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## Recommendations for the nutrition management of phenylalanine hydroxylase deficiency

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The effectiveness of a phenylalanine-restricted diet to improve the outcome of individuals with phenylalanine hydroxylase deficiency (OMIM no. 261600) has been recognized since the first patients were treated 60 years ago. However, the treatment regime is complex, costly, and often difficult to maintain for the long term. Improvements and refinements in the diet for phenylalanine hydroxylase deficiency have been made over the years, and adjunctive therapies have proven to be successful for certain patients. Yet evidence-based guidelines for managing phenylalanine hydroxylase deficiency, optimizing outcomes, and addressing all available therapies are lacking. Thus, recommendations for nutrition management were developed using evidence from peer-reviewed publications, gray literature, and consensus surveys. The areas investigated included choice of appropriate medical foods, integration of adjunctive therapies, treatment

during pregnancy, monitoring of nutritional and clinical markers, prevention of nutrient deficiencies, providing of access to care, and compliance strategies. This process has not only provided assessment and refinement of current nutrition management and monitoring recommendations but also charted a direction for future studies. This document serves as a companion to the concurrently published American College of Medical Genetics and Genomics guideline for the medical treatment of phenylalanine hydroxylase deficiency.

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**Key Words:** medical food; nutrition management of PAH deficiency; nutrition recommendations; phenylalanine hydroxylase deficiency; phenylketonuria

Nutrition therapy, first introduced 6 decades ago, remains the primary treatment for phenylalanine hydroxylase (PAH) deficiency.<sup>1-3</sup> The goals of lifelong nutrition therapy include normal physical growth and neurocognitive development, maintenance of adult health, and normal gestational outcomes in pregnant women with PAH deficiency. Knowledge of metabolism, the pathophysiology of PAH deficiency, and the role of nutrition has led to new and improved treatment options, modified low-protein foods, and medical foods that provide protein equivalents and other nutrients when intact protein food sources must be limited. **Table 1** contains definitions of modalities used in the nutrition treatment of aminoacidopathies, including PAH deficiency. Lifelong treatment is recommended because of the negative association between elevated blood phenylalanine (PHE) and neurocognition, yet national nutrition recommendations for PAH deficiency are lacking. The goals of the present evidence- and consensus-based recommendations are to translate current knowledge to patient care, foster more harmonious clinical practices, and promote healthy eating, with the

ultimate goal of ensuring better outcomes for individuals with PAH deficiency. This document serves as a companion to the concurrently published American College of Medical Genetics and Genomics (ACMG) guideline for the medical treatment of PAH deficiency.<sup>4</sup>

### MATERIALS AND METHODS

Recommendations were developed by a cooperative effort among Genetic Metabolic Dietitians International, the Southeast Regional Genetics Collaborative, and dietitians from the Diet Control and Management and Maternal PKU Workgroups from the National Institutes of Health Phenylketonuria Scientific Review Conference<sup>2</sup> held in February 2012. The evidence for these recommendations represents the synthesis of information from the National Institutes of Health 2000 (ref. 2) and Agency for Healthcare Research and Quality 2012 (ref. 1) reviews and the literature review completed by the National Institutes of Health Phenylketonuria Scientific Review Conference workgroups. PubMed was the primary database for the National Institutes of

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**Table 1** Definitions of modalities used for treatment of aminoacidopathies

**Medical food:** A food that is formulated to be consumed or administered enterally under the supervision of a physician and that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation (section 5(b), Orphan Drug Act (21 USC 360ee (b)(3)(61)).

**Modified low-protein food:** Food products specially formulated to contain less than 1 g of protein per serving. Low-protein modified food products are intended for use under the direction of a physician for the dietary treatment of hereditary metabolic diseases. Examples of commercially available low-protein food products include breads, pasta, baking mix, and imitation cheese.

**Intact protein:** Food-derived, natural protein.

**Protein equivalent:** Containing an equivalent amount of nitrogen as found in a complete protein. For medical foods, this is often used to describe the free amino acids that replace intact protein.

Health Phenylketonuria Scientific Review Conference scientific literature searches. Search terms were specific to each question (as described in the ACMG guideline<sup>4</sup>), but inclusion and exclusion criteria were the same for all questions.

Consensus-based tools used to support these recommendations were the National Institutes of Health expert panel summary (described in the companion paper), a PAH Deficiency Delphi survey,<sup>5</sup> and an Inborn Errors of Metabolism (IEM) survey (D.M. Frazier, S.C. van Calcar, et al., personal communication). The Delphi process is a component of the guideline development model that uses accepted methods for evidence analysis, with the addition of consensus techniques to address clinical practice issues for which research is lacking.<sup>6</sup> The Delphi survey, an online survey in which participants indicated their level of agreement or disagreement with practice statements, was answered by 17 experts from the seven Health Resources and Services Administration Regional Genetics and Newborn Screening Collaboratives. When the level of agreement was 80% or greater, the information was added to the evidence summaries in these recommendations. The IEM survey, also online, was conducted following the National Institutes of Health–sponsored Nutrition and Dietary Supplement Interventions for Inborn Errors of Metabolism Workshop that was held in December 2011. Information about the use of nutritional treatments and supplements by metabolic specialists managing individuals with PAH deficiency was collected from 82 survey respondents.

