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Plain Language Summary of Publication

The benefits of a prolonged-release protein substitute with similarities to natural proteins as a treatment for phenylketonuria: a plain language summary of a study in healthy adults

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Where can I find the original articles on which this summary is based?

This article summarises two scientific articles that described a study comparing a prolonged-release amino acid mixture for phenylketonuria with other protein substitutes. These articles, which were originally published in the journal *Nutrients*, are free to access at the below links:

Scheinin M, et al. Amino acid plasma profiles from a prolonged-release protein substitute for phenylketonuria: A randomized, single-dose, four-way crossover trial in healthy volunteers. *Nutrients*. 2020 Jun 2; 12(6): 1653. https://www.mdpi.com/2072-6643/12/6/1653

Scheinin M, et al. Nitrogen balance after the administration of a prolonged-release protein substitute for phenylketonuria as a single dose in healthy volunteers. *Nutrients*. 2021 Sep 14; 13(9): 3189. https://www.mdpi.com/2072-6643/13/9/3189

Summary

How to say (download PDF and double click sound icon to play sound)...

- **Amino acid:** a-MEE-noh AS-id
- **Phenylalanine:** FEE-nil-AL-uh-neen
- **Phenylketonuria:** FEE-nil-kee-ton-you-re-uh
- **Protein:** PRO-teen
- **Urea:** yoo-REE-uh
- **Nitrogen:** NY-truh-juhn

What is this summary about?

This summary describes the results of a research study that investigated the benefits of a new **protein** substitute, a prolonged-release amino acid mixture, used to treat people with phenylketonuria. This new mixture was compared with a standard immediate-release amino acid mixture to examine amino acid absorption. The study included 35 healthy adults without phenylketonuria.

Proteins: Large molecules that the human body needs to work properly; they are made up of smaller 'building blocks' called amino acids. Amino acids and proteins are present in almost all foods, but in varying amounts.

What did the researchers find?

The peak amounts of amino acids in the blood were lower and the amino acids remained in the blood for longer after the prolonged-release mixture compared with the immediate-release mixture. The overall amounts of amino acids in the blood during the study were similar with both products. The difference between the amounts of nitrogen taken up and removed from the body (which is called the 'nitrogen balance'), as well as the pattern of glucose and insulin levels in the blood, were better after the prolonged-release mixture. There were very few side effects when either of the amino acid mixtures was taken.

What do the results of the study mean?

The prolonged-release and immediate-release amino acid mixtures did not differ in terms of the overall amounts of amino acids they released into the body, but they did differ in the benefits they provided, including a more natural pattern of amino acid absorption (similar to protein eaten from food), which results in the more effective use of amino acids by the body, with the prolonged-release mixture.

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Who sponsored the study?

The study was **sponsored** by APR Applied Pharma Research S.A., Balerna, Switzerland, who developed the Physiomimic Technology™ that was used to create the prolonged-release amino acid mixture called PKU GOLIKE.

Sponsor: A sponsor is a company or organization that oversees and pays for ('funds') a research study. The sponsor may also collect and analyze the information generated during the study.

The writing and publication of this summary was also funded by APR Applied Pharma Research S.A., Balerna, Switzerland.

Who is this article for?

This summary has been written to help people with phenylketonuria, their families and caregivers, and health professionals treating people with phenylketonuria to understand the results of a study that investigated the effects of a new amino acid mixture.

This new mixture may have benefits over currently used mixtures, particularly in terms of how the amino acids get into and are used by the body, which may translate into positive effects on the day-to-day lives of people with phenylketonuria and reduce the difficulties associated with having the disorder.

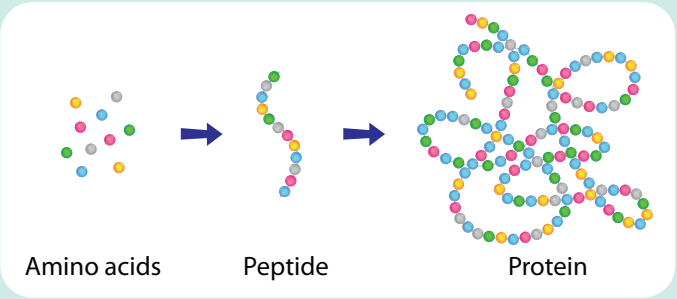
What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

This summary describes a study about a new protein substitute used to manage phenylketonuria. It explains how this new protein substitute works differently to other protein substitutes that are commonly used by people with phenylketonuria. Health professionals should make treatment decisions based on all available evidence.

