We developed European guidelines to optimise phenylketonuria (PKU) care. To develop the guidelines, we did a literature search, critical appraisal, and evidence grading according to the Scottish Intercollegiate Guidelines Network method. We used the Delphi method when little or no evidence was available. From the 70 recommendations formulated, in this Review we describe ten that we deem as having the highest priority. Diet is the cornerstone of treatment, although some patients can benefit from tetrahydrobiopterin (BH4). Untreated phenylalanine concentrations determine management of people with PKU. No intervention is required if the blood phenylalanine concentration is less than 360 μmol/L. Treatment is recommended up to the age of 12 years if the phenylalanine blood concentration is between 360 μmol/L and 600 μmol/L, and lifelong treatment is recommended if the concentration is more than 600 μmol/L. For women trying to conceive and during pregnancy (maternal PKU), untreated phenylalanine blood concentrations of more than 360 μmol/L need to be reduced. Treatment target concentrations are as follows: 120–360 μmol/L for individuals aged 0–12 years and for maternal PKU, and 120–600 μmol/L for non-pregnant individuals older than 12 years. Minimum requirements for the management and follow-up of patients with PKU are scheduled according to age, adherence to treatment, and clinical status. Nutritional, clinical, and biochemical follow-up is necessary for all patients, regardless of therapy.

Introduction

Phenylketonuria (PKU) is a rare autosomal recessive inborn error of phenylalanine metabolism with an estimated frequency in Europe of 1 in 10 000 newborn babies (panels 1 and 2).1 Deficiency of the hepatic-based enzyme phenylalanine hydroxylase (PAH) results in a complete or partial inability to convert phenylalanine (from the diet or derived from catabolism of proteins in the body) to tyrosine (figure 1),1 which can lead to high blood phenylalanine concentrations that cross the blood–brain barrier causing detrimental effects on brain development and function. Available treatments aim to decrease the blood phenylalanine concentration, which is considered the surrogate marker for brain phenylalanine concentrations. Nevertheless, the precise pathophysiology of PKU remains unclear (figure 2).1 Clinically, untreated PKU is characterised by irreversible intellectual disability, microcephaly, seizures, aberrant behaviour, psychiatric symptoms, motor disturbances, and eczematous rash. When diagnosed by newborn screening and treated immediately, patients essentially show normal development, although neuropsychological deficits and behavioural and social issues can occur.2,3 Dietary treatment consists of a low-phenylalanine diet, restrictive in natural protein combined with phenylalanine-free L-aminoacid supplements and low protein foods. Some patients with PKU respond to tetrahydrobiopterin (BH4), a naturally occurring essential cofactor for PAH that acts as a pharmaceutical chaperone (prescribed as sapropterin dihydrochloride), decreases blood phenylalanine concentrations and increases dietary phenylalanine tolerance.4 In some (mainly non-European) countries, casein glycomacropeptide or large neutral aminoacids are used for treatment, but both

Panel 1: Information on genetics and pathophysiology of phenylketonuria (PKU)

Genetics of PKU

PKU is caused by mutations in the gene encoding phenylalanine hydroxylase (PAH). The PAH gene is located on chromosome 12 (region q22-24.1) consisting of 13 exons and 12 introns, in total covering 100 kb of genetic data. More than 950 mutations in the gene encoding PAH (BIOPKU database) are known to be associated with PAH deficiency. Most of the mutations are missense, usually resulting in protein misfolding or impairment of catalytic functions. The prevalence of PKU shows considerable geographic variation; in Europe it occurs in one in 10 000 newborn babies, with a very high rate in some countries, such as Ireland and Turkey, but a very low rate in Finland.

Phenylalanine hydroxylase

Phenylalanine is hydroxylated by PAH, necessitating tetrahydrobiopterin (BH4) as a cofactor, with iron and oxygen. The structure of PAH is a tetramer. During the hydroxylation of phenylalanine, BH4 is oxidised to a 4a-hydroxy intermediate, which is subsequently regenerated to BH4 by the enzymes carbinoamine-4a-dehydratase and dihydropteridine reductase. BH4 is synthesised from guanosine triphosphate (GTP) by three additional enzymes: GTP cyclohydrolase I, 6-phyruvoyl-tetrahydropterin synthase, and sepiapterin reductase. Variants in the genes encoding the enzymes involved in BH4 metabolism result in BH4 deficiency, mostly treated with BH4 and neurotransmitter precursors. Some patients with PAH deficiency also respond to BH4. This response is referred to as BH4 responsiveness.
BH4 deficiencies

nitric oxide synthases.

Cofactor of phenylalanine hydroxylase. BH4 is a cofactor of tyrosine and BH4 also acts as a chaperone protein in some glycomacropeptide.

phenylalanine-free L-aminoacid supplements and less commonly from low phenylalanine deficiency and optimise metabolic control. Protein substitutes are mainly sourced from Protein replacements or substitutes are essential in treatment of PKU to prevent protein overtreatment and unnecessary costs.

Protein substitutes (phenylalanine-free L-aminoacid supplements and low phenylalanine glycomacropeptide protein)

Protein requirements

The lowest level of dietary protein intake that will balance the loss of nitrogen from the body, and thus maintain the body protein mass in a person at energy balance with modest levels of physical activity.

Phenylalanine tolerance

The amount of phenylalanine (mg/kg per day or mg per day) that maintains plasma phenylalanine concentrations within the target range. This amount might also be described as natural protein tolerance expressed as g per day, taking a phenylalanine content in natural protein as 50 mg of phenylalanine per gram of natural protein.

Phenylalanine-deficient patients who are deficient in phenylalanine hydroxylase. BH4 is a cofactor of tyrosine and tryptophan hydroxylase and has a role in the conversion of L-arginine to nitric oxide by nitric oxide synthases.

BH4 deficiencies

Defects in BH4 known defects for synthesis and two for regeneration (see also phenylalanine hydroxylase in panel 1).

Potential BH4 responsiveness

More than 30% reduction in blood phenylalanine in a BH4 loading test or two BH4-responsive mutations. BH4 responsiveness should be proven in a treatment trial adjusting the BH4 dosing, natural protein intake, and phenylalanine-free L-aminoacid supplement.