## BLOOD PHE AND TYROSINE (TYR) CONTROL

### Target blood PHE

Blood PHE has been used to monitor metabolic status and determine appropriate dietary PHE intake and has been shown to be a reliable predictor of clinical outcomes.<sup>7</sup> The companion ACMG PAH deficiency treatment guideline supports a life-long target blood PHE of 120–360  $\mu\text{mol/l}$  for optimal cognitive outcome.<sup>4</sup> Eighty percent of Delphi respondents supported 120–360  $\mu\text{mol/l}$  as a goal blood PHE for individuals with PAH deficiency of all ages, yet there was recognition that the goal is difficult to achieve and may not apply in all cases.<sup>5</sup> Regular blood PHE monitoring is key to the management of PAH deficiency. During infancy, early childhood, and pregnancy, more frequent monitoring is necessary to assess the increased dietary PHE needs of anabolism<sup>3</sup> (Table 2). The British Medical Research Council guidelines recommend measuring PHE concentrations at a standard time<sup>3</sup>; there was a consensus that

blood samples be collected at the same time of day, preferably 2–3 hours after a meal.<sup>5</sup> It is recommended that medical food be consumed throughout the day to maintain stable concentrations of blood PHE.<sup>8</sup>

### Target blood TYR and PHE:TYR ratio

Because both endogenous production of TYR and intact protein intake are greatly limited in PAH deficiency, monitoring is necessary to ensure that supplementation is adequate to maintain the blood TYR in the normal range. Some clinicians routinely monitor blood PHE:TYR ratios.<sup>9</sup> There are reports of impairments in executive function among individuals with high PHE:TYR ratios.<sup>9,10</sup> However, at this time the clinical relevance of PHE:TYR as a routine biomarker requires further study.

## RECOMMENDATIONS

- Maintain blood PHE between 120 and 360  $\mu\text{mol/l}$  throughout the life span for optimal outcome.
- Monitor blood PHE most frequently during times of increased anabolism: infancy, childhood, and pregnancy.
- Monitor blood PHE at a consistent time during the day, preferably 2–3 hours after eating.
- Maintain blood TYR in the normal range.

## THE INFLUENCE OF GENOTYPE ON NUTRITION TREATMENT

As described in the ACMG guideline,<sup>4</sup> individuals with PAH deficiency have been categorized by phenotype (PHE tolerance and blood PHE concentrations) and genotype.<sup>4</sup> PHE tolerance is defined as the amount of dietary PHE (mg/day) an individual with PAH deficiency can consume while maintaining blood PHE in the treatment range.<sup>11</sup> Although individuals with PAH deficiency are represented by a spectrum of residual enzyme activity, some practitioners find practical utility in referring to the older categories: “classic/severe,” “moderate,” “mild,” and “mild hyperphenylalaninemia not needing PHE restriction.”

### Treatment by phenotype and PHE tolerance

In clinical practice, PHE tolerance can often be determined by 2–5 years of age.<sup>12</sup> However, because PHE tolerance can change during periods of rapid growth or changes in lifestyle,

**Table 2** Monitoring the nutritional management of individuals with PAH deficiency<sup>a</sup>

Outcomes	Pregnancy and postpartum period					
	Infants (0–1 year)	Children (1–7 years)	Children (8–18 years)	Adults	Pregnancy	Postpartum lactation
Domain measures	(0–1 year)	(1–7 years)	(8–18 years)	Adults	Pregnancy	Postpartum lactation
Clinical assessment						
Nutrition visit in clinic (dietary intake <sup>b</sup> and nutrient analysis, nutrition-related physical findings, nutrition counseling, diet education)	Weekly to monthly	Monthly to every 6 months	Every 6–12 months	Every 6–12 months	Monthly to per trimester	At 6 weeks postpartum, then every 6 months
Anthropometrics <sup>c</sup> (weight, length or height, weight for length or BMI)	At every clinic visit <sup>b</sup> . Include head circumference	At every clinic visit <sup>b</sup> . Include head circumference through 36 months	At every clinic visit	At every clinic visit	At every clinic visit	At every clinic visit
Interval nutrition visit (diet adjustment based on blood PHE and/or counseling (either face to face or by phone/electronic communication))	Twice weekly to weekly	Weekly to monthly	Weekly to monthly	Monthly	Twice weekly to weekly	Weekly to monthly
Psychological		As outlined in the ACMG guideline Table 2 (ref. 4)				
Biochemical (routine)						
PHE (plasma, serum, or whole blood <sup>d</sup> )	Twice weekly to weekly	Weekly to monthly	Weekly to monthly	Monthly	Twice weekly to weekly	Weekly to monthly
TYR (plasma, serum, or whole blood <sup>d</sup> )	Twice weekly to weekly	Weekly to monthly	Weekly to monthly	Monthly	Twice weekly to weekly	Weekly to monthly
Amino acids, plasma	Monthly to every 3 months	At every clinic visit	At every clinic visit	At every clinic visit	Weekly to monthly	At every clinic visit
Transthyretin (prealbumin)	6–12 months	6–12 months	6–12 months	6–12 months	Monthly to per trimester	Yearly
Albumin/total protein	6–12 months	6–12 months	6–12 months	6–12 months	Per trimester	Yearly
Complete blood count	Yearly	Yearly	Yearly	Yearly	Per trimester	Yearly
Ferritin	Yearly	Yearly	Yearly	Yearly	Per trimester	Yearly
Vitamin D 25-OH	Yearly	Yearly	Yearly	Yearly	Per trimester	Yearly
Biochemical (conditional)						
Comprehensive metabolic panel, serum vitamin B <sub>12</sub> , B <sub>6</sub> , erythrocyte folate, vitamin A, zinc, copper, selenium, essential fatty acids	As indicated <sup>e</sup>	As indicated <sup>e</sup>	As indicated <sup>e</sup>	As indicated <sup>e</sup>	At first visit and then as clinically indicated	Once in the postpartum period
Radiological						
DXA	NA	NA	Every 3–5 years beginning at age 8 <sup>f</sup>	Every 5 years	NA	NA

