



Effective Health Care Program

Adjuvant Treatment for Phenylketonuria (PKU) *Executive Summary*

Background

Etiology

Phenylketonuria (PKU) is a metabolic disorder in which an inability to properly metabolize the amino acid phenylalanine (Phe) leads to a buildup of Phe in the blood, causing neurotoxicity and resulting in intellectual disability, delayed speech, seizures, and behavior abnormalities. Individuals with PKU are also susceptible to other adverse outcomes, including impaired executive function, reduced processing speed, attention problems, impaired fine motor skills, and mental health concerns (such as anxiety and depression symptoms).^{1,2}

The most severe form of PKU, classic PKU, is typically characterized by blood Phe levels exceeding 1,200 $\mu\text{mol/L}$ while on a normal diet. PKU is typically diagnosed at birth following abnormal newborn screening results. With adherence to a Phe-restricted diet, poor outcomes can be mitigated. Nonetheless, management of PKU can be difficult and onerous for the patient and the family, leading to interest in identifying new ways of managing this lifelong condition. Further, questions remain as to the empirical basis for the selection of specific blood Phe levels as targets to reflect good dietary control.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Treatment of PKU

The mainstay for treatment of PKU is a diet that restricts the intake of Phe to control the Phe concentration in the blood. The usual treatment goal is a blood Phe level



of 120 to 360 $\mu\text{mol/L}$. However, there is some variation in the target Phe level among clinics and across countries.^{3,4} In addition to the low-Phe diet, many patients take vitamins and minerals daily to replace the nutrients that are absent in their restricted diet.⁴

Historically, Phe levels were monitored closely only during the first 6 years of life (the “critical period”) because elevated Phe after that age was not believed to be detrimental. However, based on accumulated evidence over the last few decades, it is now the standard of care to recommend strict adherence to a Phe-restricted diet and routine monitoring of Phe levels throughout life.^{3,5}

In 2007 the U.S. Food and Drug Administration (FDA) approved sapropterin dihydrochloride (Kuvan[®], formerly known as Phenoptin) for the treatment of PKU under the stipulation that studies regarding the drug’s efficacy and long-term safety continue. Sapropterin dihydrochloride (hereafter, BH4) is presumed to work by enhancing residual enzyme activity present in some individuals with PKU.

In addition to a Phe-restricted diet and BH4, another potential treatment for PKU is large neutral amino acids (LNAAs). LNAAs are considered nutritional supplements and are not subject to FDA approval. In theory, LNAAs decrease the brain Phe concentration by competing with Phe for shared amino acid transporters to cross the blood-brain barrier.^{6,7}

Maternal PKU and Maternal PKU Syndrome

Poorly treated PKU in pregnant women will result in a teratogenic syndrome in the offspring, even if the offspring do not have PKU. Known as maternal PKU syndrome,⁸ it can cause microcephaly, congenital heart defects, low birth weight, craniofacial abnormalities, and intellectual disability in the child. Management of PKU during pregnancy can be very difficult. Some individuals may have loosened stringent dietary restrictions during adolescence, and restarting a diet that strictly limits protein may be challenging.⁹ Complicating factors such as morning sickness, balancing severe protein restriction with adequate energy intake, insurance coverage limitations for medical foods and modified low-protein foods, maturity of the expectant mother, and her food lifestyle before pregnancy contribute to the challenges.

Objectives

Population

We focused this review on adjuvant pharmacologic treatment and treatment with LNAAs for all individuals, including infants, children, adolescents, adults, and pregnant women with PKU. We also examined evidence for target Phe levels to minimize or avoid cognitive impairment in individuals with PKU.

Interventions

We examined the following interventions: BH4 and LNAAs. The report does not address dietary restriction as the sole treatment for PKU, as its effectiveness has been shown in numerous studies and it is the standard of care.^{5,10}

Comparators

We examined the effectiveness of BH4 plus dietary intervention (Phe-restricted diet and medical foods) compared with diet alone and the effectiveness of LNAAs plus dietary intervention compared with diet alone.

Outcomes

Our outcomes of interest for Key Question 1 included Phe levels and cognitive impairment, defined as deficits in either intelligence quotient (IQ) or measures of executive function. For measures of executive function, we sought outcomes in the following categories: working memory, attention, cognitive flexibility, planning, and inhibitory control. For treatment-related questions, we sought outcomes that included the individual’s ability to liberalize diet while maintaining appropriate blood Phe levels, nutritional outcomes, quality of life, and changes in cognition, including executive function and IQ. We also report intermediate outcomes (Phe level, Phe tolerance, and Phe variability).

Key Questions

Key Questions were:

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention

alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 6. What are the harms, including adverse events, associated with the use of BH4 or LNAAs in individuals with PKU?

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients?

Analytic Framework

The analytic framework (Figure A) summarizes the process by which treatment is chosen and modified for infants, children, adolescents, adults, or pregnant women with PKU. The treatment choice that is the basis of this review is whether to add pharmacologic therapy in the form of BH4 or LNAAs to dietary therapy. The primary target health outcome is maintenance of cognition; secondary outcomes include increasing the quality of life. Quantifying the levels of Phe provides an intermediate marker of treatment success because these levels are used to adjust the dietary intake of Phe.