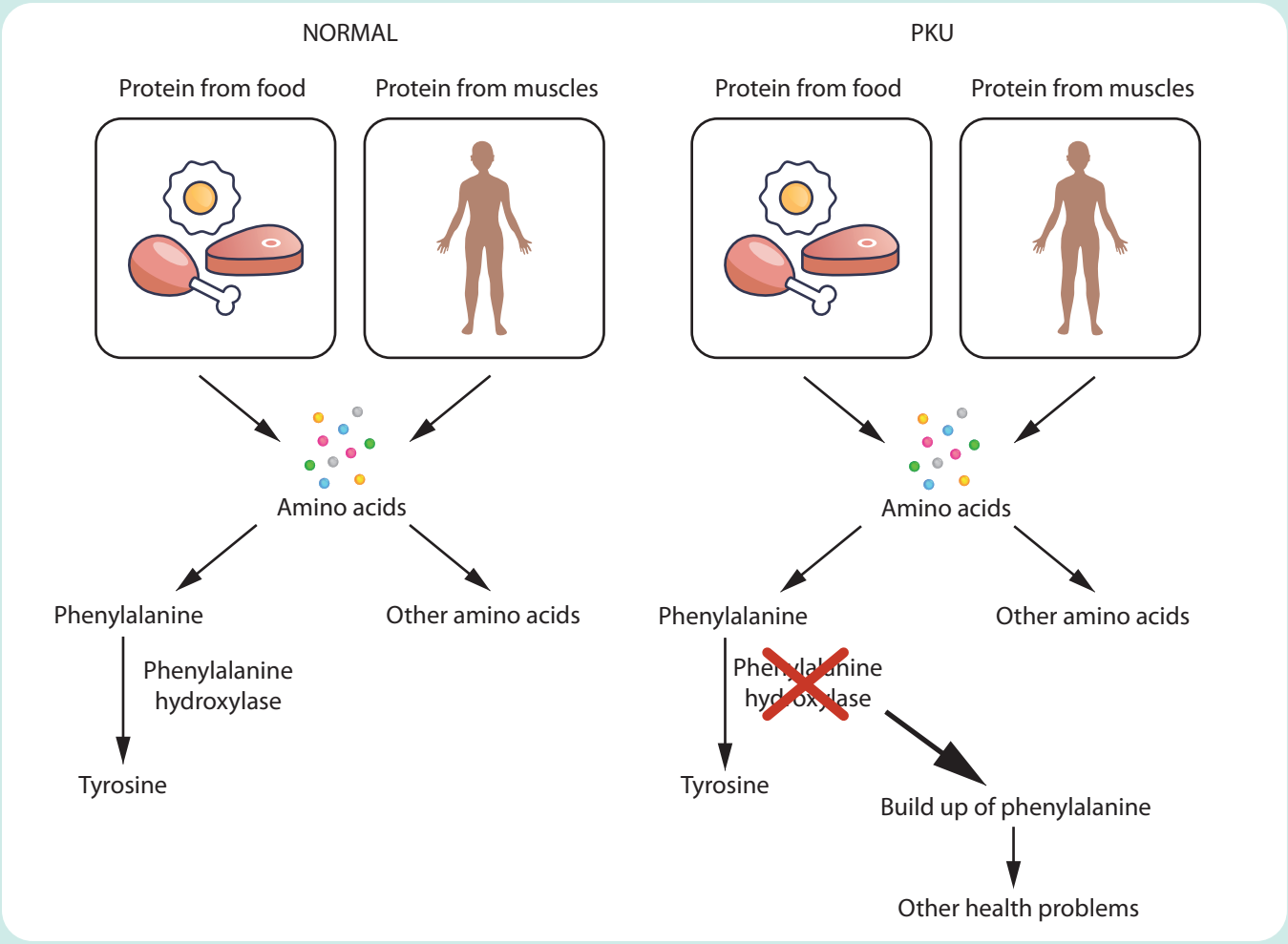
What is phenylketonuria?

Phenylketonuria is a rare inherited **genetic disorder** that causes a change in the way the body processes an amino acid called phenylalanine.