ACMG, American College of Medical Genetics and Genomics; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; NA, not applicable; PAH, phenylalanine hydroxylase; PHE, phenylalanine; TYR, tyrosine.

<sup>a</sup>Recommendations were derived from Delphi and Nominal group consensus on monitoring of aminoacidopathies and the Newborn Screening Translational Research Network. Frequency of clinical and laboratory assessments at a metabolic clinic (involving the medical geneticist, metabolic dietitian, social worker, nurse specialist, psychologist, and others) may not be possible for reasons such as travel distance, cost, and loss of work days. Coordination with primary-care and community-based providers, use of telemedicine, and frequent communication by telephone and mail should be employed. More frequent monitoring may be necessary if the individual is not in good metabolic control.

<sup>b</sup>A mechanism for assessing dietary intake, whenever PHE is monitored, should be in place. MetabolicPro (<http://www.metabolicpro.org>) is a computer program available for dietary analysis of amino acid–restricted diets.

<sup>c</sup>The Centers for Disease Control and Prevention (CDC) recommends using the 2006 World Health Organization (WHO) Child Growth Standards to evaluate growth of infants from birth to age 24 months. The CDC recommends using the 2000 CDC Growth Charts to evaluate the growth of children from age 2 to 20 years. Techniques for measurement are described on the CDC website ([http://www.cdc.gov/growthcharts/cdc\\_charts.htm](http://www.cdc.gov/growthcharts/cdc_charts.htm)).

<sup>d</sup>Monitoring protocols may include mail-in blood specimens (using filter paper cards or capillary tubes) or use of local laboratories or the State Laboratory of Public Health. Such protocols are optimal for increasing the frequency of monitoring. When plasma amino acid analysis is the only available means of PHE and TYR monitoring, access and cost may force less-frequent monitoring.

<sup>e</sup>Monitoring is indicated when nutrition assessment indicates poor adherence to diet or inadequate medical food consumption, or when there has been consumption of an incomplete medical food, clinical signs/symptoms of nutritional inadequacy including poor growth, or serious intercurrent illness. If laboratory values are abnormal, reassessment of specific analytes should be scheduled within 1 month of intervention.

<sup>f</sup>DXA is indicated in individuals who have frequent fractures and/or low serum 25-hydroxy vitamin D concentrations.

it is important to reassess PHE tolerance periodically by assessing dietary PHE intake with blood PHE.<sup>11,13</sup> Predicting PHE tolerance may be useful when communicating expectations to families, assessing responsiveness to adjunctive therapy,<sup>14</sup> and planning dietary prescriptions.

Those with little residual PAH activity (“classic PKU”) will require the most medical food as their primary source of protein equivalents.<sup>15</sup> Modified low-protein foods should be introduced early to meet critical energy needs and maintain metabolic control in this group. For individuals with mild or moderate PAH deficiency, less medical food and/or modified low-protein food is needed to maintain blood PHE control.<sup>16</sup> Such individuals are also more likely to respond to sapropterin, which has the potential for allowing liberalization of the diet. The need to treat individuals with very mild hyperphenylalaninemia remains under debate.<sup>17</sup>

Even with classification by genotype or phenotype, additional factors can affect the management of PAH deficiency. Individualized treatment plans must reflect the patient’s unique genetic makeup, general health, intercurrent illness, growth requirements, activity level, pregnancy/lactation status, and access to care.

## NUTRIENT REQUIREMENTS, SOURCES, AND MONITORING

Nutrient requirements for individuals with PAH deficiency do not differ from those of the general population, except for PHE, TYR, and protein (**Table 3**).<sup>3,18–20</sup> Concern about the nutritional

adequacy of the diet arises because the severe restriction of foods containing intact protein necessitates lifelong reliance on semisynthetic medical foods, from which some nutrients may not be as well absorbed. In addition, nonadherence to medical food consumption, or reliance on nutritionally incomplete medical foods, increases the risk of multiple nutrient deficiencies. Therefore, monitoring of nutrient intake and laboratory indexes of nutritional adequacy is recommended (**Table 2**).

### Protein and amino acids

Because medical food is the primary source of protein equivalents in the diet for PAH deficiency, it is a critical component of the diet throughout life. Recommendations for total protein intake exceed age- and sex-specific Dietary Reference Intakes because L-amino acids found in most medical foods are absorbed and oxidized more rapidly than amino acids in intact protein.<sup>21,22</sup> Traditionally, L-amino acids (without PHE) have been the source of protein equivalents in medical foods, but more recently, glycomacropeptide (GMP), an intact protein that is low in PHE, has been used as a protein source in combination with limiting L-amino acids.<sup>23</sup> L-Amino acid–based or GMP-based medical foods provide ~85% of the protein needs of individuals with a severe form of PAH deficiency.<sup>24</sup> Large neutral amino acids (LNAA) can also be used as the medical food for some individuals with PAH deficiency in conjunction with a more relaxed protein restriction.

