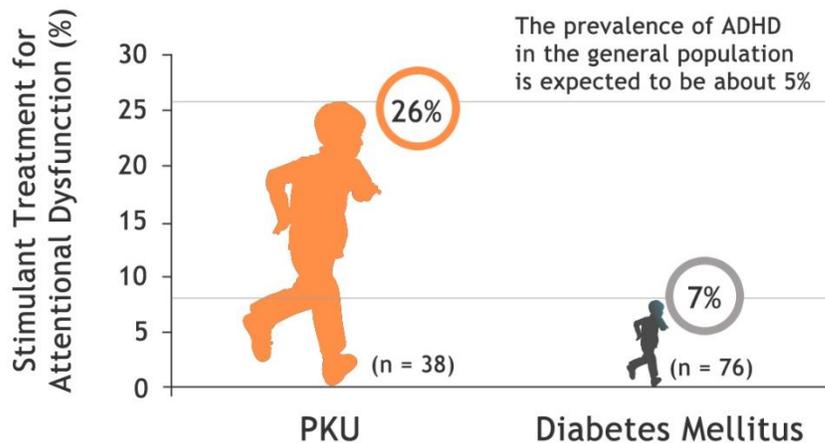
One study using the DSM-IV diagnostic criteria of ADHD found that children with PKU who were on diet treatment were 2.5 times as likely to have ADHD as those without PKU. The same authors also found that many children did not meet the full DSM-IV criteria of ADHD diagnosis but still shared many of the inattentive symptoms (but few of the impulsive or hyperactive symptoms). Thus, it appears that PKU children may be at risk for the predominantly inattentive type of ADHD. The author also stated that there seems to be a relationship between ADHD symptoms and blood Phe levels: higher levels of Phe were associated with a greater number of ADHD symptoms.

In the same review, the author described what would be considered “circumstantial” but strong evidence for ADHD in PKU from another study. This was based on the discovery that stimulant medications used to treat ADHD were also being prescribed at a high level to kids with PKU (26% of PKU children in this study were prescribed stimulant medication compared to only 5% in the general population of non-PKU children).²⁶

This study examined how often stimulant medications were prescribed to 38 youths with diet-treated PKU (23 males, 15 females; age range 5–20 years). There was a “control” group of 76 youths with type 1 diabetes (46 males, 30 females; age range 5–20 years). Children with type 1 diabetes were chosen as the control group since diabetes and PKU have some things in common, such as diet alteration and the requirement for family support to help maintain metabolic control.

The study found that 26% of the PKU patients (7 boys and 3 girls) had been prescribed a stimulant medication because of inattentive problems, while only 6.5% (4 boys and 1 girl) of the diabetes control group were prescribed a stimulant medication. Additionally, the stimulant prescriptions were higher in the PKU group than for the general population (5%).

Of particular interest was the mean blood Phe level for the past year in the stimulant-using group: it was 792 $\mu\text{mol/L}$ (13.2 mg/dL), compared to 486 $\mu\text{mol/L}$ (8.1 mg/dL) in the non-stimulant-using PKU group. The author suggests the possibility of stimulant medications being used to manage cases where dietary Phe intake is less well controlled. Future research should investigate if stricter dietary management improves the inattentive symptoms. It might be that there is no need for the stimulant medication, just better Phe control. The author also notes that, in spite of better Phe control, it is possible the ADHD inattentive symptoms may persist, since Phe levels in individuals with well-treated PKU are still 2–10 times as high as in the general population.



Learning disabilities and academic performance

What do learning disabilities and academic performance mean?⁸ Academic performance is how well a person performs in school. It is based on scholastic outcomes, such as educational level obtained. Learning disability is a clinical diagnosis made by a trained professional. Learning disabilities include a number of disorders that may affect acquiring, organizing, retaining, understanding or using of information. These disorders affect learning in individuals who otherwise have normal intellectual abilities for thinking and/or reasoning. Thus, a person can have poor academic performance with no learning disability.

Why people with PKU may have learning and academic performance difficulties:⁸ There are many reasons why psychologists and researchers have focused on academic performance issues and learning disabilities as potential problem areas in people with diet-treated PKU:

1. The potentially lower levels of the neurotransmitter dopamine and the observed white matter abnormalities seen in PKU patients provide physical evidence for altered brain function, suggesting that individuals with PKU may be at risk for learning disabilities and lower academic performance.
2. Clinicians, teachers and parents have observed lower academic performance and learning disabilities in diet-treated PKU patients despite their having normal-range intelligence.
3. The potential for people with PKU to have learning disabilities and academic performance difficulties is also supported by the evidence of cognitive deficits in executive function (EF) and speed of processing. Problems in these domains can lead to learning and academic difficulties.
4. The knowledge that people with PKU may be more likely than normal to have inattentive symptoms of ADHD is also an important consideration, because it is well-known that ADHD can lead to learning disabilities and lower academic performance.