In maternal PKU, treatment is intended to prevent impairment in the infant (who typically does *not* have PKU) caused by the teratogenic effects of excessively high Phe levels in the maternal bloodstream.

Methods

Input From Stakeholders

The topic was nominated in a public process. With Key Informant input, we drafted initial Key Questions, which the Agency for Healthcare Research and Quality (AHRQ) reviewed and posted to a public Web site for public comment. Using public input, we drafted final Key Questions, which AHRQ reviewed. We convened a Technical Expert Panel (TEP) to provide input during the project on issues such as setting inclusion/exclusion criteria and refining the analytic framework.

Data Sources and Selection

Data Sources

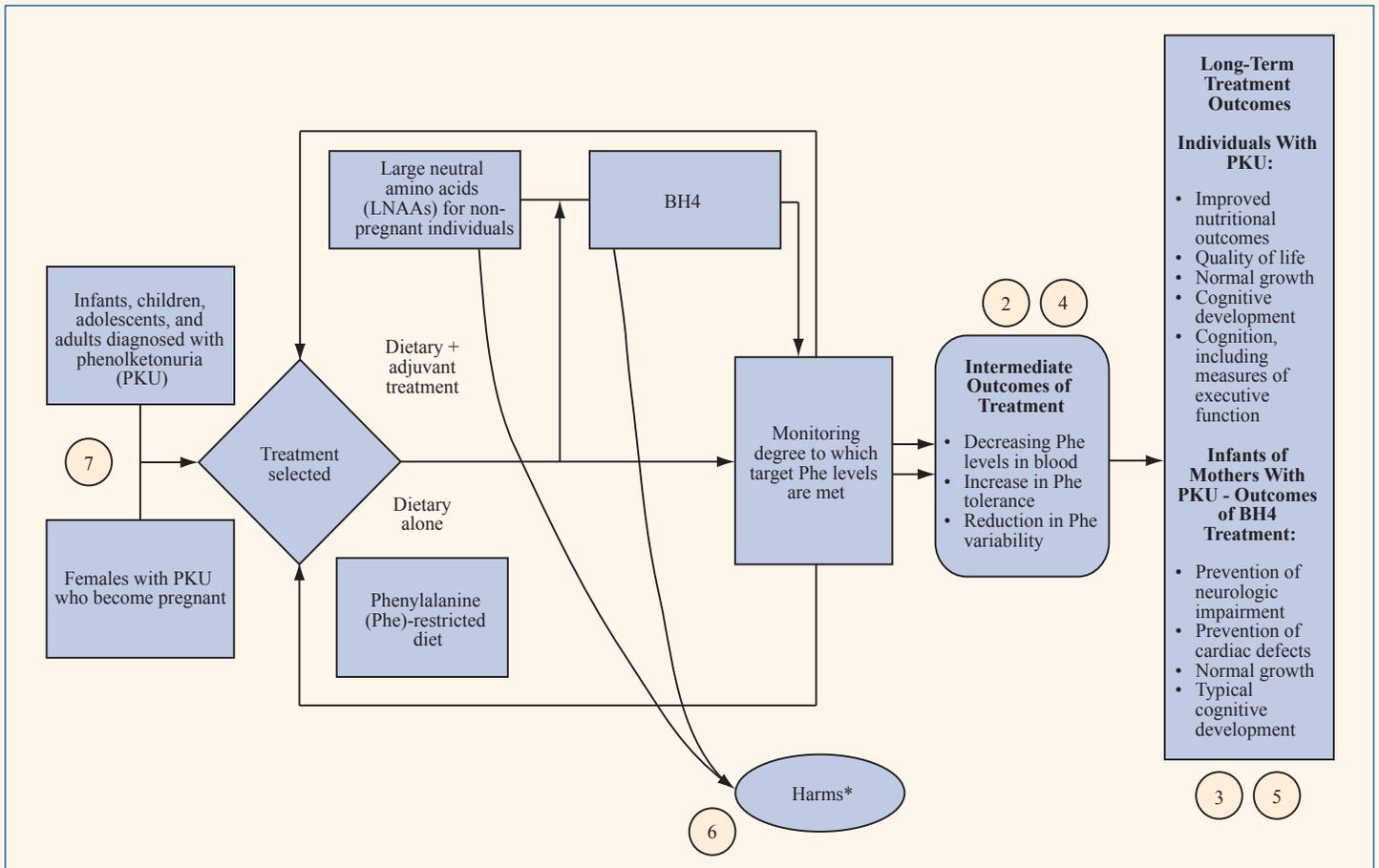
We searched five databases: MEDLINE® via the PubMed interface, PsycINFO (CSA Illumina interface; psychology and psychiatry literature), Embase Drugs and Pharmacology, the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database, and the National Agricultural Library (AGRICOLA) database. We hand-searched reference lists of included articles and recent reviews for additional studies and invited TEP members to provide additional citations.