BH4 responsiveness

In this Review we defined BH4 responsiveness as an increase of 100% or more in natural protein or improved biochemical control (>75% of phenylalanine levels in target range), or both, on a dose of BH4 that ranges between 1–20 mg/kg bodyweight (with a maximum dose of 1000 or 1400 mg per day in some countries).

PKU management differs across Europe, with various local and national guidelines. A need exists for more standardised management tailored for optimal outcomes. The development of these European guidelines was driven both by health professionals and the patient organisation European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU). Generally, guidelines should result in measurable improvements in patient care, consistent, high-quality treatment without inequity, and awareness of rare diseases. Here we report on the development of European PKU guidelines by 19 European PKU experts, and we highlight ten clinical recommendations (out of a total of 70) that we deem as having the highest priority for implementation. The key recommendations were based on the best available evidence for management of PKU that would achieve optimal clinical and neuropsychological outcomes without overtreatment and unnecessary costs.

Guideline development

The scientific advisory committee of the ESPKU was tasked with organising a group of European PKU experts. 19 health professionals were invited on the basis of their experience and expertise rather than nationality; one of them declined and one resigned for personal reasons. The 17 professionals included the following: paediatric and adult metabolic physicians, a paediatric neurologist, a biochemist, metabolic dietitians, neuropsychologists, and psychologists. They were divided into five working groups on (1) nutritional treatment and biochemical or nutritional follow-up (Working Group A); (2) neurocognitive outcomes including imaging (Working Group B); (3) psychosocial outcome, and adherence (Working Group C); (4) adult and maternal PKU; and late diagnosis of PKU and untreated PKU (Working Group D); and (5) diagnosis of PKU including treatment initiation and drugs in PKU (Working Group E). The working groups were supported by a project assistant and guidelines leader. We consulted an obstetrician for maternal PKU. We developed the guidelines between October, 2012, and December, 2015.

We developed the guidelines with the Appraisal of Guidelines, Research, and Evaluation in Europe method. We did the literature search, critical appraisal, and evidence grading according to the Scottish Intercollegiate Guidelines Network (SIGN) method (version 2011) using eight levels of evidence being transferred into grades of recommendations (from A [highest] to D [lowest], with an extra recommendation for so-called good practice points that are not based on any evidence).

All working groups defined key questions, after which they searched the published work for relevant papers with the help of the project assistant. All working groups and plenary sessions, to discuss as adequately as possible the statements without enough evidence,
were facilitated by the guidelines leader or project assistant, or both. We sent a concept of the full guidelines worldwide to 14 external consultants (physicians and dietitians or nutritionists) and the board of the ESPKU. Further data about the process (including the questions for each of the key recommendations reached) are shown in the appendix.

**Guidelines**

**Overview**

The main topics of these guidelines are (1) diagnosis, treatment initiation, and treatment duration; (2) treatment targets; (3) practical issues in dietary and BH4 treatment; (4) follow-up; and (5) special conditions (maternal PKU; late PKU diagnosis and untreated PKU). In the final section, we discuss the future goals of PKU management. Panel 3 lists the ten key statements arising from these main topics. Some aspects of this Review are lacking a discussion in depth in part related to the length of the paper but also in part related to a lack of evidence. Where this is the case it is stated.

**Diagnosis and treatment initiation and duration**

Most of the statements on diagnosis and classification are experience-based rather than evidence-based. PAH deficiency is usually classified as mild, moderate, or severe (also referred to as classic) PKU. This classification is commonly based on the highest untreated blood phenylalanine concentration following a clinical diagnosis or at newborn screening. However, blood samples for newborn screening might be collected before infants have achieved their peak phenylalanine concentration without treatment. Since this sample collection time limits the use of the traditional classification for severity, a new classification is proposed on the basis of whether patients with PAH deficiency—to maintain blood phenylalanine concentrations in the recommended range—do not need treatment, or require dietary intervention, or BH4, or both.

Newborn screening for PKU meets all accepted screening criteria including cost–benefit ratio. Therefore, newborn screening for PKU should be done in every European country. This screening not only needs a robust infrastructure in which blood is taken from all newborn babies within a few days of birth, but also a well equipped laboratory that can manage and assess bloodspots efficiently. Low-income countries might consider using newborn screening laboratory facilities of another country efficiently. Low-income countries might consider using a laboratory that can manage and assess bloodspots babies within a few days of birth, but also a well equipped infrastructure in which blood is taken from all newborn babies at birth.

“With regards to the duration of treatment, we advise treatment until age 12 years in individuals with untreated phenylalanine concentrations of more than 360 μmol/L and 600 μmol/L is less clear; only Weglage and colleagues have adequately studied patients with untreated phenylalanine concentrations within this range and suggested it was safe. However, in that study only seven of the 31 patients had an untreated phenylalanine concentration of more than 500 μmol/L, and on such evidence we consider it inappropriate to recommend that untreated phenylalanine concentrations of 360–600 μmol/L are safe. Therefore, we advise treatment for any child with untreated phenylalanine concentrations of more than 360 μmol/L. This advice is not based on conclusive evidence and further data are still required for a definitive recommendation.”

For more on the BIOPKU database see http://www.biopku.org/home/ pah.asp

Figure 1: Phenylalanine hydroxylating system

BH4=tetrahydrobiopterin. GTP=guanosine triphosphate.
600 μmol/L, providing blood phenylalanine remains less than 600 μmol/L without treatment afterwards. We suggest this duration because of scarce and inconsistent evidence and the necessity for good metabolic control to retain cognitive function, especially during the first 12 years of life. In untreated women with phenylalanine concentrations of more than 360 μmol/L, treatment is also required preconception and during pregnancy with the aim of reducing phenylalanine concentrations to less than 360 μmol/L.

In adults continuing treatment for PKU, results of health-related quality of life surveys suggest that this quality of life is normal, with an improvement of health-related quality of life in some patients who had returned to a low phenylalanine diet having discontinued PKU treatment. However, non-PKU generic health-related quality of life questionnaires are insensitive to the subtle negative effects of PKU, which has led to the development of a validated PKU-specific questionnaire (PKU-QOL).

On the basis of these data, we advise treatment for life for patients with untreated phenylalanine concentrations of more than 600 μmol/L, even though it is acknowledged that dietary management is associated with a substantial patient burden.