How learning disabilities are diagnosed and academic performance is measured:^{8,27}

Psychologists use a comprehensive manual to diagnose learning disabilities, called the Diagnostic and Statistical Manual for Mental Disorders (DSM), which provides criteria for diagnoses. This is the same manual used for diagnosing other disorders that affect the mind, such as ADHD. The latest version of the DSM, known as the DSM-IV, uses the following criteria to diagnose learning disabilities:

- An individual's achievement on standardized measures of academic attainment is substantially below expectations for age, schooling, and level of intelligence.
- To diagnose a learning disability, it is not enough for academic achievement to be substantially below what would be expected on the basis of intelligence. It must be accompanied by significant interference with academic achievement or activities of daily living that require an academic skill. For example, someone who has a relatively high IQ but has just average academic performance wouldn't likely be diagnosed with a learning disability.

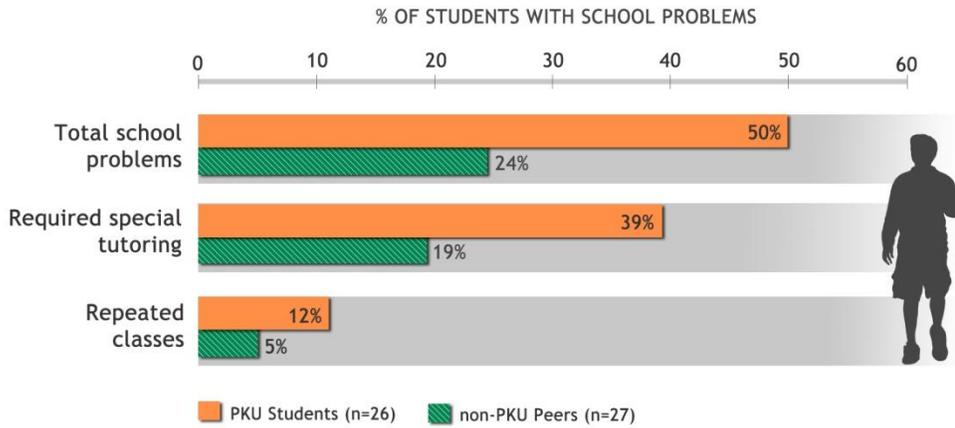
Academic performance is mainly an observation made by teacher and parents. These include grades, repeated years, the need for specialized help, and the education level obtained. However, there are standardized psychological tests that are used by clinicians to evaluate academic achievement. One such commonly used test is called the Wide Range Achievement Test (WRAT), which can assess an individual's achievement in academic domains such as reading, spelling and math.

Evidence for learning disabilities and academic performance difficulties in people with PKU:⁸ The author of a recent review looked at academic performance and learning disability studies published on individuals with early-and-continuously-treated PKU. In terms of academic performance, it appears that in the academic realms of reading and spelling, people with PKU are on par with the average population. However, two large studies have found a significant trend of below-average performance in math compared to the general population and the individual's non-affected siblings. Math difficulties in PKU were not unexpected, given that math skills require a high degree of abstract reasoning and problem-solving ability. These cognitive abilities involve executive functions (EF), which may be compromised in some individuals with controlled PKU.

In terms of blood Phe levels and academic performance, studies show that individuals with PKU who maintained a strict diet had significantly higher scores in all academic realms (spelling, reading, and math) in late childhood and early adolescence compared to those who did not stick to a strict diet. These studies were all based on the scores of the WRAT standardized academic achievement test performed in clinical settings.

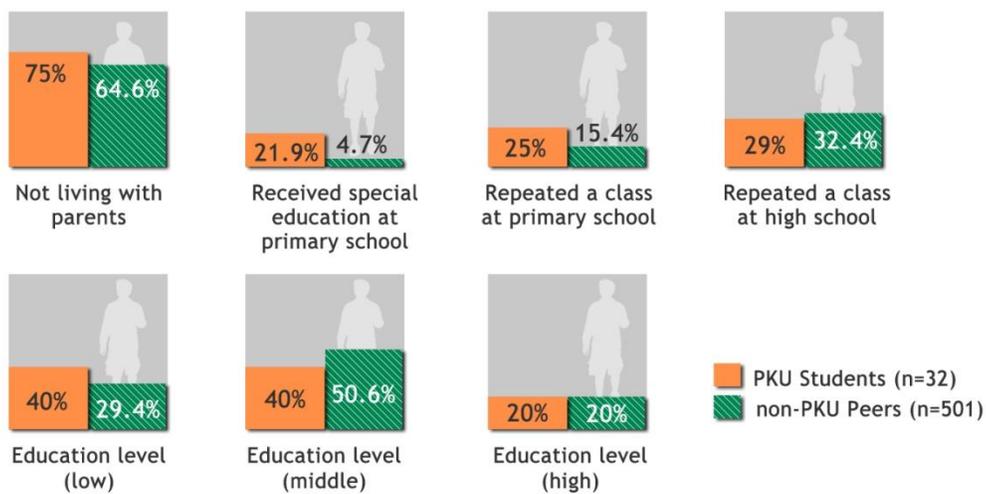
Other studies have looked at real-world academic performance by assessing each individual's day-to-day classroom performance as reported by their teachers. In one such study the authors followed 26 youths (14 males, 12 females; average age of 12.3 years) with early-and-continuously-treated PKU.²⁷ The study also used 21 classmates who didn't have PKU, matched by age and sex, for "controls" for comparison. The average intelligence levels of the two groups were the same. The study found that 50% (13/26) of the youths with PKU had school difficulties, 38.5% (10/26) required special tutoring and