We also searched Internet resources to identify regulatory information and current research; resources included the Web sites of regulatory agencies and clinical trials registries. Additionally, we searched commercial databases and a number of PKU-related Web sites specifically for any legal procedures related to the drug that might be a source of additional data. We also searched compilations of abstracts presented at major scientific meetings addressing PKU for treatment-related presentations given from 2006 (where possible) to 2011.

Inclusion and Exclusion Criteria

Table A summarizes the criteria we used to assess studies for inclusion in the review. As noted, this report focuses on the use of adjuvant treatments for PKU and does not address dietary restriction alone. The effectiveness of dietary restriction has been demonstrated in previous studies,^{5,10} and it is well established as the cornerstone of PKU therapy.³

Figure A. Analytic framework for treatment questions



BH4 = sapropterin dihydrochloride; LNAAs = large neutral amino acids; Phe = phenylalanine; PKU = phenylketonuria

* Encompasses a full range of specific negative effects, including the narrower definition of adverse events. Can include costs, medical side effects, poor quality of life, etc.

Note: Numbers in circles indicate the positioning of Key Questions in the treatment process.

Table A. Inclusion and exclusion criteria

Overall Exclusion Criteria

- Did not include at least 10 individuals with PKU
- Did not address treatment of PKU or did not provide data to assess association between Phe levels and cognitive outcomes (IQ, measures of core domains of executive function)
- Did not address outcome measures of interest
- Were not published in English

Exclusion Criteria for Studies Addressing IQ and Phe Levels

- Did not meet overall criteria above
- Did not include early-treated individuals with PKU (as specified in study)
- Did not provide Phe level and IQ data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
- Did not provide a correlation between Phe level and IQ

Table A. Inclusion and exclusion criteria (continued)

Exclusion Criteria for Studies Addressing Measures of Executive Function and Phe Levels

- Did not meet overall criteria above
- Did not include early-treated individuals with PKU (as specified in study)
- Did not provide Phe data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
- Did not provide executive function data for each participant or mean/median data plus measure of variance (e.g., standard deviation)
- Did not provide a correlation between Phe level and a measure of executive function
- Did not include a control group of healthy individuals to provide a normative measure

Exclusion Criteria for Studies of Maternal PKU/Maternal PKU Syndrome and Phe Levels

- Did not meet overall criteria above
- Did not provide Phe level and IQ data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
- Did not provide a correlation between maternal Phe level and offspring IQ

IQ = intelligence quotient; Phe = phenylalanine; PKU = phenylketonuria

Screening of Studies

Two reviewers separately evaluated each abstract. If one reviewer concluded that the article could be eligible, we retained it. Two reviewers independently read the full text of each included article to determine eligibility, with disagreements resolved via third-party adjudication.

Data Extraction and Quality Assessment

Data Extraction

All team members entered information into the evidence tables. After initial data extraction, a second team member edited entries for accuracy, completeness, and consistency. In addition to outcomes for treatment effect, we extracted data on harms/adverse effects.

Quality Assessment

Two reviewers independently assessed quality, with differences resolved through discussion, review of the publications, and consensus with the team. We rated studies as good, fair, or poor quality and retained poor studies as part of the evidence base discussed in this review. More information about our quality assessment methods is in the full report.

Data Synthesis and Analysis

Evidence Synthesis

We meta-analyzed studies addressing the relationship between Phe level and IQ. We defined measurements of

Phe reported in studies as concurrent (<6 weeks) with IQ testing or historical (taken more than 1 year prior), or both. We also considered measurements taken before age 6 to constitute the critical period. We estimated two models, one for each type of Phe measurement (concurrent and historical), using Bayesian hierarchical mixed-effects models estimated using Markov chain Monte Carlo methods.¹¹ In both analyses, we were interested in predicting the probability of an IQ below 85 at varying levels of blood Phe.

We used summary tables to synthesize studies addressing the treatment of PKU and summarized the results qualitatively.

Strength of Evidence

The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence. Strength of evidence can be regarded as insufficient, low, moderate, or high. We established methods for assessing the strength of evidence based on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews,¹² developed by AHRQ's Evidence-based Practice Center Program. We assessed the strength of evidence for key outcomes identified by the clinical investigators to be most clinically important: cognitive outcomes including IQ and executive function, nutritional outcomes, quality of life, and liberalization of diet. Secondary outcomes included changes in blood Phe levels, Phe variability, and Phe tolerance.

Results

Our searches retrieved 2,469 citations (Figure B). We reviewed the full text of 797 studies. Of the 797 full-text articles reviewed, we retained 69 articles (comprising 46 unique studies).