**Treatment targets**

Blood phenylalanine is the primary marker for guiding available treatments. Table 1 lists the studies that were included through use of the SIGN method to achieve the highest level of evidence available for the statements that describe age-related target ranges. For children up to the age of 12 years, the results of meta-analyses by Albrecht and colleagues and Waisbren and colleagues suggested safe upper target blood phenylalanine concentrations of 320 μmol/L and 420 μmol/L, and Fonnesbeck and colleagues indicated that a mean concentration of 400 μmol/L was associated with an increased risk of an IQ less than 85. Some evidence also exists that shows more favourable outcomes when the mean blood phenylalanine concentrations are less than 240 μmol/L or 240 μmol/L rather than 360 μmol/L (mean age <12 years). Jahja and colleagues reported a better neuropsychological task performance by patients with PKU when blood phenylalanine concentrations were less than 240 μmol/L than...
patients with concentrations between 240 μmol/L and 360 μmol/L (mean age <12 years); however, despite being statistically significant, differences of inhibitory control and cognitive flexibility, and motor control were not clinically significant.

Therefore, in view of the overall available evidence, we advise 360 μmol/L as the upper target phenylalanine blood concentration for the first 12 years of life. Data about adolescents and adults are scarce, necessitating further data collection within long-term international collaborative studies. Using the data shown in table 1, we advise an upper target phenylalanine blood concentration of 600 μmol/L for all individuals older than 12 years. This statement is different when compared to the upper target phenylalanine concentration of 360 μmol/L for adults with PKU, as advised by the American College of Genetics and Genomics.\(^{45}\) The upper target of 360 μmol/L is based on Panel 3: Key recommendations for patients with phenylketonuria (PKU)

The grades range from ✓ (no possibility to assess the level of evidence because of a lack of any published work on this issue) to as high as B. The key recommendations were either based on evidence (if level of evidence was A or B using the SIGN method) or by consensus (using the Delphi method) if the level of evidence was C or D, or the so-called good practice points that are not based on any evidence if the level was ✓.

**Statement 1**

**Grade of recommendation: ✓**

To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as either not requiring treatment, or requiring diet or tetrahydrobiopterin (BH4), or both.

**Statement 2**

**Grade of recommendation**: C

In the differential diagnosis of hyperphenylalaninaemia, of any degree, BH4 deficiencies should be excluded by measurement of pterins in blood or urine and dihydropteridine reductase activity in dried blood spot.

**Statement 3**

**Grade of recommendation**: D/C

Patients with untreated blood phenylalanine concentrations less than 360 μmol/L do not require treatment. Patients with untreated blood phenylalanine levels more than 360 μmol/L should be treated. Patients with untreated phenylalanine levels between 360 μmol/L and 600 μmol/L should be treated until the age of 12 years. Patients with untreated phenylalanine levels more than 600 μmol/L should be treated for life.

**Statement 4**

**Grade of recommendation**: C

All adults with PKU should have life-long, systematic follow-up in specialised metabolic centres, because of specific risks that might occur during adulthood.

**Statement 5**

**Grade of recommendation**: B

In treated patients with PKU up to the age of 12 years, target phenylalanine concentrations should be 120–360 μmol/L.

**Statement 6**

**Grade of recommendation**: D

In treated patients with PKU aged 12 years or older, the target phenylalanine concentrations should be 120–600 μmol/L.

**Statement 7**

**Grade of recommendation**: B

In pregnant patients treated for PKU the target phenylalanine concentrations should be 120–360 μmol/L.

**Statement 8**

**Grade of recommendation**: B

Women with untreated blood phenylalanine concentrations less than 360 μmol/L do not require treatment to lower blood phenylalanine before or during pregnancy.

**Statement 9**

**Grade of recommendation**: C

An annual nutritional review is required for any patient who is on a prescribed low phenylalanine diet or is self-restricting high protein foods. Such review must include a clinical examination including the anthropometric parameters (weight, height, BMI). We also recommended that plasma aminoacids, plasma homocysteine or methylmalonic acid, haemoglobin, mean corpuscular volume, and ferritin are measured. All other micronutrients (vitamins and minerals including calcium, zinc, selenium) or hormones (parathyroid hormone) can be considered if clinically indicated.

**Statement 10**

**Grade of recommendation**: ✓

In patients younger than 12 years, when more than 50% of the phenylalanine concentrations are out of target range over a period of 6 months, consider: (1) increased frequency of blood phenylalanine monitoring and outpatient visits and re-education, (2) psychology consultation or social worker intervention, and (3) hospital admission. When around 100% of blood phenylalanine concentrations are out of target range over a period of 6 months and there are other signs of failure of adherence, such as lack of cooperation, clinic non-attendance, or unresolved issues outside PKU consider consultation with social services and child safeguarding measures.

*Level of evidence is chosen as C because of the high number of data notwithstanding that most included papers are of descriptive nature.*
a meta-analysis with three starting conditions: measures of cognitive outcomes other than IQ are either used non-uniformly across studies or are too difficult to combine; IQ variation is not an important component of variation of bias; and the effect of historical (lifetime) and momentary phenylalanine concentrations after 6 years of age is seen as one factor only.\textsuperscript{19} We acknowledge the importance of this meta-analysis,\textsuperscript{19} and think that the bias due to variation in IQ measures and variation of individual IQ over time should not be underestimated. Additionally, the effect of the metabolic control on adult IQ as a measure of neurocognitive outcome should not be overestimated, and in adulthood, the target phenylalanine concentration should be decided by the effect of phenylalanine concentrations in adult age.