11.5% (3/26) had to repeat a year. All percentages were higher than those of the control classmate participants (23.8%, 19% and 4.8%, respectively, for school problems, special tutoring and repeated classes; see figure below).



The results from these small studies are not conclusive evidence by any means. Other studies have looked at larger groups of people and found that although children with PKU did receive significantly more special tutoring in school, they did not have significantly more repeated years, and many went on to obtain high education levels at a rate similar to the large non-PKU control population (see figure below).²⁸ Additionally, there are no studies reporting a higher-than-average frequency of clinically diagnosed learning disabilities in the PKU population compared to the general population.⁸

PKU PATIENTS HAVE SIMILAR LIVING CONDITIONS, EDUCATION, AND EMPLOYMENT TO NON-PKU PEERS



Psychiatric symptoms and disorders in PKU

What is a psychiatric disorder?^{29,30,25} A **psychiatric disorder** is a clinical diagnosis based on a set of criteria that only a trained expert such as a psychiatrist or psychologist can assess. Psychiatric disorders may be characterized by behavioral and/or psychological abnormalities, often accompanied by physical symptoms. The psychiatric symptoms may significantly affect many aspects of a person's day-to-day life, causing significant distress or impairment in social and work settings.

In all, there are more than 300 different types of psychiatric disorders that have their own criteria for diagnosis. The disorders are typically categorized into larger disorder families based on the predominant psychiatric symptom. For example, Anxiety Disorders include disorders in which anxiety is the main symptom, such as phobias, social anxiety and post-traumatic stress disorders.

Why people with PKU may have psychiatric symptoms and disorders:^{31,12,32} There are 3 main reasons why psychologists and psychiatrists have focused on the potential for psychiatric symptoms and disorders in people with diet-treated PKU.

1. The strict PKU diet can be stressful to maintain over the long term, and psychosocial stressors such as this or others (e.g., unemployment, loss of a loved one) are known to play an important part in mental health and contribute to psychiatric symptoms and disorders. In terms of PKU and other chronic diseases, this psychosocial stressor is generally referred to as “the burden of chronic disease” or “treatment fatigue.”
2. Many psychiatric disorders are rooted in altered brain chemistry and function. The potentially lower levels of the neurotransmitter dopamine and the observed white matter abnormalities seen in people with diet-treated PKU provide physical evidence of altered brain function and a basis for investigating the presence of psychiatric disorders in PKU.
3. Deficits in cognitive abilities, such as executive function (EF) and speed of information processing, in people with diet-treated PKU may play an important role in some aspects of mental health.

How psychiatric disorders are diagnosed:^{29,25} Psychologists and psychiatrists use a comprehensive manual to diagnose psychiatric disorders, called the Diagnostic and Statistical Manual for Mental Disorders (DSM; the latest version is known as DSM-IV), which provides criteria for diagnoses. The book is the “bible” for any psychologist or psychiatrist who diagnoses psychiatric disorders in the US and many other countries. It is also the same manual used to diagnose others disorders of the mind, such as learning disabilities and ADHD.

As mentioned previously, there are more than 300 different psychiatric disorders that use different diagnostic criteria. Diagnosing psychiatric disorders is mainly based on what the symptoms are, how long they last and how much they interfere with day-to-day function. However, the DSM-IV criteria also look at underlying issues such as psychosocial stressors (family problems, employment status, etc.) and the highest level of function attained in the previous year. After taking everything into consideration, the psychologist

or psychiatrist will recommend a treatment action plan to relieve symptoms and treat the underlying cause of the problem. Treatment may include a combination of medication, behavior therapy and stress-management techniques.

Evidence for psychiatric symptoms in people with PKU:^{31,12,32} In two recent reviews of studies of PKU involving psychiatric disorders and symptoms, the conclusions were similar: it appears that people with PKU do not have a significantly different overall rate of psychiatric disorders than the general population.^{31,12} However, there does seem to be a pattern of psychiatric symptoms found in PKU, including increased occurrences of depressed moods, anxiety, phobias and the feeling of social isolation, as well as decreased feelings of autonomy, positive emotions, school achievement and social competence (see Figure 3 and Table 2).