Normal protein status, assessed by monitoring plasma amino acids and prealbumin, is achievable when total protein is

**Table 3** Recommended intakes of PHE, TYR, and protein for individuals with PAH deficiency

Age	PHE (mg/day)	TYR (mg/day)	Protein <sup>a</sup> (g/kg)
Infant to <4 years <sup>b</sup>			
0 to <3 months <sup>c</sup>	130–430	1,100–1,300	3–3.5
3 to <6 months	135–400	1,400–2,100	3–3.5
6 to <9 months	145–370	2500–3000	2.5–3
9 to <12 months	135–330	2,500–3,000	2.5–3
	<b>(mg/day)</b>	<b>(mg/day)</b>	<b>(g/day)</b>
1 to <4 years <sup>d</sup>	200–320	2,800–3,500	≥30
After early childhood <sup>e</sup>			
>4 years to adult	200–1,100	4,000–6,000	120–140% RDA for age <sup>f</sup>
Pregnancy/lactation <sup>g</sup>			
Trimester 1	265–770	6,000–7,600	≥70
Trimester 2	400–1,650	6,000–7,600	≥70
Trimester 3	700–2,275	6,000–7,600	≥70
Lactation <sup>h</sup>	700–2,275	6,000–7,600	≥70

DRI, dietary reference intake; PAH, phenylalanine hydroxylase; PHE, phenylalanine; RDA, recommended dietary allowance; TYR, tyrosine.

<sup>a</sup>Protein recommendations for individuals consuming PHE-free amino acid–based medical foods as part of their protein source.

<sup>b</sup>Recommended intakes for infants and children <4 years of age are adapted from ref. 20 and are for individuals with a severe form of PAH deficiency treated with a PHE-restricted diet alone.

<sup>c</sup>PHE requirements for premature infants with PAH deficiency may be higher.

<sup>d</sup>PHE tolerance is usually stable by 2–5 years of age as PHE requirements are based on a combination of size (increasing with age) and rate of growth (decreasing with age). For any individual, PHE intake is adjusted based on frequent blood PHE monitoring.

<sup>e</sup>Adapted from ref. 12. Range of PHE intake is for entire spectrum of PAH deficiency (mild to severe).

<sup>f</sup>Recommended protein intake greater than the RDA is necessary to support normal growth in PAH deficiency.

<sup>g</sup>Recommendations are slightly higher for pregnant women ≤19 years of age.

<sup>h</sup>DRI recommends that, for all women, nutrient intake during lactation be the same as during the third trimester of pregnancy.

provided in appropriate amounts.<sup>18,21</sup> Prealbumin is an acceptable measure of protein status in individuals with PAH deficiency.<sup>25</sup> Mild protein insufficiency, as indicated by a prealbumin concentration of <20 mg/dl, has been associated with decreased linear growth.<sup>26</sup>

TYR is conditionally essential in PAH deficiency and must be added to the diet to maintain blood concentrations in the normal range. By itself, TYR supplementation does not improve neurological outcomes.<sup>27</sup> All medical foods for the treatment of PAH deficiency are supplemented with TYR;<sup>15</sup> therefore, individuals who do not adhere to their prescribed intake of medical food may have inadequate blood concentrations of TYR. In addition, TYR has a low solubility and may settle out of prepared medical foods during storage.<sup>15</sup> Most clinicians monitor blood TYR routinely in individuals with PAH deficiency,<sup>9</sup> and low plasma TYR has been documented among individuals treated with diet.<sup>28</sup> One cause could be a diurnal variation in blood TYR.<sup>29</sup> Supplementation beyond that provided by medical food with TYR is indicated only if blood TYR concentrations are consistently below the normal range. Fewer than 20% of clinicians in the IEM survey (D.M. Frazier, S.C. van Calcar, et al., personal communication) routinely prescribe TYR supplementation.

### Energy

Because energy expenditure varies from person to person, energy requirements must be individually assessed. Most evidence suggests that energy requirements are not increased in PAH deficiency, and carbohydrate and fat intakes are within established recommendations.<sup>30,31</sup>

### Essential fatty acids

With adequate fat intake, children with PAH deficiency are found to have normal essential fatty acid (EFA) status.<sup>32</sup> Medical foods supplemented with sources of long-chain polyunsaturated fatty acids increase blood concentrations of EFA.<sup>33</sup> When a fat-free medical food is provided or the diet contains inadequate sources of linoleic and  $\alpha$ -linolenic acid, EFA status should be monitored.<sup>5</sup> Both the IEM survey (D.M. Frazier, S.C. van Calcar, et al., personal communication) and the Delphi survey<sup>5</sup> suggest that supplementation with precursor EFA, or with preformed docosahexaenoic acid (DHA), may be necessary in these individuals. In infancy, including breast milk or standard formulas containing DHA and arachidonic acid, as well as medical foods that contain DHA/arachidonic acid, can help ensure adequacy.