Key Question 1a: Evidence for Optimal Phe Levels To Minimize Cognitive Impairment

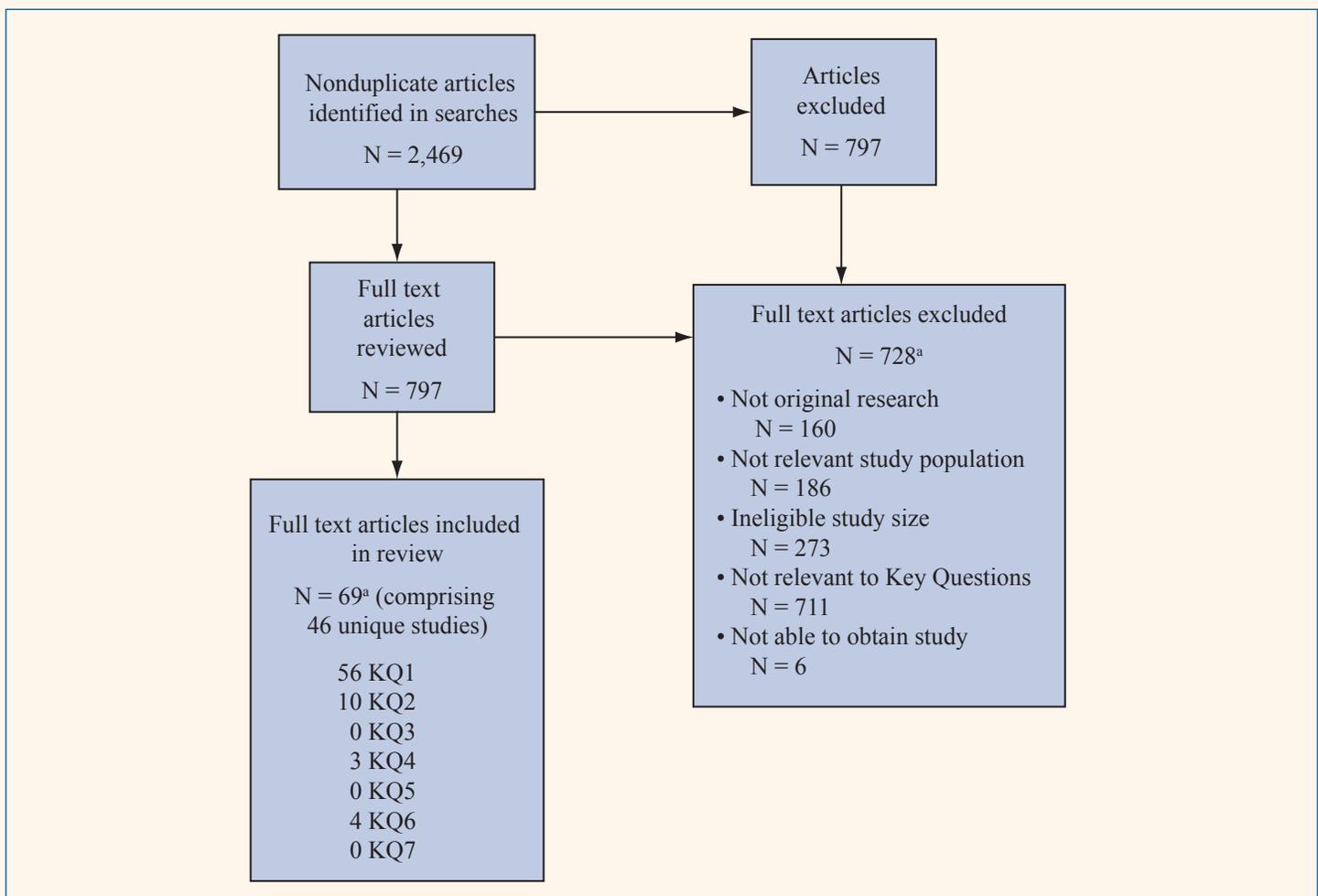
Phe Levels and Impairments in IQ

Seventeen unique studies (reported in 21 publications) met our criteria and addressed the relationship between Phe levels and IQ.¹³⁻³³ We rated one study^{20,21} as good quality

and five studies as fair quality.^{16,18,24,27,32,33} The remaining studies^{13-15,17,19,22,23,25,26,28-31} were rated as poor quality.

The studies included a total of 432 individuals with PKU. A majority of studies included primarily participants under age 25 at intake,^{13-16,18,20,23,24,27,28,31,33} with five studies including only participants under age 15 at intake.^{13,16,24,28,31} Dietary control varied among the studies, with five studies reporting that all participants were adhering to a restricted diet,^{13,14,16,25,31} seven reporting a mix of dietary control (some participants on and some off a restricted diet),^{17-23,33} and three reporting that participants had discontinued a restricted diet.^{15,24,26} Dietary status was not clearly reported in the remaining two studies.²⁷⁻³⁰