Figure 3: Psychiatric symptoms affecting people with PKU

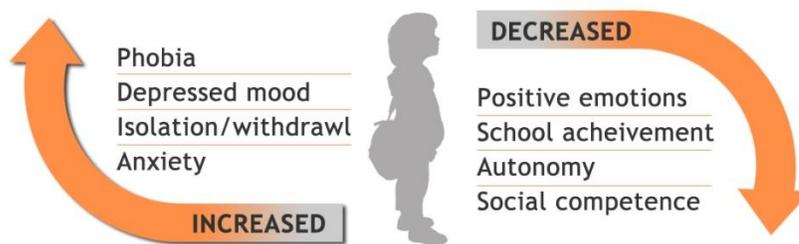


Table 2: Psychiatric, emotional and behavioral symptoms found in people with PKU¹²

Untreated individuals	Early-treated children and adolescents	Early-treated adults
<ul style="list-style-type: none"> • Psychotic symptoms • Autistic behaviors • Hyperactivity • Aggression • Anxiety • Depressed mood • Impaired social skills associated with profound intellectual disability • Social withdrawal 	<ul style="list-style-type: none"> • Attentional problems • School problems • Less achievement motivation • Decreased social competence • Decreased autonomy • Low self-esteem 	<ul style="list-style-type: none"> • Depressed mood • Generalized anxiety • Phobias • Decreased positive emotions • Low self-esteem • Social maturity deficits • Social isolation/withdrawal • Lack of autonomy

The main question is whether the psychiatric symptoms observed in people with PKU have to do with increased blood Phe levels or with "treatment fatigue" from maintaining the strict low-Phe diet. Although both are likely to be contributing factors, evidence suggests that psychiatric symptoms are more likely to be more common and severe when

blood Phe levels are high. Individuals with poor metabolic control during the critical years of brain development (childhood and adolescence) are more likely to show more symptoms that are more serious. Adults also appear to be at risk for increased psychiatric symptoms based on blood Phe levels (see Table 2).

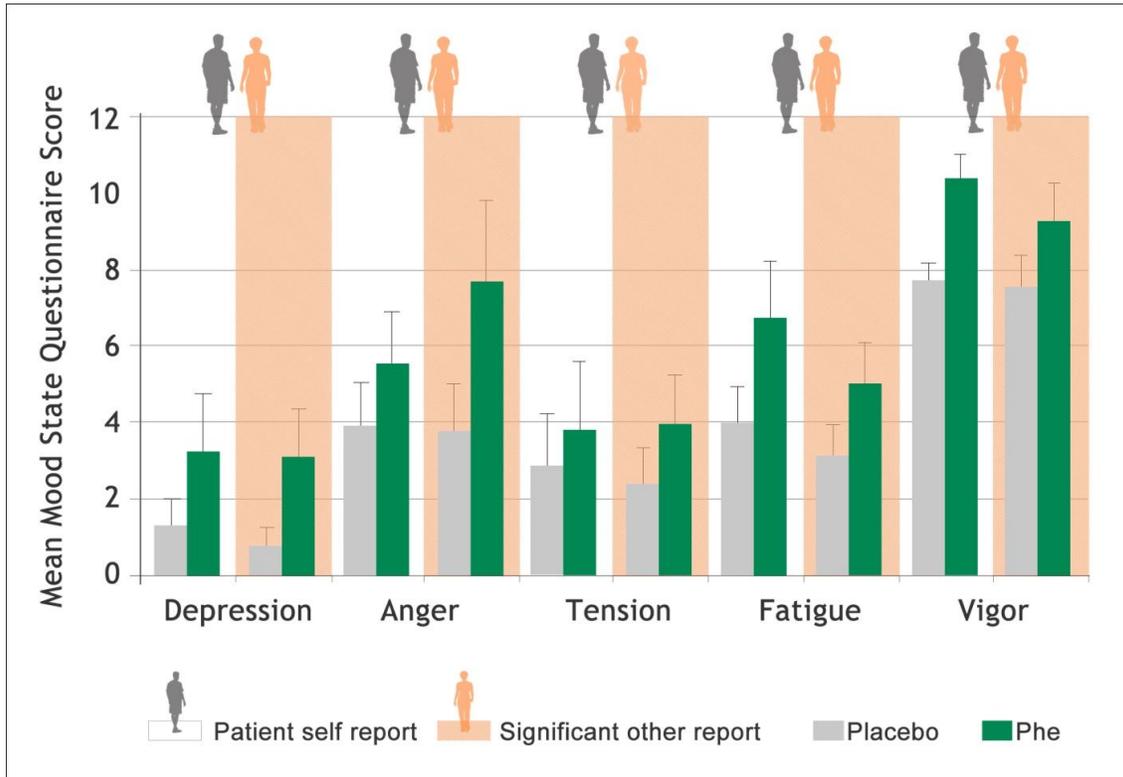
A recent study has given us one of the most compelling pieces of evidence for the involvement of elevated blood Phe in affecting mood and behavior of people with PKU.³² This study involved a randomized double-blind placebo controlled trial – a type of trial called the “gold standard” in clinical experiments. In the study, 9 continuously-treated adults with well-controlled PKU underwent two 4-week supplementation periods: one with Phe (to increase blood Phe levels) and one with placebos (“sugar pills”). The subjects didn’t know what they were taking in either period and were randomly assigned either Phe pills or placebo in the first 4-week period. After the 4 weeks, there was a period of at least 4 weeks in which the subjects went back to their normal routine (i.e., were not taking either Phe pills or placebo). Then the second period of supplementation started and lasted 4 weeks. During the second period, if subjects were receiving placebo in the first period, then they received Phe pills in the second period, and vice versa.