### Micronutrients

Most medical foods available in the United States are supplemented with vitamins and minerals to provide micronutrients in amounts that meet recommendations. When a medical food does not contain adequate amounts of micronutrients or an individual's intake is inadequate, a vitamin and mineral supplement should be included in the treatment plan. Additional biochemical monitoring (Table 2) is indicated when there is a question about inadequate or excessive intake.

Minerals, including copper, manganese, and zinc,<sup>34</sup> as well as selenium,<sup>35</sup> have been reported as being deficient in the diet for PAH deficiency. However, these minerals are now added to most medical foods. Iron deficiency (without anemia) has been reported among individuals with PAH deficiency, and routine evaluation of iron status is recommended.<sup>36,37</sup>

Vitamin B<sub>12</sub>, as well as B<sub>6</sub>, deficiency may occur if there is inadequate consumption of medical food or animal protein.<sup>38</sup> Severe megaloblastic anemia has been reported in adolescents and adults with PAH deficiency who are off-diet.<sup>39</sup> Because B<sub>12</sub> deficiency can cause neurological deficits,<sup>40</sup> including memory loss, such symptoms could be erroneously attributed to high blood PHE. Supplementation is indicated if B<sub>12</sub> markers remain low.<sup>40</sup> In addition, higher than normal plasma B<sub>12</sub> levels have been reported in some on-diet individuals with PAH deficiency.<sup>41</sup> Both excessive and inadequate intakes of the fat-soluble vitamins A and D are possible with inappropriate medical food intake. Monitoring for clinical signs with subsequent biochemical testing is warranted.

There may be concerns with bone density that are unique to PAH deficiency. Decreased bone mineral density and bone mineral content, indicated by dual-energy X-ray absorptiometry, have been noted.<sup>42,43</sup> Osteopenia, defined as bone mineral density one or more SDs from normal reference for age and sex, is also seen<sup>44</sup> but cannot be attributed to vitamin D concentrations alone. Some reports indicate that bone density is associated with adherence to nutrition therapy,<sup>45</sup> whereas others note decreased density across groups, stratified by calcium and phosphorus intakes<sup>42</sup> and/or as compared with controls without PAH deficiency.<sup>43</sup> Aberrant findings in protein markers, correlating to bone resorption or absorption, have also been reported.<sup>46,47</sup> Further research is warranted to look at the effects of PAH deficiency itself, PAH deficiency management, and nutrient intake on bone density.

### Anthropometrics

With adequate nutrient intake, appropriate growth can be expected for individuals with PAH deficiency.<sup>18,19</sup> Impaired linear growth has been noted in children with PAH deficiency who had low plasma prealbumin concentrations.<sup>26</sup> There is conflicting evidence as to whether or not the rates of overweight and obesity in children with PAH deficiency are similar to those of the general population.<sup>30,48</sup>

### Clinical indicators

Physical findings associated with poorly controlled PAH deficiency include osteopenia<sup>45</sup> and dermatological problems.<sup>49</sup> Asthma, recurrent headache, eczema, neurological signs, hyperactivity, and/or lethargy have all been reported in adults with PAH deficiency who discontinued dietary treatment.<sup>50</sup> Psychological symptoms include phobias and depression.<sup>51</sup> The majority of physical signs and symptoms of PAH deficiency reported in the literature resolved when blood PHE concentrations were reduced to the treatment range.



## RECOMMENDATIONS

- Provide the same nutrient intakes as those of the general population, except for PHE, TYR, and protein.
- Assess the need for vitamin/mineral supplementation when a medical food without complete vitamins and minerals is used or when there is insufficient adherence with medical food intake.
- Monitor nutrition status by assessing anthropometrics, clinical signs and symptoms, nutrient intake, and laboratory indexes of metabolic control and nutrition adequacy (Table 2).

## NUTRITION STRATEGIES FOR MANAGEMENT OF INDIVIDUALS WITH PAH DEFICIENCY

### Selecting medical food

Medical foods provide necessary protein equivalents in the diets of individuals with PAH deficiency, and selecting the appropriate medical food can affect both dietary compliance and nutritional status. There are more than 30 medical foods available for the treatment of PAH deficiency, and they can be classified by the age for which they are intended and by macronutrient composition (Table 4). Infant medical foods typically lack only PHE. Products designed for children,

adolescents, and adults vary widely in protein, fat, vitamin, and mineral content to meet individual taste and nutrient needs, but many are nutritionally incomplete. The macro- and micronutrient profiles of many medical foods for IEM are available at <http://www.gmdi.org>. Medical food should be consumed throughout the day and divided into at least three servings because more frequent consumption of medical foods is associated with better PHE tolerance<sup>13</sup> and improved plasma PHE concentrations.<sup>8</sup>

Medical foods are available in a variety of flavors and in different forms (i.e., powders, ready-to-drink liquids, tablets, and bars). Convenience packaging and alternative forms of medical foods typically cost more than the powdered forms. Although insurance coverage of medical foods is mandated in some states, there are exceptions and limitations. Therefore, access to medical food is not guaranteed in the United States, and obtaining coverage can be an arduous process.<sup>52</sup> This is due, in part, to the fact that medical foods are not prescription medications but have a unique classification by the Food and Drug Administration that was intended to promote the development of more products for PAH deficiency and other orphan diseases.<sup>53</sup> The classification allows a less costly regulatory process necessary to get medical foods to market.