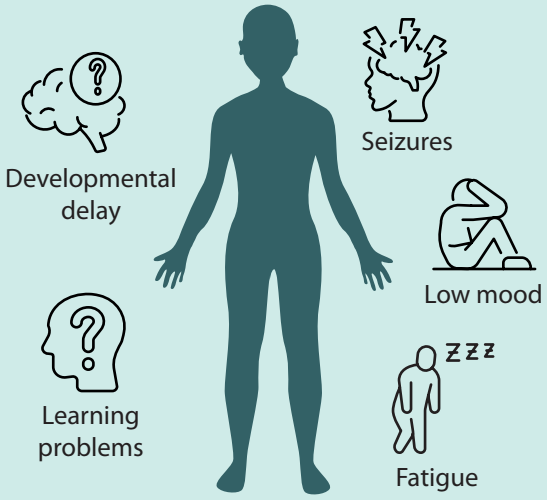


Genetic disorder: A health problem that is caused by an abnormality in a person's genes; the disorder is inherited from one or both parents.
Enzymes: Substances found in the body that speed up chemical reactions, such as the formation and break down of other substances.
Tyrosine: This is important for proper brain functioning and, therefore, a lack of tyrosine in people with phenylketonuria can have serious consequences.

- People with phenylketonuria lack an **enzyme** called phenylalanine hydroxylase in their liver; this enzyme is responsible for breaking down phenylalanine.
- Because phenylalanine cannot be broken down properly in people with phenylketonuria, it builds up to toxic levels in the blood and the brain.



- Furthermore, this abnormal processing of phenylalanine means that it is not converted into **tyrosine**.
  - » As a result, people with phenylketonuria have lower levels of tyrosine than people without the disorder.
- If phenylketonuria is not managed properly, this may lead to health issues, including damage to the brain and nervous system, resulting in:



Phenylketonuria cannot be cured.

- However, with the proper treatment of phenylketonuria (see below), toxic levels of phenylalanine in the brain and blood can be avoided.
- For this reason, many countries have a system for testing new-born babies to identify phenylketonuria.
  - » This allows treatment for phenylketonuria to be started soon after birth in affected babies, which can reduce the long-term effects of the disorder.
  - » The treatment has to be continued throughout life.

How is phenylketonuria treated?

The most widely used treatment for people with phenylketonuria is a special diet that contains a limited and controlled amount of phenylalanine.

- Phenylalanine cannot be completely eliminated from the diet because some is needed by the body for essential purposes.
- The diet is called a 'phenylalanine-restricted diet', and it involves restricting the amounts and types of many foods and, in particular, avoiding foods that contain large amounts of phenylalanine.
  - » Many foods that contain a lot of phenylalanine are those that are also high in protein, including meat, fish, eggs, cheese, and vegetables called 'legumes' (also known as 'pulses', such as beans, lentils, and peas).
  - » Phenylalanine is also found in the artificial sweetener aspartame that is commonly added to soft drinks and chewing gum, so these must also be avoided.

Phenylalanine-restricted diet

It is important that the phenylalanine-restricted diet is continued throughout life.

- However, following this diet can be challenging, as it affects all aspects of life, including going out with friends, attending social events, and eating out (such as in school/work canteens and restaurants).
  - » For these reasons, the phenylalanine-restricted diet is hard to maintain. The amount of phenylalanine that a person with phenylketonuria consumes each day while on the phenylalanine-restricted diet must be carefully calculated and monitored.

Despite being on the phenylalanine-restricted diet, people with phenylketonuria do need to consume other amino acids, vitamins, and minerals.

To make sure they receive enough of these other important compounds, people on the phenylalanine-restricted diet must take a **protein substitute**.

Protein substitute: A synthetic source of protein that does not contain any phenylalanine (or only very low amounts). Taking a protein substitute every day will help ensure that the body has sufficient protein for growth and repair of body tissues and to maintain control of blood phenylalanine levels. The protein substitute is usually in the form of a liquid, or a powder that is mixed with water to make a liquid or a gel.

The protein substitute is usually sourced from a mixture of amino acids that does not contain any phenylalanine, or from a glycomacropeptide-based protein substitute.