In each period, the subjects were given a “mood state” questionnaire to complete to evaluate their mood, with researchers noting when they had high and low blood Phe levels. Additionally, a friend or relative of each patient completed a questionnaire about the patient’s mood.

The average blood Phe level in the placebo period was 709 $\mu\text{mol/L}$ (11.8 mg/dL), while the average blood Phe level in the Phe pill period was 1,259 $\mu\text{mol/L}$ (21 mg/dL). When blood Phe levels were higher, the patients reported a significant increase in depression symptoms and fatigue and felt less vigorous (see Figure 4). Spouses, relatives and friends also observed increased depression and fatigue when blood Phe levels were high (see Figure 4). They also reported that the patients appeared to be more angry when blood Phe levels were high (see Figure 4).

Thus, the study suggests that high blood Phe levels have a direct negative effect on mood in adult patients with PKU. Because of the effect on mood, the study supports the “diet for life” treatment recommendation. It is important to note that a similar study cannot be done ethically with PKU children because of the irreversible brain damage that high Phe levels can cause during this critical period of brain development. However, the results of this study in adults point to the potential for similar mood problems in children during periods of elevated blood Phe levels.

Figure 4: Relation of Phe levels to mood



4. Theories for Elevated Phe Levels Altering Brain Function in PKU

Summary

- Phenylketonuria (PKU) is characterized by elevated blood levels of the amino acid phenylalanine (Phe), which is mainly obtained from eating proteins. The symptoms of PKU almost exclusively concern the brain, so how does an elevated blood Phe level affect the brain?
 - The brain is protected by a surrounding layer called the blood brain barrier (BBB), which allows some material to cross while preventing others. The brain needs certain material to cross the BBB to allow for normal functioning. One of the raw materials the brain requires are amino acids including Phe for building brain proteins and making chemical messengers called neurotransmitters.
 - The way Phe and other amino acids get across the BBB and into your brain are by using transporters. This is similar to a bus (the transporter) carrying people (the amino acids) to a destination, each seat gets taken up by an amino acid and the next stop is the brain. This analogy provides a visual description of the main theory of how elevated blood Phe can affect normal functioning of the brain.
 - Imagine that elevated blood Phe in PKU can lead to Phe taking up more seats on the bus, which may cause two things:
 - More Phe gets transported into the brain
 - Less of the other amino acids that share this bus get transported to the brain because Phe is taking up their spots!

Phenylketonuria (PKU) is characterized by elevated blood levels of the amino acid phenylalanine (Phe), which is mainly obtained from eating proteins. But the symptoms of PKU almost exclusively concern the brain. So what is going on? How does an elevated blood Phe level affect the brain? Unlocking this mystery involves understanding how Phe gets into the brain in the first place.⁷

First, it's important to understand that the brain is a very sensitive system. The body doesn't allow just anything floating around in the blood stream to enter it. The brain is protected by a surrounding layer called the blood brain barrier (BBB), which allows some material to cross while preventing others. Second, the brain needs certain material to cross the BBB to allow for normal functioning. One of the raw materials the brain requires are amino acids including Phe. Amino acids cross the BBB to support functions such as building brain proteins and making brain neurotransmitters. Thus, it would appear that the movement of Phe across the BBB would be important for the brain symptoms observed in PKU.

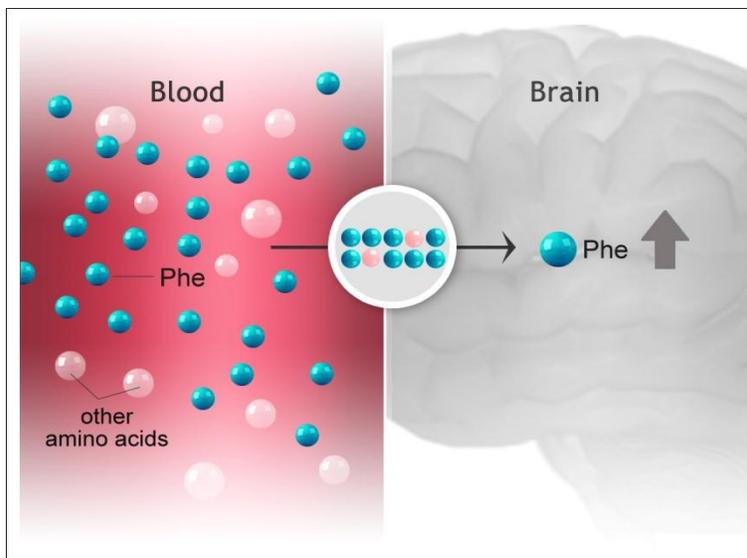
Research has shown that the transport of all amino acids into the brain involves 9 different transporters. One of these is called the large neutral amino acid transporter 1 (LAT1), which transports Phe and 8 other amino acids: valine, isoleucine, leucine, methionine, threonine, tryptophan, tyrosine, and histidine.