**Table 4** Classification of medical foods<sup>a</sup>

Classification	Amino acids, fat, carbohydrate, vitamins, and minerals	Amino acids, carbohydrate, vitamins, and minerals	Amino acids	Glycomacropeptide	Large neutral amino acids
Nutrient profile	Most complete	Most vitamins and minerals, no fat	Few or no vitamins and minerals and no fat	Variable depending on product; contains PHE	Variable depending on product
Energy/protein ratio (kcal/g protein) <sup>b</sup>	High to medium	Medium to low	Low	Variable	Low
Forms	Powder	Powder, ready-to-drink	Powder, capsules, tablets	Powder, ready-to-drink, bars, pudding	Powder, tablets
Products designed for infants	Periflex Infant <sup>e</sup> , Phenex-1 <sup>f</sup> , Phenyl-Free1 <sup>g</sup>	None	None	None	None
Products designed for children <sup>c</sup>	Periflex Junior <sup>e</sup> , Phenex-2 <sup>f</sup> , PhenylAde Essential <sup>e</sup> , Phenyl-Free 2 <sup>g</sup>	Lophlex <sup>e</sup> , PhenylAde 40 <sup>e</sup> , PKU Coolers <sup>h</sup> , PKU Gel <sup>h</sup> , Maxamaid XP <sup>e</sup>	None	BetterMilk <12 <sup>i</sup> , Complete bars <12 <sup>i</sup> , Restore <sup>i</sup>	None
Products designed for adolescents and adults <sup>d</sup>	Periflex Advance, Phenex-2 <sup>f</sup> , PhenylAde Essential <sup>e</sup> , Phenyl-Free 2 <sup>g</sup> , Phenyl-Free 2HP <sup>g</sup>	Lophlex LQ <sup>e</sup> , PhenylAde RTD <sup>e</sup> , PhenylAde 40 <sup>e</sup> , PhenylAde 60 <sup>e</sup> , PKU Coolers <sup>h</sup> , Maxamum XP <sup>e</sup>	PhenylAde Amino Acid Blend <sup>e</sup> and Amino Acid Blend MTE <sup>e</sup> , Phlexy-10 <sup>e</sup>	BetterMilk 12+ <sup>i</sup> , Complete bars <sup>i</sup> , Restore <sup>i</sup> , Restore Lite <sup>i</sup> , Swirl <sup>i</sup>	Lanaflex  PheBloc <sup>e</sup>

PHE, phenylalanine.

<sup>a</sup>Examples of products available in the United States as of May 2013. Inclusion in table does not represent endorsement.

<sup>b</sup>Energy/protein ratio categories (kcal/g): low, 4–9; medium, 10–19; high, >20.

<sup>c</sup>Some products are not appropriate for children <4 years; check manufacturer's information for nutrient profile.

<sup>d</sup>Some products may be used before adolescence, especially if used in combination with other products, depending on clinical circumstances.

<sup>e</sup>Nutricia North America, Gaithersburg, MD.

<sup>f</sup>Abbott Nutrition, Columbus, OH.

<sup>g</sup>Mead Johnson Nutrition, Evansville, IN.

<sup>h</sup>Vitaflo USA, Alexandria, VA.

<sup>i</sup>Cambrooke Foods, Ayer, MA.

### Glycomacropeptide

GMP is an intact whey protein low in PHE, TYR, histidine, leucine, tryptophan, and arginine. All except PHE must be added as free L-amino acids to provide an appropriate protein source for PAH deficiency.<sup>54</sup> Although long-term efficacy and growth studies are lacking, a short-term inpatient study found no safety concerns when GMP products replaced amino acid–based medical food.<sup>54</sup> Various markers pointed to improved protein utilization,<sup>54</sup> and lower ghrelin concentrations suggested improved satiety when GMP products replaced each subject's usual amino acid–based medical food as the protein source.<sup>55</sup> Medical food products incorporating GMP are an alternative to PHE-free amino acid formulas. Because GMP contains a small amount of PHE (2–5 mg PHE per gram of protein),<sup>54</sup> the allowance of PHE from food may need to be reduced to maintain PHE intake within PHE tolerance limits.<sup>23</sup>

### Large neutral amino acids

The theory behind LNAA use as a medical food is described in the ACMG guideline.<sup>4</sup> LNAAs are not recommended for young children or pregnant women but should be considered for adults with PAH deficiency who are not in good metabolic control and do not adhere to other treatment options.<sup>5</sup> LNAA therapy has been shown to improve executive function in some adults.<sup>56</sup> When using LNAAs, 25–30% of total protein needs are provided by LNAAs, with the remaining 70–75% coming from dietary protein sources.<sup>57</sup> Protein intake and plasma amino acids should be monitored to prevent essential amino acid deficiencies. It is difficult to monitor the success of LNAA therapy because blood PHE remains high, and measurement of PHE concentration in the brain is impractical. Blood and urine melatonin have been suggested as surrogate markers for serotonin and may be useful in monitoring treatment.<sup>58</sup> Serotonin has been shown to be deficient in individuals with PAH deficiency who exhibit executive function defects.<sup>58</sup>

### Providing dietary PHE

Because PHE is an essential amino acid, limited amounts from intact protein must be provided for anabolic processes regardless of the medical food chosen. For infants, the source of PHE can be either breast milk<sup>59</sup> or infant formula (containing DHA/arachidonic acid). A variety of strategies for introducing breast milk have been described.<sup>59</sup> Although there is little consensus about the best way to incorporate breast milk into the diet of an infant with PAH deficiency, there is agreement that feeding at the breast, as well as feeding expressed breast milk by bottle, results in good metabolic control.<sup>60</sup> Later in the first year, breast milk or infant formula is slowly removed in exchange for limited amounts of intact protein from solid foods containing an equivalent amount of PHE.