- The glycomacropeptide-based protein substitute is made from casein, the protein found in milk that gives it its white colour.
- It does contain a small amount of phenylalanine and this must be considered when the daily phenylalanine allowance is calculated.

Protein substitutes should be taken at least three times each day.

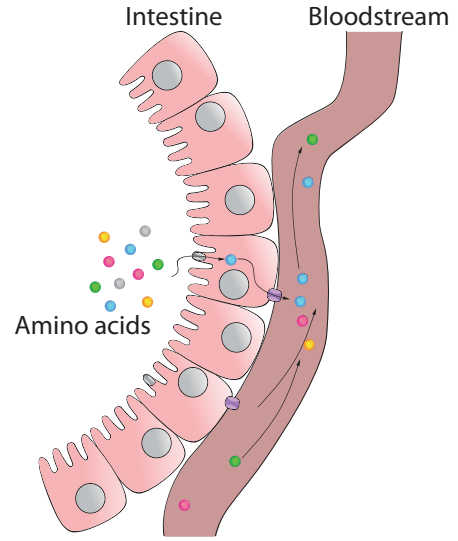
- Unfortunately, most amino acid mixtures have a very strong smell and taste, and may leave an aftertaste or cause bad breath.
  - » This means that some people find it very hard to take the mixtures every day, as they should.

Further, amino acids from the mixture are **absorbed** more quickly than they would be if they had come directly from natural protein in food.

This affects how well the mixture works.

- Specifically, because the amino acids are absorbed quickly, they rapidly build up to higher amounts than the body can use.
  - » Excess amino acids are then broken down into a waste product called urea, which contains nitrogen, and urea is removed from the body in the urine.
  - » The amount of nitrogen that is ready to be removed from the blood can be assessed by measuring a substance called blood urea nitrogen.
- The quick build up and then removal of amino acids reduces the time they are in the blood and are available to be used by the body.
- The amino acids also control the amount of glucose in the blood by affecting the release of insulin, a hormone that controls blood glucose levels and how hungry people feel (called 'satiety').

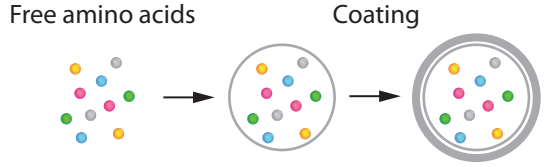
Absorption: The process by which substances that are swallowed pass through the wall of the intestines into the blood.



Overall, the difficulties people with phenylketonuria face with the currently available amino acid mixtures and the phenylalanine-restricted diet mean there is a need for better treatment options to improve their lives.

To overcome these problems, a new form of amino acid mixture has been developed that contains the amino acids within small granules that are coated with two layers of additives.

- » Placing the amino acids in these granules slows down their absorption from the intestines.
- » The mixture is called a 'prolonged-release' amino acid mixture.



The aim of this prolonged-release mixture is to reduce the quick increase and decrease in the amounts of amino acids in the blood that occur with the traditional 'immediate-release' amino acid mixtures usually used to treat phenylketonuria.

- Therefore, the prolonged-release amino acid mixture should 'smooth out' the overall amounts of amino acids available, to give a more **physiological profile**.
- The mixture may be particularly helpful for the evening meal/night-time dose of amino acid mixture, to ensure a better balance of amino acids in the blood overnight and before breakfast.
- Another advantage of the prolonged-release mixture is that the coating of the granules masks the taste and smell of the amino acids, helping to make the mixture more acceptable to take than immediate-release amino acid mixtures.

Physiological profile: A pattern that is more like the one that occurs when amino acids come directly from protein-containing foods.

Why was the study carried out?

- The main reason for performing the study was to investigate the pattern of amino acid absorption and the amounts of amino acids, blood urea nitrogen and urea in the body after the new prolonged-release amino acid mixture was taken.
  - » This was compared with patterns found after an immediate-release amino acid mixture was taken.
- The information obtained from the study would determine how the new prolonged-release mixture compares with the immediate-release mixture, and whether the new mixture gives a more physiological profile of amino acid absorption.
  - » This information could help improve the daily lives of people with phenylketonuria.

Who took part in the study?

- Men and women without phenylketonuria
- Aged between 18 and 45 years
- Who were not obese and did not smoke
- The study took place in Finland.