Think of this transporter as a bus with a limited number of seats. It picks up amino acids from the blood. When Phe levels are elevated, they compete (and win) against the other amino acids for seating. Next stop the brain! This analogy provides a visual description of the primary underlying theory of how elevated blood Phe can affect normal functioning of the brain (see Figure 5).

Simply imagine that elevated blood Phe in PKU can lead to Phe taking up more seats on the bus, which may cause two things:

- More Phe gets transported into the brain
- Less of the 8 other amino acids that share this bus get transported to the brain because Phe is taking up their spots!

Figure 5: How Phe affects amino acid transport to the brain

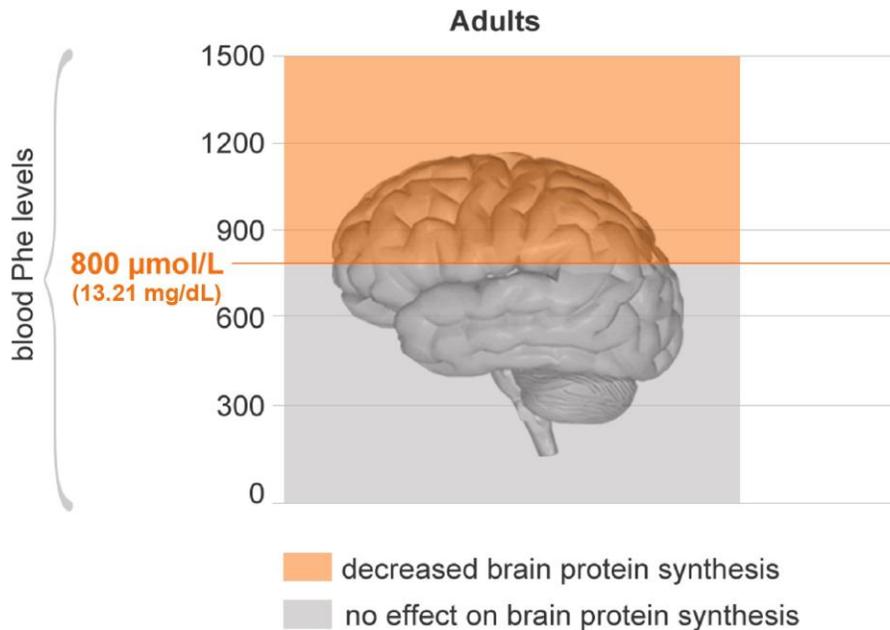


Although it is not yet technically feasible to accurately measure these amino acids in the brain, there is supporting physical and cognitive evidence for this hypothesis. There is a study that provides perhaps one of the best pieces of evidence for how elevated Phe can affect brain functioning through this transport mechanism. The study examines protein synthesis in the adult PKU brain, which relies on amino acids being transported across the BBB.³³ In this study, brain protein synthesis was measured in 16 PKU patients, aged 16 to 47 years (25 ± 7) by giving them a special identifiable form of **tyrosine** (one of the amino acids that shares the same transport mechanism as Phe), which can be measured using sophisticated brain imaging technology. At the start, individual Phe levels ranged from $233 \mu\text{mol/L}$ (3.85 mg/dL) to $1362 \mu\text{mol/L}$ (22.5 mg/dL) (mean: $587 \pm 300 \mu\text{mol/L}$ [$9.7 \text{ mg/dL} \pm 5 \text{ mg/dL}$]).

Study data suggests that **brain protein synthesis** in adults with PKU is abnormally low when blood Phe levels are elevated above a certain range. Protection from this potential abnormality in adulthood appears to occur at blood Phe concentrations $<600\text{-}800 \mu\text{mol/L}$ ($9.9\text{-}13.2 \text{ mg/dL}$) (see Figure 6). Thus it appears that elevated Phe can slow the transport

of tyrosine, and presumably other amino acids that share the same mechanism (i.e., transporter), into the brain. Those that had higher blood Phe levels showed poorer brain protein synthesis.