As the absolute phenylalanine concentration is the most crucial factor in directing treatment, phenylalanine measurements should be robust. The accuracy of aminoacid analysers, high-performance liquid chromatography, and tandem mass spectrometry is well established, but phenylalanine concentrations from dried blood spots are 8–26\% lower than venous blood

<table>
<thead>
<tr>
<th>Studied population</th>
<th>Measurement of Phe</th>
<th>Measured outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, adolescents, and adults with PKU; range of n=2–77</td>
<td>Concurrent Phe, lifetime Phe, or Phe during childhood</td>
<td>White matter alteration by magnetic resonance imaging</td>
<td>No white matter changes when blood Phe concentrations were &lt;300–600 μmol/L</td>
</tr>
<tr>
<td>Meta-analysis of 40 studies reported in 40 papers; 3361 patients with PKU aged 0–32 years</td>
<td>(1) Phe concentrations during critical period (birth to 6 or 12 years); and (2) lifetime Phe</td>
<td>IQ</td>
<td>(1) Phe range 423–750 μmol/L: each increase of 100 μmol/L results in 1·3–3·1 point reduction of IQ points; and (2) Phe range 394–666 μmol/L: each increase of 100 μmol/L results in 1·9–4·1 point reduction of IQ points</td>
</tr>
<tr>
<td>Meta-analysis of 17 studies reported in 21 papers; 432 patients with PKU aged 2–32 years</td>
<td>(1) Phe concentrations during critical period of age &lt;6 years; (2) lifetime Phe for age ≥6 years; and (3) IQ measurement concurrent with Phe in both periods</td>
<td>Probability of lower IQ (&lt;85); general population probability was approximately 15%</td>
<td>(1) Probability of IQ &lt;85 during the critical period (&lt;6 years) is 19% with Phe concentrations of 400 μmol/L and 30% with Phe concentration of 600 μmol/L; (2) probability of historical Phe concentrations during the non-critical period (≥6 years) to result in IQ &lt;85 is 14% with Phe concentration of 400 μmol/L and 20% with Phe concentration of 600 μmol/L; and (3) concurrently measured Phe was weakly correlated with probability of low IQ</td>
</tr>
<tr>
<td>28 adult patients with PKU younger than 32 years with a relaxed diet in young adulthood, 16 adult patients with PKU older than 32 years with a relaxed diet from age 10 years, and 46 controls</td>
<td>Lifetime and concurrent Phe</td>
<td>IQ and EF</td>
<td>Stable outcomes in 5-year interval for both groups. Older group had lower IQ and poorer EF than younger group. IQ and EF were inversely associated with lifetime Phe</td>
</tr>
<tr>
<td>37 patients with PKU (0·5–7 years) and 86 controls</td>
<td>Concurrent Phe (defined as mean Phe during a 6-week period before testing) &lt;360 μmol/L and ≥360–600 μmol/L</td>
<td>EF</td>
<td>Those with concurrent Phe of 360–600 μmol/L did less well in EF tasks (working memory and inhibitory abilities) than concurrent Phe &lt;360 μmol/L and controls</td>
</tr>
<tr>
<td>14 patients with PKU (mean age 10·8 years, range 8–13 years) and 14 age-sex-IQ-SES-matched controls (mean age 10·9 years, range 8–13 years)</td>
<td>Lifetime Phe ≤400 μmol/L (n=5) and &gt;400 μmol/L (n=9)</td>
<td>EF</td>
<td>Patients with lifetime Phe &gt;400 μmol/L did worse than those with lifetime Phe ≤400 μmol/L in all tests of EF</td>
</tr>
<tr>
<td>67 patients with PKU (7–14 years) and 73 age-matched controls</td>
<td>Concurrently measured Phe ≥360 μmol/L (n=29) and &gt;360 μmol/L (n=38)</td>
<td>Neuropsychological speed tests, including tests of EF</td>
<td>Those with concurrent Phe &gt;360 μmol/L did significantly worse in several tests regarding EF than healthy controls. Patients with concurrent Phe concentrations &gt;360 μmol/L did not differ from controls and were significantly better than patients with concurrent Phe concentrations &gt;360 μmol/L</td>
</tr>
<tr>
<td>53 patients with PKU (61 with good metabolic control and 32 with poor metabolic control) and 60 controls; mean age of both groups was 8–7 years</td>
<td>Mean concurrent Phe of cluster with good metabolic control was 240 μmol/L (n=30) and with poor metabolic control was 620 μmol/L (n=31)</td>
<td>Neuropsychological speed tests, including tests of EF</td>
<td>Sustained attention and calculation speed of long-term well-controlled children (from birth to age 9 years) were vulnerable to high concurrent Phe concentrations, whereas children with low concurrent concentrations could not counterbalance the effects of long-term (from birth to age 9 years) poor dietary control</td>
</tr>
<tr>
<td>15 patients with PKU (17–24 years) and 19 controls (18–24 years)</td>
<td>Phe measured at three timepoints concurrently with assessed outcomes; strict diet with aminoacid supplement vs no diet</td>
<td>Neuropsychological speed tests, including tests of EF; tested three times with intervals of 4–5 weeks</td>
<td>Better neuropsychological task performance for patient group on diet (mean Phe of 630 μmol/L [range 280–966]) vs patient group off diet (mean Phe of 1220 μmol/L [720–1800] and 1410 μmol/L [1040–2200])</td>
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(Table 1 continues on next page)
samples. Data from studies investigating neurocognitive outcomes are largely based on plasma phenylalanine concentrations, whereas routine practice is dried blood spots measurements. The guideline statements here on phenylalanine targets present the upper target phenylalanine concentrations, whereas the published work discusses means or medians. Consequently, the guideline statements are stricter than study findings. However, this difference might also compensate for other factors, such as dried blood spots instead of plasma phenylalanine concentrations, and not testing blood phenylalanine after an overnight fast, which is usually the highest point in 24 h. We advise that blood phenylalanine samples are taken at the same time of day and under the same nutritional conditions in each individual patient.

Other markers, such as the phenylalanine-to-tyrosine ratio or the variation in the phenylalanine concentration, could be of additional value, but any advantage offered in addition to blood phenylalanine measurements still remains to be determined, particularly as tyrosine concentrations vary considerably throughout 24 h. We advise not testing blood phenylalanine after an overnight fast, instead of plasma phenylalanine concentrations, and routine practice is dried blood spots measurements. The guideline published work discusses means or medians.