- Only people without phenylketonuria were invited to take part because the researchers felt that some of the study requirements, such as frequent taking of blood samples, would place too much burden on people with phenylketonuria.
  - » Other studies have shown that the absorption of amino acids is similar in people without phenylketonuria to that in people with the disorder.
  - » Therefore, results obtained from people without phenylketonuria would be relevant to people with phenylketonuria.
- Women who were pregnant or breast-feeding, and anyone who was not in general good health or was vegetarian or vegan, could not take part.
- 35 people joined the study.

What happened in the study?

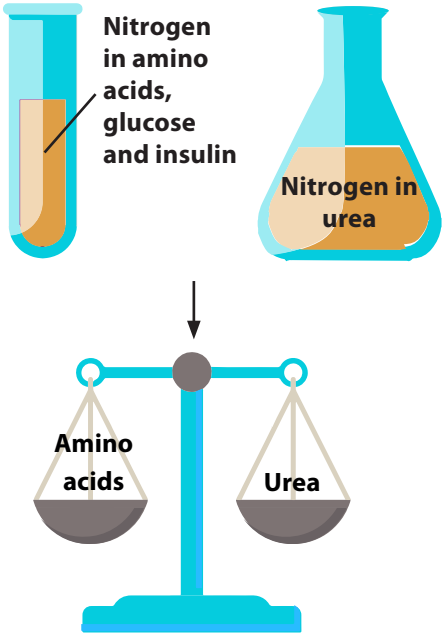
- On the first day of the study, those involved were assigned by chance to take either the prolonged-release or the immediate-release amino acid mixture.

Prolonged release mixture ⟷ Between 9 and 14 days later, they took the other mixture. ⟷ **Immediate-release mixture**

  - » Therefore, at the end of the study, each person had taken both the prolonged-release mixture and the immediate-release mixture.
- Blood concentrations of a specific class of amino acid called '**essential amino acids**' were measured in each person:
  - » just before each person took each amino acid mixture, and
  - » over the following 7 hours.
- The concentration of urea in the urine was also assessed before, and over the 7 hours after, each type of amino acid mixture was taken.
- The researchers assessed the blood results to determine the highest, or 'peak', amount of essential amino acids in the body of participants.

Essential amino acids: Amino acids that the human body cannot build using other substances and so they have to be obtained from food. Phenylalanine is an essential amino acid.

  - » This allowed the researchers to compare the results of the prolonged-release amino acid mixture with those of the traditional immediate-release amino acid mixture.
- The amounts of other classes of amino acid known as 'large neutral' amino acids and 'branched-chain' amino acids, of all amino acids together ('total' amino acids), and of phenylalanine alone were also determined.
- The amount of tyrosine in the blood was also assessed.
- In addition, the blood was examined to determine the amount of nitrogen present.
  - » This was measured in two ways – the amount of nitrogen that was part of amino acids and the amount of blood urea nitrogen (that was ready to be removed from the body).
  - » These two measures can be used to work out the 'nitrogen balance', which is the difference between the amount of nitrogen that has been taken into the body (in the form of nitrogen in amino acids) and the amount of nitrogen removed from the body (as part of blood urea nitrogen).
- Blood levels of glucose and insulin were also investigated.
- The people who took part in the study were also asked how well they liked the taste and smell of the prolonged-release and the immediate-release amino acid mixtures.



What were the main findings of the study?

- Of the 35 people who joined the study, 30 completed it: ♂ **15 women** ♀ **15 men** Their average age was 27 years.
- All 30 people took the immediate-release mixture as instructed and 28 people took the prolonged-release mixture as instructed.
- The prolonged-release mixture showed a more physiological amino acid absorption profile than the immediate-release mixture.
  - » The peak amount of essential amino acids was **27%** ↓ after the prolonged-release mixture was taken.
    - The peak amounts of the other two classes of amino acid and of total amino acids were also lower after the prolonged-release mixture was taken.
  - » The amount of each of the three classes of amino acid (but not total amino acids) found in the blood was higher 7 hours after the prolonged-release mixture was taken than at the same time after the immediate-release mixture was taken.

The amount of phenylalanine found in the blood over the 7 hours of the study changed less with the prolonged-release mixture.