Figure B. Flow of studies identified for the review



KQ = Key Question; N = number

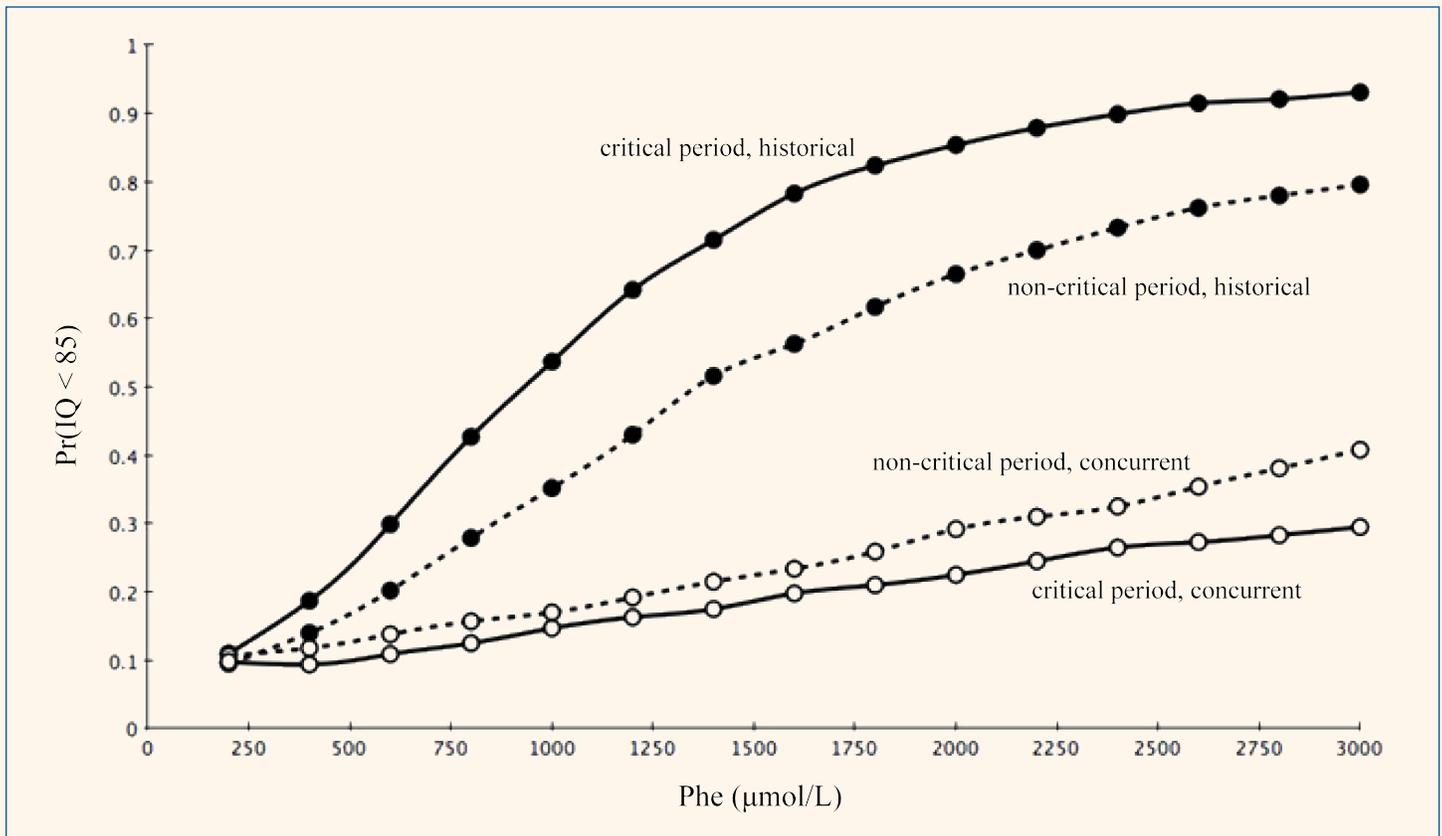
^aThe total number of (1) articles in the exclusion categories and (2) those addressing each Key Question exceed the (1) number of articles excluded and (2) total number included because most of the articles fit into multiple exclusion categories or addressed more than one Key Question.

We developed two meta-analytic models (Figure C). The first represents the relationship of Phe and IQ when Phe was measured “historically” (more than 12 months before IQ measurement). In the second model, Phe and IQ were measured concurrently (within 6 weeks of each other). Note that the two lines corresponding to historical measures of Phe in Figure C (top two lines) both demonstrate increasing probability of low IQ at higher blood Phe levels, regardless of whether IQ was measured

during childhood (solid line) or beyond (dashed line), with a stronger association seen between Phe measured in early childhood and later IQ.

The two lower lines in the figure describe probability of IQ <85 as a function of Phe when measured concurrently. There is a lack of strong association in measurements taken concurrently during the critical period, as noted by the relatively flat line.

Figure C. Probability of IQ < 85 at varying blood Phe levels and Phe measurement times



IQ = intelligence quotient; Phe = phenylalanine; Pr = probability

Phe Levels and Impairments in Executive Function

Nineteen unique studies, reported in 26 papers,^{20,21,23,25,28-31,34-51} provided data on Phe levels and on measures of executive function. After reviewing these as possible candidates for meta-analysis, clinical and statistical experts determined that a meta-analysis would not be appropriate for any component of executive function, as not enough studies used the same type of neuropsychological measure to allow for combining of data. Further, these studies cannot be meaningfully aggregated since the measures of executive function relevant for individuals with PKU have not yet been established.

Overall, while Phe levels correlate with various assessments of executive function in some papers, the degree to which they are correlated and the correlation on individual measures are inconsistent.