Figure 6: Increased Phe levels decrease brain protein synthesis



Knowing the potential mechanism of how elevated blood Phe affects the brain through altering the transport of a certain group of amino acids across the BBB helps in the understanding of how/why certain PKU therapies work:

- Restricted Phe diet and/or **PAH cofactor** (Kuvan; BH_4) therapies: Reduces blood Phe levels resulting in Phe taking up less seats on the bus, which allows room for the other amino acids to be transported across the BBB.
- Large neutral amino acid (LNAA) therapy (e.g., vPreKUnil, NeoPhe, PheBLOC): Decreases the amount of Phe entering the brain, and increases the amount of the other amino acids which share the same transporter across the BBB. Higher levels of these other amino acids in the blood stream compete for “seats on the bus” with elevated blood Phe.

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 (BH₄; tetrahydrobiopterin; sapropterin; Kuvan[®]):** 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[™] 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.³⁴

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^{16,35}

Historically, cognitive and social-emotional problems have been under-diagnosed or insufficiently treated in many metabolic clinics.¹⁶ 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.³⁵ 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).

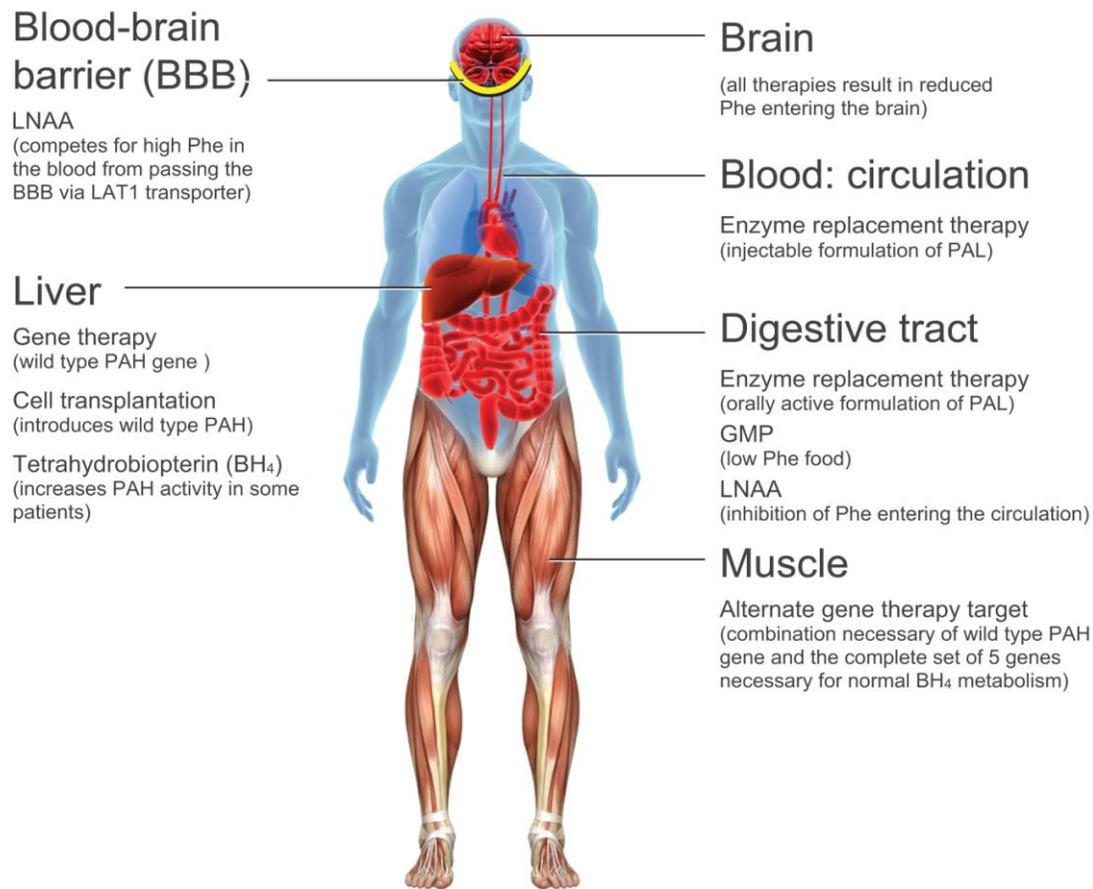
Results from this study show that 29% of patients screened positive for psychiatric distress (26 out of 89 patients). More adults than children tested positive (43% vs.17%). In addition, patients who screened positive had significantly higher mean blood Phe levels ($749 \pm 575 \mu\text{mol/L}$, or $12.37 \pm 9.5 \text{ mg/dL}$) 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."*³⁵

Supplemental or alternative PKU therapies to the low-Phe diet⁴

- 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.³⁶ 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** (BH₄; tetrahydrobiopterin; sapropterin; Kuvan[®]): Sapropterin is a man-made form of the **cofactor** BH₄, 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.³⁷ Phase 2 studies with a larger population of PKU patients receiving varying doses of PEG-PAL are currently underway.³⁸

- **Hepatocyte transplantation:**³⁹ 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.³⁹ 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.