### Tracking dietary PHE

There is little consensus about the best method for tracking dietary PHE intake. As long as data are available on the PHE

content of individual food items, the most precise method of tracking PHE intake is counting milligrams of PHE. An exchange system (1 exchange = 15 mg PHE) is easier for some patients and families. Those with higher PHE tolerance may be able to achieve good PHE control by counting grams of protein. This has the advantage of allowing the use of food labels as a guide. A more liberal approach of allowing “free” consumption of fruits, vegetables, and low-PHE foods (<100 mg PHE/100 g) allows for similar blood PHE control to that of other tracking methods.<sup>61</sup> This system has been used by clinics in Europe with good success but is not common practice in the United States.<sup>5</sup>

### Modified low-protein foods

Individuals with severe forms of PAH deficiency and low PHE tolerance often rely on modified low-protein foods to provide energy and variety in their diets.<sup>15</sup> Modified low-protein foods, including low-protein breads and pasta, use the starch portion of the grain rather than the higher-protein flour.<sup>62</sup> It is important to note that these products do not have the usual vitamin enrichment found in regular grain products. As a source of energy, these products can help to prevent weight loss, catabolism, and the resulting elevated blood PHE.<sup>15</sup> Third-party reimbursement for modified low-protein foods is not universally available.<sup>52</sup>

### Sapropterin (tetrahydrobiopterin) therapy

Sapropterin dihydrochloride (sapropterin) is the pharmaceutical form of tetrahydrobiopterin, a cofactor required for PAH activity. Given in therapeutic doses, sapropterin appears to enhance PAH activity in certain individuals with PAH deficiency.<sup>63</sup> The ACMG PAH deficiency guideline recommends a trial of sapropterin therapy for all individuals.<sup>4</sup> The benefits of response fall into two categories: for individuals who are non-adherent or unable to maintain diet restriction and medical food intake, sapropterin may lower blood PHE without further diet modification; and for individuals who maintain blood PHE within the therapeutic range by dietary adherence, sapropterin may allow liberalization of dietary PHE and less medical food intake.<sup>64</sup>

Although sapropterin therapy may support significant dietary liberalization, it seldom allows individuals to maintain appropriate blood PHE without some PHE restriction and medical food. Regular monitoring of blood PHE, dietary adequacy, and nutritional status continue to be essential. Individualized patient counseling includes planning and calculating the diet with a higher PHE or protein allowance, choosing appropriate natural protein sources, reading labels, distributing high-PHE/intact protein foods throughout the day, meeting micronutrient/vitamin requirements when the medical food prescription is decreased, and understanding the importance of consistent sapropterin dosing.<sup>65,66</sup> Longer-term follow-up will be necessary to determine whether individuals with PAH deficiency remain adherent to sapropterin and dietary recommendations and if there is an impact on outcome.

## Nutrition counseling and education

Nutrition counseling and education involve teaching individuals with PAH deficiency and/or their caregivers the importance of the diet in maintaining appropriate blood PHE, normal growth, and health maintenance while ensuring that they have the necessary skills to adhere to the diet throughout the life span. Education techniques and materials must be appropriate for the individual's learning style,<sup>67</sup> access to care, acceptance of the diet, and/or readiness for change. Research into effective education and counseling strategies for PAH deficiency is lacking.

### RECOMMENDATIONS

- Evaluate individual nutritional needs, ability to adhere to recommendations, and access to treatment options when choosing appropriate interventions (medical food, modified low-protein food, sapropterin, and LNAAs) to achieve blood PHE in the target range.
- Provide counseling and education specific to the needs of the individual with PAH deficiency (and/or his/her caregivers) to help maintain appropriate blood PHE throughout the life span.
- Recommend that medical food be consumed throughout the day for optimal metabolic control.
- Include breast milk and/or infant formula as sources of PHE in the diet of an infant with PAH deficiency.
- Track PHE intake by any of several methods, including counting milligrams or exchanges of PHE or grams of protein.
- Consider use of LNAAs in adults with PAH deficiency who are not in good metabolic control and not able to adhere to other treatment options.
- Individualize the diets of responders to sapropterin with appropriate PHE, medical foods, or modified low-protein food intake and/or vitamin/mineral supplementation to ensure adequate nutrient intake.