Phe Levels and Impairments Related to Maternal PKU and Maternal PKU Syndrome

Data predominantly from one longitudinal study provide support for the increased risk observed of poor cognitive outcomes in the offspring of women with high maternal blood Phe concentrations. The Maternal PKU Collaborative Study was initiated in 1984 to study the implications of maternal PKU, and specifically to assess

outcomes when Phe is controlled in pregnant women. The study reported that timing of maternal metabolic control, defined as the number of weeks gestation before plasma Phe levels remained consistently lower than 605 $\mu\text{mol/L}$, was associated with lower child cognitive scores at 4 and 7 years of age.

A model of the form of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood⁵² confirmed that the relationship between maternal blood Phe and offspring cognitive outcomes was not linear, that a threshold of 360 $\mu\text{mol/L}$ is the level at which cognitive impairment was significantly more common in offspring of mothers with PKU than in controls, and that a linear relationship between Phe levels and impaired cognitive outcomes occurred after this threshold. Importantly, while other factors, including maternal characteristics, severity of mutations, and offspring head circumference, contributed strongly to outcomes at 1 year of age, by age 2, maternal Phe strongly overtook other factors in predicting cognitive impairment.

Key Question 1b: Evidence for Optimal Phe Levels To Minimize Cognitive Impairment for Different Age Groups

We examined the potential effect of age in the meta-analysis of the relationship of Phe and IQ. Any influence of age was adequately represented by whether the Phe measurements were historical or concurrent and whether they were taken in the critical period.

Key Question 2: Effectiveness of BH4 in PKU

Ten studies evaluated the effects of BH4⁵³⁻⁶² in patients with PKU. These studies included two randomized controlled trials (RCTs) (one of good quality⁵⁴ and one of fair quality⁵⁵), two uncontrolled open-label trials of good^{53,58} and one of fair⁶⁰ quality, one poor-quality prospective cohort,⁶² and four poor-quality case series.^{56,57,59,61} No study included more than 80 participants in the treatment arm, and the total number of individuals treated in all studies was 284. Participants ranged in age from birth to 58 years, and most had demonstrated responsiveness to BH4 in a loading study. Of note, the definitions of positive response to BH4 differed and are described in the full report.

BH4 was studied in doses that ranged from 5 mg/kg/day to 26 mg/kg/day, over time periods of up to 22 weeks in trials and 9 years in one case series. The degree to which participants adhered to a restricted diet varied by study, and baseline Phe levels ranged from below 300 to

over 1,300 $\mu\text{mol/L}$. All randomized and open-label trials and three case series evaluated the short-term outcome of reduction in Phe levels. Five studies reported on Phe tolerance (amount of daily Phe intake at which blood Phe stays steady),^{55,57-59,61} and two reported on Phe variability.^{56,62} Only one study⁵⁹ assessed our primary outcomes of interest, including measures of cognition and nutritional status. No study evaluated quality-of-life outcomes.

Phe levels were reduced by at least 30 percent (the level used in studies submitted to the FDA to assess responsiveness) in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies. In the one RCT that compared the effect of placebo on the likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group.⁵⁴ Data from the uncontrolled open-label trial⁵³ following this RCT⁵⁴ suggested a sustained response for up to 22 weeks duration, with 46 percent achieving a 30-percent reduction in Phe levels.

In the second RCT,⁵⁵ similarly positive effects were reported at a dosage of 20 mg/kg/day in children on Phe-restricted diets. At week 3, those receiving BH4 had a greater reduction in Phe levels at their baseline dietary Phe intake. In the other uncontrolled open-label trial,⁵⁸ BH4 (7 to 20 mg/kg/day) was associated with reduced Phe levels among participants both on and off Phe-restricted diets. Overall, participants' responses to different dosages of BH4 varied, with individualized dose adjustments needed according to target plasma Phe and dietary intake. Response also varied by different baseline Phe levels, with those with the highest baseline levels having lower response rates.

These two studies^{55,58} also examined the effect of BH4 use on Phe tolerance in individuals responsive to BH4, as did three case series.^{57,59,61} In all five studies, Phe tolerance improved over time. Only the RCT,⁵⁵ however, provides comparative data with a placebo group. At a dosage of 20 mg/kg/day over 10 weeks, participants in the treatment group increased their Phe tolerance (daily medical foods tolerated) from 0 mg/kg at baseline to 20.9 mg/kg/day while maintaining blood Phe levels at <360 $\mu\text{mol/L}$, compared with an increase of 2.9 mg/kg/day in the placebo group. However, response varied substantially within the treatment group, with 33 percent tolerating an increase of between 31 and 50 mg/kg/day in supplement form but the rest of the participants tolerating lower levels of supplementary Phe. The degree to which this variability is

associated with other factors possibly associated with Phe tolerance is unknown.

One small case series reported on IQ and nutritional outcomes for up to 1 year on 5 mg/kg/day BH4 treatment.⁵⁹ After 1 year of treatment, the 11 participants discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were similar to scores before treatment and development quotients were within normal limits.

Key Question 3: Effectiveness of BH4 in Pregnant Women With PKU

We did not identify any studies addressing this question.