### Practical issues in dietary and BH4 treatment

Dietary phenylalanine restriction is the mainstay of treatment. This treatment consists of three parts: natural protein restriction using individual phenylalanine tolerance, phenylalanine-free L-aminoacid supplements (usually with added vitamins and minerals) to meet protein and non-protein requirements, and low protein food to meet energy requirements. Although we have longstanding experience with dietary treatment, it is only since the 2008 introduction of sapropterin dihydrochloride that more of our treatment is evidence-based rather than experience-based, but important evidence gaps still exist in several areas. Patients with the most severe PAH deficiency usually tolerate a daily intake of less than 350 mg phenylalanine, and therefore the quality of aminoacid supplements is important. Total protein intake should supply the age-related safe levels of protein intake (FAO/WHO/UNU 2007) with an intake of aminoacid supplements has been linked to proteinuria and decreased glomerular filtration rate. 59

#### Table 1: Evidence for target phenylalanine concentrations during childhood, adolescence, and adulthood

<table>
<thead>
<tr>
<th>Study population</th>
<th>Measurement of Phe</th>
<th>Measured outcome</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Jahja et al (2014)</td>
<td>Phe measured concurrently with outcome</td>
<td>Improved mood and neuropsychological task performance with lower Phe concentrations</td>
<td>Patients with PKU aged 6–15 years with mean lifetime Phe concentrations  240 μmol/L on performed speed EF tasks</td>
</tr>
<tr>
<td>ten Hoedt et al (2011)</td>
<td>Mean Phe during treatment with placebo capsules and Phe-containing capsules</td>
<td>IQ, mood, and neuropsychological speed tests, including tests of EF</td>
<td>Improved mood and neuropsychological task performance with lower Phe concentrations (Phe 709 μmol/L [SD 322] for placebo vs 1259 μmol/L [32] for experimental condition)</td>
</tr>
<tr>
<td>Hoeksm et al (2009)</td>
<td>Cerebral protein synthesis rate by brain positron emission tomography studies</td>
<td>Recommended Phe concentrations &lt;600–800 μmol/L (because plasma Phe concentrations &gt;600–800 μmol/L decreased cerebral protein synthesis rates)</td>
<td></td>
</tr>
<tr>
<td>Sanayama et al (2011)</td>
<td>Oxidative stress markers, antioxidant concentrations, and enzyme activities in erythrocytes</td>
<td>Recommended Phe concentrations &lt;700–800 μmol/L because the oxidative stress changed greatly at 700–800 μmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Phe=phenylalanine. PKU=phenylketonuria. EF=executive function. IQ=intelligence quotient. SES=socioeconomic status. Evidence included for target Phe concentrations during childhood (<12 years), adolescence (12–18 years), and adulthood (≥18 years).

For more on the FAO/WHO/UNU 2007 report see http://apps.who.int/iris/bitstream/10665/43411/1/WHO_TRS_935_eng.pdf?ua=1
Review

at least three times throughout the day, to minimise fluctuations in blood phenylalanine variability.59

Low protein foods should contain 50 mg of phenylalanine or less per 100 g (equivalent to 1 g of protein per 100 g) of dry product. Fruit and vegetables (excluding potatoes) containing less than 75 mg of phenylalanine per 100 g of food product should not adversely affect blood phenylalanine control and can be included without restriction in the diet.60

The optimal amount of tyrosine provided in a low phenylalanine diet is unknown, but additional supplementation in excess of amounts provided by aminoacid supplements is not associated with a benefit.60 At present, no statement can be given regarding daily practice with reference to supplementation of large neutral aminocoids treatment (figure 2) or the use of glycomacropeptide because of insufficient evidence.

As illness and fever cause increased catabolism and higher blood phenylalanine concentrations, aminocoid supplements and energy requirements should be met during infection. Antipyretics or analgesics, such as paracetamol and ibuprofen, should be considered to control temperature and improve appetite.

Aspartame (E951) is an intense sweeter composed of 50% phenylalanine,61–63 and needs to be avoided in patients with PKU. In neotame, a similar artificial sweeter to aspartame, phenylalanine content is comparable but bioavailability is largely reduced.64 Some medications contain aspartame (such as antibiotics), and short treatment courses might need to be given if no alternatives are readily available.

Patients with PKU, especially with a higher residual PAH activity, might respond to BH4 administration with a significant increase in phenylalanine tolerance, or decrease in blood phenylalanine concentrations, or both.65–67 All patients warrant testing for BH4 responsiveness either by genotyping or BH4 loading.68 According to the group’s consensus, in any patient without two known null mutations for PKU or two known BH4 responsive mutations, a 48 h BH4 loading test should be done by analysing the blood phenylalanine concentrations before and after a single daily dose (20 mg/kg per day) on two consecutive days.69 In the neonatal period, to avoid delays in dietary treatment, a 24 h instead of 48 h BH4 loading test is advised before starting the diet. Treatment with BH4 should only be prescribed in cases of proven BH4 responsiveness defined as an increase in the amount of natural protein of 100% or more or improved biochemical control (phenylalanine >75% in target range) and proven by a trial (of up to 6 months) of treatment with BH4. The treatment trial starts at 10–20 mg of BH4 per kg bodyweight and natural protein intake is increased (with the advice of a dietician), the BH4 dose is adjusted, and the aminoacid supplements are decreased accordingly, while blood phenylalanine concentrations are still maintained in the target range. BH4 treatment should be stopped if blood phenylalanine concentrations are consistently above the upper target range, with a lack of response to an increase in BH4 dose. If nutritional status deteriorates (eg, development of obesity or nutritional deficiencies), discontinuation of BH4 treatment should be discussed. BH4 treatment can be given during pregnancy, but only if women are known to be BH4 responders and dietary treatment alone is unsuccessful.

Follow-up and adherence

Treatment and follow-up of patients should be done in specialised metabolic centres, with at least an experienced metabolic physician and dietician for both children and adults, and a specialised metabolic laboratory. Establishing adult metabolic teams and centres to care for and monitor older patients with PKU is important. Ideally, these teams will be led by an adult metabolic disease physician who can coordinate care and liaise with different specialties as necessary. Access to a neuropsychologist, or psychologist, and a social worker is strongly advised, but this advice is on the basis of clinical rather than evidence-based practice.

Follow-up includes home blood sampling and outpatient visits, the frequency of both being largely dependent on age (table 2). Various life events, such as change of school, starting work, and living independently, as well as adherence issues (eg, during adolescence) might necessitate a higher frequency of blood phenylalanine testing or visits. The transition process not only includes the transition of patients from paediatric to adult care, but also the transition of the responsibility for treatment from parents to the patient. The pathway to greater autonomy generally starts at around 12 years with progression to adult services from the age of 16 years.