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Glossary

amino acid: One of several molecules that join together to form proteins. There are 20 common amino acids found in proteins.

attention deficit hyperactivity disorder (ADHD): A disorder that may be characterized by a pattern of inattention (inability to concentrate) sometimes combined with hyperactivity and impulsivity that is persistent and developmentally inappropriate, and occurs in at least two different settings.

blood-brain barrier: A network of blood vessels and tissue that is made up of closely spaced cells and helps keep harmful substances from reaching the brain. The blood-brain barrier lets some substances, such as water, oxygen, carbon dioxide, and general anesthetics, pass into the brain. It also keeps out bacteria and other substances, such as many anticancer drugs.

brain protein synthesis: Brain protein synthesis is the group of processes that are involved in the generation of mature brain protein molecules required for normal brain functioning.

cofactor: Something that must join with another substance to produce a given result. There are many different cofactors in the body. One example is BH₄, which is a cofactor required for PAH to convert Phe to Tyr in the liver.

conceptual reasoning: The ability to problem solve by a creative search for new ideas or solutions.

dopamine: One of the neurotransmitters in the brain. It is derived from tyrosine and is converted to norepinephrine and epinephrine. Dopamine is important in regulating movement. It communicates with the nerves via a family of receptors.

enzyme: A protein that speeds up chemical reactions in the body.

enzyme substitution therapy: A method of injecting enzymes to substitute for those that are missing or altered because of genetic mutations.

essential amino acids: Amino acids that cannot be synthesized in the body and can only be obtained through food supply.

executive function (EF): Deliberate, conscious control over your own thoughts, actions and emotions.

gene therapy: Treatment that alters a gene. For example, in studies of gene therapy for cancer, researchers are trying to improve the body's natural ability to fight the disease or to make the cancer cells more sensitive to other kinds of therapy.

hepatocyte: A liver cell.

impulse/inhibitory control: The ability to suppress actions and distractions that would otherwise interfere with the attainment of a goal.

information processing speed: How quickly you can react to incoming information, process it, understand it and use it.

magnetic resonance imaging (MRI): A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or X-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints and the inside of bones.

maternal PKU syndrome: A condition caused by elevated Phe harming the developing fetus. Children born to mothers who have untreated PKU can have mental retardation, heart defects, small heads, low birth weight and cognitive and behavioral problems.

mental/cognitive flexibility: The ability to switch between tasks in response to changing task demands.

myelin sheath: An insulating layer found on neuronal axons (long extensions of nerve cells). This structure allows nerve impulses to travel faster by keeping the electrical current inside the nerve.

neurotransmitter: A chemical that is made by nerve cells and used to communicate with other cells, including other nerve cells and muscle cells.

phenylalanine (Phe): An essential amino acid in humans (provided by food). Phenylalanine plays a key role in the production of other amino acids and is important in the structure and function of many proteins and enzymes. Phenylalanine is converted to tyrosine, which is used in the production of dopamine and norepinephrine neurotransmitters.

phenylalanine hydroxylase (PAH): An enzyme that helps change phenylalanine to tyrosine. In PKU, PAH is mutated and possesses less activity than a normal PAH. There are over 500 different known mutations of PAH that can cause PKU, some more severe than others.

phenylketonuria (PKU): An inherited disorder that causes a build-up of phenylalanine (an amino acid) in the blood. This can cause mental retardation, behavioral and movement problems, seizures and delayed development. Using a blood test, PKU can easily be found in newborns. The treatment is a diet low in phenylalanine.

protein: A molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures such as skin and hair and of substances such as enzymes, cytokines and antibodies.

psychiatric disorder: A disorder characterized by behavioral and/or psychological abnormalities, often accompanied by physical symptoms. The psychiatric symptoms may significantly affect many aspects of a person's day-to-day life, causing significant distress or impairment in social and work settings.

selective and sustained attention: The ability to keep focus over time on attaining a goal.

tryptophan: The least plentiful of all amino acids and an essential amino acid in humans (provided by food). Tryptophan is found in most proteins. Tryptophan is converted to 5-hydroxy-tryptophan (5-HTP), which is converted in turn to serotonin, a neurotransmitter essential in regulating appetite, sleep, mood, and pain. Tryptophan is a natural sedative. It is present in dairy products, meats, brown rice, fish, and soybeans.

tyrosine (Tyr): Considered a non-essential amino acid; however, in patients with phenylketonuria who lack phenylalanine hydroxylase and cannot convert phenylalanine into tyrosine, it is considered an essential nutrient. Tyrosine plays a role in protein synthesis and is necessary for the production of some neurotransmitters and hormones.

white matter: The nerve tissue forming the bulk of the deep parts of the brain and the outer parts of the spinal cord. It is white because of a white-colored insulating layer on the nerve fibers, the myelin sheath. It is composed of nerve cell extensions (axons), which connect various grey matter areas of the brain to each other and carry nerve impulses to and from the nerve cell bodies within the central nervous system (neurons).

working memory: The ability to hold information in your mind and work with it over a short period of time.