Key Question 4: Effectiveness of LNAA in PKU

Three studies addressed the effects of LNAA,^{7,63,64} including a fair-quality⁶³ and poor-quality⁶⁴ RCT and a poor-quality uncontrolled open-label trial.⁷ The studies included a total of 47 participants. Participant numbers in the RCT treatment arms were 16⁶³ and 20⁶⁴ on LNAA, while the uncontrolled open-label trial included 11.⁷ Participants were between 11 and 45 years of age. The trials were short, with treatment between 1 and 8 weeks, and dosages ranged from 250 mg/kg/day to 1g/kg/day. Two of the three studies measured reductions in Phe levels,^{7,64} and one assessed cognitive outcomes.⁶³

This fair-quality study⁶³ reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a Phe-free medical food for their nutritional needs did not experience a decrease in Phe, although those not adhering to diet or not using their formula did. In all three studies, blood Phe decreased after 1 week of treatment but remained above clinically acceptable levels.

Key Question 5: Effectiveness of LNAA in Pregnant Women With PKU

We did not identify any studies addressing this question.

Key Question 6: Harms of Adjuvant Treatment for PKU

Of the 10 studies examining the effectiveness of BH4 in participants with PKU, 4 studies^{53-55,60} reported any type of harm related to the intervention drug. The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting, but harms were not significantly more common in the treatment

arm than in the placebo. One trial of LNAA⁶³ assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use.

Key Question 7: Effectiveness of BH4 and LNAA for Subgroups of Individuals With PKU

We did not locate any studies addressing this question.

Discussion

Key Findings

Increased Phe is associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at Phe over 400 $\mu\text{mol/L}$ and leveling off at about 80 percent at 2,000 $\mu\text{mol/L}$. This supports the typical target goal for Phe level in individuals with PKU (120 to 360 $\mu\text{mol/L}$).³

Notably, the negative association between Phe and IQ is strongest when Phe is measured at least 1 year prior to IQ testing. The Phe level obtained more than 1 year before IQ testing is likely to be a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship lends support to the principle that cognitive effects accumulate over a long time period, and thus concurrent measurements are poor predictors of a cognitive effect. The strongest associations are seen in the group for which historical measurements were taken during the critical period (<6 years old) and associated with later IQ, although historical measurements taken after the critical period are also associated with risk of low IQ. Hence, control of Phe levels during the critical period is particularly important, and there is no evidence that control can be relaxed after early childhood. Current clinical practice is to maintain Phe control even in adulthood, which is supported by this analysis.

Currently, findings on the association of Phe levels and any specific measure of executive function are inconsistent, and too few studies have used the same outcome measures to combine their data in any meaningful way. This is an important area for future research, with foundational research needed to validate specific outcomes for measuring executive function in individuals with PKU. In maternal PKU, current evidence supports the need to achieve dietary control as early as possible in pregnancy, and ideally to maintain a Phe level of 120 to 360 $\mu\text{mol/L}$.

The FDA approved BH4 in 2007 as a potential adjuvant treatment with dietary control. Two RCTs and three uncontrolled open-label trials are currently available in the literature; there is substantial overlap in the participants

across the studies. Phe levels were reduced by at least 30 percent (the usual research target) in up to half of treated participants (32 to 50 percent). In the one RCT that compared the effect of placebo on likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group.⁵⁴ In a 2.6-year uncontrolled open-label trial of BH4, most of the 90 study completers were reported to have reached clinical targets in Phe levels. No studies have linked these results to longer term clinical or patient-reported outcomes. The strength of evidence for the effects of BH4 on lowering Phe levels in BH4-responsive individuals in the short term is moderate, as is the strength of evidence for a lack of harms of BH4. The strength of the evidence for the effects of BH4 on cognitive outcomes is low based on a combination of evidence from the RCTs on Phe and evidence from the meta-analysis of the relationship of Phe and IQ. The strength of the evidence is insufficient for all other outcomes (Phe tolerance and the ability to liberalize the diet, Phe variability, quality of life, and nutritional outcomes).

In theory, supplementation of a Phe-restricted diet with large neutral amino acids might have beneficial effect on cognition, as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However, there is insufficient evidence to suggest that LNAAs could be a viable treatment option for reducing Phe levels or increasing Phe tolerance. There have been only three very small studies (total number of participants, only 47), and there is no evidence that Phe levels were reduced to clinically meaningful levels in the short time they were studied.

Applicability of Evidence

The degree to which current research may not be applicable to the clinical population with PKU is a concern, given the small size and homogeneous populations in each of the studies. For example, the two RCTs of BH4^{54,55} each focused on a distinctly different population—one on a slightly older population nonadherent to diet and one on a somewhat younger group with tight dietary control. Thus, it is unclear whether the results should be synthesized, or whether either study can confirm the results of the other. Nonetheless, individuals from both studied populations are likely to be seen in routine clinical care, and clinicians should find the results applicable to some of their patients. Of greater concern is the focus on intermediate outcomes; current evidence is

lacking on clinically relevant and longer term outcomes, including ability to liberalize the diet, cognitive effects, and quality of life.

Future Research

The existing research gaps related to the use of adjuvant pharmacologic therapy in PKU are both substantive and methodologic. Research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for specific studies. Furthermore, in part because it affects so few people, funding for PKU research is limited, and to date, treatment research is almost exclusively supported by the pharmaceutical industry. Other rare conditions have benefited from an overall research agenda. Thus, we recommend a multicollaborator process that includes a public-private partnership that could create a powerful tool for the future of PKU research in the form of a longer term (perhaps 10-year) research agenda. Furthermore, there is tremendous potential for development of a multicenter research consortium to comprehensively evaluate the complete system of care for individuals with PKU.