Outpatient visits include taking a medical and dietary history, collecting anthropometric data, such as body mass index, undertaking a physical and neurological examination, especially observing for clinical signs of phenylalanine toxicity and nutrient (including phenylalanine) deficiency,69–72 and discussing issues of treatment and outcome (such as neurological and psychiatric issues, behaviour, and mood). Table 2 lists the additional investigations necessary, and these focus on potential nutritional deficiencies (especially iron and vitamin B12).73–76 Neurocognitive measures, and bone mineral density. Clinical symptoms of nutrient deficiency are rare and are mostly described because of vitamin B12 deficiency (if micronutrient supplementation, which is usually added to aminoacid supplements, is stopped or partially taken, alongside a meat-free diet).77–79 The incidence of osteopenia and osteoporosis in PKU is somewhat higher than in the general population, but only one study indicated that increased risk of fractures exists.79–80 Follow-up is advised with dual-energy x-ray absorptiometry scanning once during late adolescence. If normal, a repeat scan is unnecessary. If abnormal, repetition with or without a change of treatment should follow after 1 year. Additionally, micronutrient deficiencies (selenium, zinc, coenzyme Q10, and...
L-carnitine) have been linked to oxidative stress in PKU, and oxidative stress is associated with poor metabolic control. However, because of the lack of clinical symptoms associated with oxidative stress, and the absence of increased oxidative stress with adequate metabolic control, we do not propose routine biochemical monitoring of oxidative stress.

Routine neurocognitive assessments should be done at ages 12 years and 18 years in all patients, since blood phenylalanine treatment targets and life-phase changes occur at these ages (including change of school, living situation, starting work, and becoming an adult). We also advise measurement of quality of life and discussion of psychosocial functioning during clinic visits with PKU-specific health-related quality of life instruments. To achieve long-term adherence, changing the attitude and motivation of the patient might be more effective than improving knowledge. Regular professional health support might be needed throughout life to encourage normal, healthy feeding behaviours, with a positive acceptance of a low phenylalanine diet.

As health-care providers have a legal obligation to protect and care for each child in their care, the following considerations are proposed when a child (<12 years of age) is in poor metabolic control. When more than 50% of the phenylalanine concentrations are out of the target range during a period of 6 months (approximately 13 measurements per year), health-care providers should consider increased frequency of blood phenylalanine monitoring and outpatient visits, and re-education, plus psychology consultation or social worker interventions, and hospital admission. When around 100% of measured blood phenylalanine concentrations are out of the target range during a period of 6 months and other signs of failure of adherence; safety issues; or lack of cooperation, clinic non-

<table>
<thead>
<tr>
<th></th>
<th>Childhood (&lt;12 years)</th>
<th>Adolescence (12–18 years)</th>
<th>Adulthood (&gt;18 years), excluding maternal PKU</th>
<th>Maternal PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visit</td>
<td>Every 2 months at age 0–1 years and twice per year at age 1–12 years given good clinical and metabolic control; extra clinic visit as indicated</td>
<td>Twice per year given good clinical and metabolic control; extra clinic visit as indicated</td>
<td>Once per year given good clinical and metabolic control; extra clinic visit as indicated</td>
<td>Once during each trimester given good clinical and metabolic control; extra clinic visit as indicated</td>
</tr>
<tr>
<td>Clinical nutritional assessment</td>
<td>Dietary assessment (3 day food record or 24 h recall), anthropometric parameters (weight, height, BMI), and clinical features of micronutrient and Phe deficiency (especially anorexia, listlessness, alopecia, and perineal rash) at every outpatient visit</td>
<td>Dietary assessment (3 day food record or 24 h recall), anthropometric parameters (weight, height, BMI), and clinical features of micronutrient and Phe deficiency at every outpatient visit</td>
<td>Dietary assessment (3 day food record or 24 h recall), anthropometric parameters (weight, height, BMI), and clinical features of micronutrient and Phe deficiency every 12–24 months</td>
<td>Dietary assessment (3 day food record or 24 h recall) and weight at every outpatient visit</td>
</tr>
<tr>
<td>Metabolic control assessment</td>
<td>Weekly Phe at age 0–1 year and fortnightly Phe at age 1–12 years; increased frequency as indicated. Plasma aminoacids annually</td>
<td>Monthly Phe. Increased frequency as indicated; plasma aminoacids annually</td>
<td>Monthly Phe. Increased frequency as indicated; plasma aminoacids annually</td>
<td>Pre-conceptually: weekly; Pregnancy: twice weekly; increased frequency as indicated</td>
</tr>
<tr>
<td>Biochemical nutritional assessment</td>
<td>Annual measurement of plasma homocysteine or methylenalonic acid, or both, homocobolin, mean corpuscular volume, and ferritin; all other micronutrients (vitamins and minerals including calcium, zinc, and selenium) or hormones (parathyroid hormone) if clinically indicated</td>
<td>Annual measurement of plasma homocysteine or methylenalonic acid, or both, homocobolin, mean corpuscular volume, and ferritin; all other micronutrients (vitamins and minerals including calcium, zinc, and selenium) or hormones (parathyroid hormone) if clinically indicated</td>
<td>Annual measurement of plasma homocysteine or methylenalonic acid, or both, homocobolin, mean corpuscular volume, and ferritin; all other micronutrients (vitamins and minerals including calcium, zinc, and selenium) or hormones (parathyroid hormone) if clinically indicated</td>
<td>Folic acid, vitamin B12, plasma homocobolin or methylenalonic acid, or both, ferritin, full blood count assessed pre-conceptually and at the start of pregnancy; assess when indicated during pregnancy</td>
</tr>
<tr>
<td>Bone density</td>
<td>BMD measurement only indicated when there are specific clinical reasons or when patients are known to be at particular risk of metabolic bone disease</td>
<td>First BMD measurement should be done during late adolescence, when BMD is abnormal, the measurement (with or without change of treatment) should be repeated after 1 year, if the results are still low but stable, yearly BMD is unnecessary. When BMD is normal, no repeat measurement is necessary; further study needs only be considered when clinical reasons exist to do so</td>
<td>BMD measurement only indicated when specific clinical reasons exist or when patients are known to be at particular risk of metabolic bone disease</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Neurocognitive examination</td>
<td>Neurocognitive testing only when indicated</td>
<td>Testing at age 12 years. Proposed domains of testing for Phe toxic effects are IQ, perception or visuospatial functioning, EF (division into inhibitory control, working memory, and cognitive flexibility), and motor control. Extra neurocognitive tests as indicated</td>
<td>Testing at age 18 years. Proposed domains of testing for Phe toxic effects are IQ, perception or visuospatial functioning, EF (division into inhibitory control, working memory, and cognitive flexibility), and motor control. Extra neurocognitive tests as indicated</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

(Table 2 continues on next page)
attendance, or unresolved issues outside PKU, are also apparent, health-care providers should consider consultation with social services and child safeguarding measures. These proposals are based on the Delphi consensus method and are suggested in order to improve the outcome of patients from families who are resistant to routine advice and commonly fail to engage successfully with health professionals.