- The overall amounts of all classes of amino acids and of tyrosine that were detected in the blood over the course of the study were similar with the two mixtures, indicating that they were '**bioequivalent**'.
- The nitrogen balance was better after the prolonged-release mixture than the immediate-release mixture.
  - » The amounts of blood urea nitrogen and of urea in the urine were both lower with the prolonged-release mixture.

Bioequivalent: If two products are bioequivalent it means that there is no difference between them with regards to their availability in the blood.

  - » The changes in blood urea nitrogen over time were smaller with the prolonged-release mixture.
  - » These findings suggest that the amino acids released from the prolonged-release mixture are not broken down so quickly and so were being used more efficiently by the body.
- The prolonged-release mixture also caused smaller changes in the amounts of glucose and insulin in the blood than the immediate-release mixture.
- There was no difference between how well people liked the taste and smell of the prolonged-release mixture compared with the immediate-release mixture.

What were the side effects?

87% of the people who took the amino acid mixtures reported **at least one side effect** during their participation in the study.

- The most common were headache and common cold.

97.5% of the side effects were not thought to be caused by the amino acid mixtures.

- The exceptions were one case of headache (with the prolonged-release mixture) and one of nausea (with the immediate-release mixture).

What do the results of the study mean?

- The results of the study show that the prolonged-release and immediate-release mixtures provide, overall, the same amounts of amino acids to the body.
- However, the prolonged-release mixture resulted in a more physiological amino acid absorption profile and, because of this, the amino acids were used more efficiently by the body.
  - » This includes the important amino acid tyrosine.
- The prolonged-release mixture was also associated with smaller changes in insulin and glucose levels in the blood.
  - » In addition, taking the mixture did not cause any serious side effects.
- Therefore, compared with the currently available immediate-release amino acid mixtures, the new prolonged-release amino acid mixture may provide people who have phenylketonuria with a new treatment option that will help to manage their symptoms.

Where can I find more information about the study and phenylketonuria?

Original articles

This article summarises two scientific articles that described a study comparing a prolonged-release amino acid mixture for phenylketonuria with other protein substitutes. These articles, which were originally published in the journal *Nutrients*, are free to access:

Scheinin M, et al. Amino acid plasma profiles from a prolonged-release protein substitute for phenylketonuria: A randomized, single-dose, four-way crossover trial in healthy volunteers. *Nutrients*. 2020 Jun 2; 12(6): 1653.

Scheinin M, et al. Nitrogen balance after the administration of a prolonged-release protein substitute for phenylketonuria as a single dose in healthy volunteers. *Nutrients*. 2021 Sep 14; 13(9): 3189.

You can access the two original articles via these links https://www.mdpi.com/2072-6643/12/6/1653 and https://www.mdpi.com/2072-6643/13/9/3189.

Trial registration

You can find complete information about the study on the following website: https://www.isrctn.com/ISRCTN11016729.

Educational resources

You can read more about amino acid mixtures in the management of phenylketonuria in the following article on protein substitutes ('protein substitutes' is a broader term that includes amino acid mixtures and all other categories of pharmaceuticals [including, for example, glycomacropeptides] that provide an alternative source of amino acids or proteins to natural food intake):

Daly A, et al. Protein substitutes in PKU; Their historical evolution. *Nutrients*. 2021 Feb 2; 13(2): 484.

The article is free to access and available at: https://www.mdpi.com/2072-6643/13/2/484.

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Declaration of interest

AM has received research funding and honoraria from Nutricia, Vitaflo International, Metax, Cambrookes, Applied Pharma Research, Meta Health, PIAM, PTC Therapeutics, and Biomarin. She is a member of the advisory board for Danone-Nutricia, Arla and Vitaflo International. ACM has participated in strategic advisory boards and received honoraria as a consultant and as a speaker for Merck Serono, BioMarin, Nestlé Health Science (Vitaflo), Applied Pharma Research, Actelion, Retrophin, Censa, PTC Therapeutics, and Arla Food. ACM has also received research grants from SHS, Merck Serono, Dr Schär, Vitaflo, and Nutricia. MS was employed by CRST Oy and the University of Turku; CRST Oy conducted the study described in this work as contract research for Applied Pharma Research S.A. NC has been involved in the design of phenylketonuria awareness campaigns funded by BioMarin, and has participated as a speaker in events sponsored by Applied Pharma Research, BioMarin, and PIAM. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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