## TREATMENT IN SPECIAL CIRCUMSTANCES

### Pregnancy in women with PAH deficiency

High maternal blood PHE is associated with poor outcomes in offspring, including low birth weight, microcephaly, congenital heart defects, and intellectual disability. Maintaining maternal blood PHE between 120 and 360  $\mu\text{mol/l}$  before and during pregnancy results in the best outcome for offspring.<sup>2</sup> However, 30% of clinics surveyed recommend 120–240  $\mu\text{mol/l}$  as the target range for maternal blood PHE.<sup>5</sup>

Most studies have not evaluated the effect of nutrition (beyond maternal blood PHE) on outcomes. In the Maternal PKU Collaborative Study, maternal protein intake and energy were significantly and negatively correlated with blood PHE throughout the entire pregnancy.<sup>68</sup> Women with low protein intake secondary to inadequate consumption of medical food also had low overall nutrient intake and a higher incidence of congenital anomalies in their offspring.<sup>69</sup> Adequate energy and fat intake, as well as adequate weight gain, have all been associated with better pregnancy outcomes.<sup>68</sup> Control of nausea and vomiting, especially in early pregnancy, is key to preventing

catabolic weight loss and elevated PHE levels. Neither TYR intake nor blood TYR has been reported to be associated with outcomes in maternal PAH deficiency.<sup>70</sup> Fat and essential fatty acid intakes may be very low in individuals with PAH deficiency when their medical food contains no fat. DHA supplementation of 200–300 mg/day should be provided to all pregnant women with PAH deficiency.<sup>5</sup> Specific monitoring recommendations during pregnancy for women with PAH deficiency are outlined in **Table 2**. The use of adjunctive therapies in managing blood PHE during pregnancy is a matter of debate. LNAA monotherapy is not recommended, because it does not result in adequate control of blood PHE. Because sapropterin can lower blood PHE, its use should be considered on a case-by-case basis.<sup>5</sup> Women are encouraged to continue the diet in the postpartum period and can breast-feed their non-PAH-deficient infant regardless of maternal blood PHE levels.

### RECOMMENDATIONS

- Maintain blood PHE between 120 and 360  $\mu\text{mol/l}$  before conception and throughout pregnancy.
- Monitor dietary intake of pregnant women with PAH deficiency to ensure nutrient adequacy.
- Consider sapropterin use on a case-by-case basis for pregnant women who have difficulty adhering to the diet.
- Do not recommend LNAAs for use in pregnant women with PAH deficiency.

### Sick days and catabolism

Infection, inflammation, and injury induce a catabolic state, with increased endogenous protein breakdown and impaired anabolism. For individuals with PAH deficiency, this can lead to increased blood PHE; however, there are no published data, nor is there consensus regarding “sick day” management. Specialized parenteral nutrition solutions have been used when adequate enteral intake is not possible.<sup>71</sup>

### Late-treated PAH deficiency

Improvements in behavior and functioning have been documented in previously untreated individuals with PAH deficiency who have been placed on diet therapy.<sup>72,73</sup> In children for whom therapy was delayed, improvement in IQ may occur after nutrition therapy is initiated.<sup>72,73</sup> Choice of treatment modality should be based on feasibility and effectiveness for the individual patient. Among the concerns are comorbidities, contraindications due to prescribed medications, and limited access to care.

## PSYCHOSOCIAL SUPPORT

Treatment for PAH deficiency is complex, and adherence to recommendations diminishes with age.<sup>74</sup> The companion ACMG PAH deficiency treatment guideline<sup>4</sup> discusses the problems and challenges faced by individuals with PAH deficiency as they transition into adulthood.<sup>4</sup> Adherence improves if individuals have a social support system; an understanding of the benefits of treatment; access to appropriate care, medical foods and



modified low-protein foods; and a belief that PAH deficiency is manageable.<sup>75</sup> Special support and advocacy are frequently necessary to secure access to the medical foods required by individuals with PAH deficiency.<sup>2,51</sup> Creative approaches for clinic- and community-based programs, such as age-specific educational programs, camps, and other support programs, hold promise for improving adherence and quality of life.

## RECOMMENDATIONS

- Ensure access to medical and modified low-protein foods.
- Provide connections to sources of social support, such as camps, mentoring programs, and other support groups.

## CONCLUSION

Nutrition management of PAH deficiency has resulted in remarkable outcomes for individuals who have benefitted from early diagnosis and treatment. These positive outcomes are the sum of dedicated research, clinical attentiveness, and patient adherence. Although much has been learned about providing proper nutrition on a PHE-restricted diet, many aspects of diet and health in individuals with PAH deficiency require further investigation. These include issues such as adequacy of absorption of nutrients from medical foods, bone density, weight status, long-term neurocognitive outcomes, and oxidative stress, as well as the roles of less available nutrients (e.g., menaquinone and vitamin K<sub>2</sub>) and functional nonnutrients (e.g., nucleosides, nucleotides, pre- and probiotics, and polyphenolic compounds). How to balance nutrition management with other treatments, such as LNAAs, sapropterin, and PEGylated phenylalanine lyase, and the impact of genotype on treatment are still being explored. Continued research should also examine approaches that promote adherence to therapy. The health-care system must ensure that individuals with PAH deficiency have access to the care necessary for optimal outcomes.

These recommendations for the nutrition management of individuals with PAH deficiency reflect the latest in scientific understanding and clinical practice. The workgroup is continuing, with evidence and consensus methodology, to develop comprehensive nutritional management guidelines, resources, and tools for PAH deficiency that will be made available on the Genetic Metabolic Dietitians International and the Southeast Regional Genetics Collaborative websites.

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## DISCLOSURE

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