Special conditions

Within treatment for PKU, some specific conditions require a very specific treatment strategy. These groups include maternal PKU and late diagnosed or untreated PKU. Treatment for women with PKU also aims to prevent fetal effects of high maternal phenylalanine concentrations, called maternal PKU syndrome.79 Blood phenylalanine concentrations should ideally be kept between 120 μmol/L and 360 μmol/L from preconception onwards.80–84 Maintaining these concentrations necessitates continuous education throughout preadolescence, adolescence, and adulthood.85 Contraceptive strategies should only be discontinued after stable phenylalanine concentrations within the target range have been achieved for at least 2 weeks, thus preventing sustained phenylalanine concentrations above or below the target range.86 Phenylalanine intake must immediately be increased by 50–100 mg per day when blood phenylalanine is 120 μmol/L or less at anytime during pregnancy. However, no treatment is necessary if untreated blood phenylalanine concentrations are less than 360 μmol/L.87–89 Stable weight gain during pregnancy improves outcome,90,91 and energy intake should be monitored to ensure it is adequate but not excessive.

Referral to a fertility centre should be considered for patients with well controlled phenylalanine concentrations who do not conceive within 6 months. Women with an unplanned pregnancy should be seen within 24 h to initiate immediate dietary treatment. Treatment will require intensive intervention—eg, consider the use of the support of a home “Resource Mother”45,92 (available in the USA) or even hospital admission.93 Treatment might be difficult because of nausea, which can necessitate dietary adjustments such as small and frequent low protein meals and snacks,94 tube feeding, safe antiemetic therapy, and acid-reducing medications.

Blood phenylalanine concentration should be checked at least once weekly before pregnancy and at least twice

| Table 2: Minimum requirements for the clinical management and follow-up of patients with PKU |

<table>
<thead>
<tr>
<th>Childhood (≤12 years)</th>
<th>Adolescence (12–18 years)</th>
<th>Adulthood (≥18 years), excluding maternal PKU</th>
<th>Maternal PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive issues function examination (eg, clinically relevant behavioural problems)</td>
<td>Annual clinical assessment or discussion</td>
<td>Annual clinical assessment or discussion; screening at age 12 years</td>
<td>Annual clinical assessment or discussion; screening at age 18 years</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>If neurodegeneration occurs</td>
<td>If neurodegeneration occurs</td>
<td>Annual clinical examination</td>
</tr>
<tr>
<td>Investigations of psychosocial functioning and wellbeing, and health-related quality of life</td>
<td>Annual clinical assessment or discussion; once during childhood PKU-specific quality of life questionnaire</td>
<td>Annual clinical assessment or discussion; once during adolescence PKU-specific quality of life questionnaire</td>
<td>Annual clinical assessment or discussion; once during adulthood PKU-specific quality of life questionnaire</td>
</tr>
<tr>
<td>Psychiatric examination</td>
<td>At onset of symptoms of psychiatric disturbances</td>
<td>At onset of symptoms of psychiatric disturbances</td>
<td>At onset of symptoms of psychiatric disturbances</td>
</tr>
<tr>
<td>Neuroimaging examination (MRI)</td>
<td>When there is an unexpected clinical course and/or unexpected neurological deficits</td>
<td>When there is an unexpected clinical course and/or unexpected neurological deficits</td>
<td>When there is an unexpected clinical course and/or unexpected neurological deficits</td>
</tr>
<tr>
<td>Investigations specific to age group</td>
<td></td>
<td></td>
<td>Ultrasound at 18–22 weeks of pregnancy with screening for organ development (especially if a lack of optimal metabolic control exists), echocardiogram in all infants who are conceived by women with either high blood Phe concentrations or poor maternal blood Phe control during pregnancy</td>
</tr>
</tbody>
</table>

PKU=phenylketonuria. Phe=phenylalanine. BMD=bone mineral density. IQ=intelligence quotient. EF=executive function.
might directly affect cerebral metabolism, such as the
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consideration.95–97 Patients with PKU who are diagnosed
treatment (eg, immigrants), also need special
screening failures or lack of newborn screening or
with untreated PKU, especially because of newborn
mother and the infant.

We encourage breastfeeding and do not consider there
to be contraindications for breastfeeding in maternal
PKU, but clinical experience would suggest that the
 provision of breast feeding to an infant with PKU whose
mother also has PKU requires careful monitoring with
regard to the phenylalanine concentrations both in the
mother and the infant.

Patients with PKU who are diagnosed late or patients
with untreated PKU, especially because of newborn
screening failures or lack of newborn screening or
treatment (eg, immigrants), also need special
consideration.95–97 Patients with PKU who are diagnosed
late can improve their IQ with treatment,95–99 and
improvements in seizures and behaviour can occur in
patients with untreated PKU.96 Therefore, regardless of
age, we advise the identification of these patients.
Treatment for patients with a late diagnosis of PKU
should always be considered, whereas in patients with
untreated PKU, introduction of treatment is on an
individual basis. If treatment is started, a treatment trial
of 6 months should be given before the outcomes are
assessed (including motor function [less tremors or
spasticity] and behaviour [less restless and irritable, more
alert or responsive, and less aggressive with decreased
frequency and severity of self-injury behaviours]), but
further data are required to give clear recommendations
for the care of late diagnosed or untreated PKU.

Conclusion and future directions
To set a standard of care for all patients with PKU in
Europe, we have developed this first set of European
guidelines for the diagnosis and treatment on the basis
of the highest quality of available evidence. We have
identified knowledge gaps that require further research
to direct better care for the future.

Optimisation of all current treatment strategies is
essential, with a focus on adult and elderly patients and
a definition of their difficulties and any explanatory
pathophysiological mechanisms. Such future treatment
strategies might target the blood phenylalanine
concentrations through the use of phenylalanine
ammonia-lyase modified with polyethylene glycol, new
chaperones, and gene treatment.100 Other treatments
might directly affect cerebral metabolism, such as the

use of large neutral amino acids. Both glycomacropeptide
and large neutral amino acids are already being used in
some countries but require further proof of safety and
efficacy.101,102 We also need to improve the quality of care
delivered by some PKU centres, particularly in low-
income and middle-income countries, to achieve
acceptable care for all patients with PKU in Europe.4

To facilitate attainment of these objectives, the ESPKU
and the development of European Reference Networks
for PKU are important. Especially for rare diseases, an
international consortia to investigate outcomes in
relation to treatment strategies would be very useful.
The European Reference Network for metabolic
diseases, including PKU, is an important international
consortium that can facilitate studying outcomes
associated with varying treatments options and target
phenylalanine concentrations in different age ranges.

The availability of a device for home monitoring
might further optimise outcomes,103 as a shorter
turnaround time to attain blood phenylalanine
concentrations could help patients improve phenylalanine
control.

Contributors
FvS led the project, chaired the plenary discussions, and was the lead
writer of the manuscript. AMJvW co-chaired the plenary discussions
and was the second lead writer of the manuscript. All other authors
contributed in the plenary discussions, and co-wrote and approved the
manuscript. FvS contributed to groups B and E (initialisation of treatment
[primary topic of group E] and methods of measuring phenylalanine
[as a subtopic of group E]). AMJvW was the project assistant and assisted
all working groups in the literature search, selection, and grading of
evidence, and processed the data. KA, FF, AM, and JHW were members
of working group A (nutritional treatment and nutritional and
biochemical follow-up). AB, JC, SCH, and VL were members of working
group B (neurocognitive outcomes including imaging). AMB, SK, and
MVvR were members of working group C (psychosocial outcomes and
adherence). MG, FM, and FKT were members of working group D
(adult and maternal phenylketonuria [PKU], late diagnosed, and
untreated PKU). AB-Q, NB, and ACM were members of working group

Search and selection criteria
We searched PubMed (MEDLINE), Embase, the NHS Economic
Evaluations Database (NEED), the Cochrane Library, and
reference lists for relevant publications in English. We used the
search terms listed in the appendix. All literature that was
reviewed was published up to Dec 31, 2015, and was without
any exclusion of publications before a specified year. In total,
975 publications were reviewed. The quality of the studies was
assessed by two group members independently, or by group
discussion, or both, before we developed the conclusions into
recommendations. Recommendations with no or low level of
evidence were discussed with all participants during
five face-to-face plenary sessions until consensus was reached,
in line with the Delphi method. The key recommendations
were either based on evidence (if level of evidence was A or B
[SIGN method]) or on consensus (Delphi method) if the level
of evidence was C or D, or are so-called good practice points
that are not based on any evidence.
E (diagnosis of PKU and drugs in PKU). KA worked on the large neutral amino acids main topic. AB-Q worked on the emergent therapies main topic. AB and VL worked on the magnetic resonance imaging main topic. NB worked on the diagnosis, differential diagnosis, genotyping, and BH4 loading test main topics. AMB worked on the psychosocial functioning (including quality of life) and mental health main topics. JC worked on the target phenylalanine levels, biochemical markers, and neurocognitive functioning main topics. SK worked on the frequency of visits and phenylalanine levels measurement main topics. AM worked on the dietary treatment main topic and contributed to group D on dietary treatment in maternal PKU and untreated or late-treated adults. FM worked on the adult PKU main topic. ACM worked on the BH4 treatment main topic. MvR worked on the adherence main topic and contributed to group D on untreated or late-treated adults. JHH worked on the parental nutrition main topic.

Declaration of interests
KA has been a member of the European Nutrition Expert Panel (Merck Serono International). AB-Q has received honoraria as a speaker for Nutricia International, Vitafluo International, Merck Serono, and Recordati, and is a member of the European Nutrition Expert Panel (supported by Merck Serono International), the Sapropterin Advisory Board (supported by Merck Serono International and BioMarin), and KAMPER Advisory Board (supported by Merck Serono International, BioMarin). NB has been a member of the Merck Serono and BioMarin and Censa Pharmaceuticals scientific advisory boards for phenylketonuria (PKU), and has received grants and honoraria from Merck Serono and BioMarin. AM, AB, FF, MG, and ACM have been members of scientific advisory boards for PKU (supported by Merck Serono, BioMarin, and Nutricia International). AM has received research grants from Nutricia International and honoraria from Merck Serono, BioMarin, and Nutricia International. JC and MG have received honoraria as consultants and speakers from Merck Serono and Nutricia International/Danone. FF has received honoraria from BioMarin, Merck Serono, and Nutricia International/Danone. SCH has participated in strategic advisory boards and received consultant and speaker honoraria from Merck Serono, Biomarin, and Nutricia International. SK has received honoraria from Merck Serono and BioMarin. VI has received honoraria as a consultant from Nutricia International. AM has received research funding and honoraria from Nutricia International, Vitafluo International, and Merck Serono, chairs the European Nutrition Expert Panel (supported by Merck Serono International), has been a member of the Sapropterin advisory board (supported by Merck Serono International), is a member of the Advisory Board Element (Danone-Nutricia), and is a member of the scientific advisory board of Arla Foods International. FM has received consultant and speaker honoraria from Merck Serono, Nutricia International, Vitafluo International, and Arla Foods International, and research grants from Merck Serono. ACM has received research funding from Nutricia International, Vitafluo International, and Merck Serono, and has received honoraria as a speaker from Merck Serono and Arla Foods International. MvR was a member of the European Nutritionist Expert Panel in PKU (supported by Merck Serono International; until 2015), is a member of the ELEMENT (Leading Education in Metabolic Error Nutritional Therapy) steering committee for Nutricia International, and has received grants and fees for educational and research activities from Nutricia International and Orphan Europe. FJvS is a member of scientific advisory boards for PKU and amnioncensis defects that are supported by Merck Serono (past), BioMarin, Arla Foods International, SoBi, and Nutricia International, has received research grants from Nutricia International, SoBi, Alexion, and Merck Serono, and honoraria as a consultant and speaker from Merck Serono and Nutricia International/Danone, and honoraria as a speaker from Vitafluo International. FKT has received grants from Vitafluo and honoraria as a speaker from Merck Serono. AMjW and JHH declare no competing interests.

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