Funding from private or public entities should help establish a long-term prospective registry through which the consortium could collect comprehensive and detailed data on individuals with PKU. This could include additional support or linkage with the existing registry that is specific to use of Kuvan, the Phenylketonuria Demographic, Outcomes, and Safety (PKUDOS) registry. The expanded registry could include, but need not be limited to, data on short- and long-term outcomes of treatment, such as executive function, nutritional status, growth, and quality of life. Ideally, this registry would include a biorepository that would help identify any genotype-phenotype correlations and provide a multidimensional perspective on the effectiveness in practice of treatments, both in the short and long term.

One corollary might be a committee of experts and individuals with PKU to focus on harmonizing data collection; standardizing outcomes assessments; requiring specific and stringent standards for conducting double-blind placebo-controlled trials that adhere to the high standards required for synthesis and use in treatment guidelines; and selecting and implementing studies that clarify the short- and long-term outcomes of treatments and interventions for individuals with PKU, including psychological outcomes. For example, since dietary restriction is the essential cornerstone in the treatment of PKU, it would be helpful to study various methods that would improve adherence to dietary management and

other intervention strategies in order to improve outcomes throughout the lifespan, especially for adolescents and adults with PKU. With the establishment of a multicenter consortium, registry, and biorepository, PKU could serve as a model for studying the short- and long-term outcomes of treated inborn metabolic diseases. The field already has a starting position, with the Maternal PKU Collaborative Study a case in point.

Future Research on the Relationship of Phe and Cognition

A significant limitation in the current body of research on the relationship between blood Phe level and cognitive outcomes is the lack of consistent methodologies using standardized tools and measures and consistent data collection across centers. The result is that many studies provide incomplete data that cannot be used in meta-analyses. In future research, details about familial IQ, socioeconomic status, maternal education, age at initial treatment, and concurrent medications should be fully described so they might be used in a more extensive meta-analysis of Phe-IQ associations.

One basic need is to better understand the degree to which the perceived association changes by age, with the practical implication of understanding the degree of dietary control necessary across age groups. Because tight control is important, an understanding is needed of the supports that might be helpful as individuals age. Related to this is the need for additional measures beyond Phe to assess adequate control. This requires an understanding of what outcomes are clinically important, and their relative value to patients and their families. For this to be possible, complete and accurate measurement of Phe and cognition over fairly long periods of time is necessary, perhaps through a long-term followup study or through the multisite collaboration suggested above. Finally, the effects of mild hyperphenylalaninemia as opposed to those of classic, mild, and moderate PKU should also be clarified.

Although research is being conducted on executive function outcomes for individuals with PKU, there is no consensus on which measures of executive function are most appropriate. This highlights the need for fundamental research, because measures of executive function tend to be better reflections of success with day-to-day activities than targeted measures such as IQ. It is plausible that some measures of executive function may be more sensitive to changes in Phe than IQ. The sensitivity, validity, and acceptability of individual executive function measures in PKU have yet to be established or agreed upon, and current research reflects a reliance on a wide range of

outcomes, making synthesis of relationships and pooling of results difficult.

Given the reported association between PKU and an increased incidence of inattention, anxiety, and depressive symptoms, additional studies on these and other psychological issues in PKU are also warranted.

Future Research on Pharmacologic and Other Adjuvant Treatment

BH4. Research on the use of BH4 as an adjuvant therapy in PKU management consists of small, tightly controlled multisite efficacy studies, two of which are RCTs. The greatest research need in this area is thus for larger studies. Given the known difficulty of accruing large numbers of participants, however, researchers should also use existing datasets and, as recommended, use a consortium and multisite approach to gathering data.

Ideally, studies will be conducted in both tightly controlled and nonadherent populations, and among different age groups, with appropriate design and power for subgroup analyses. Research should continue to include RCTs, but prospective cohort studies that may have the potential to provide additional effectiveness data (including data on treatment outside of a controlled clinical setting), adherence data, and longer term evidence would also be helpful to support understanding of the role of BH4 in clinical care. These studies should provide substantially more detail on the range of benefits and harms associated with treatment. For example, a better understanding is needed of the effects of BH4 in children less than 4 years of age and pregnant women, and while it may be challenging or inappropriate to conduct RCTs in these populations, observational cohorts or registry data are essential.

Data are not currently available to understand potential modifiers of treatment effectiveness in order to select the best populations for targeting further research and treatment. Moreover, the variability in responsiveness to BH4 is unexplained, and subpopulations that have a unique response to this medication have not been well characterized. Causes of variability may be multifactorial and likely include individual patient and genotype differences, drug dose, and individual patient behavior such as dietary adherence. It is unclear, in particular, why a high proportion of individuals who have an initial response in loading studies at screening do not have a durable response in efficacy trials, while those who do have a response demonstrate a significant effect. The degree to which this observed variation may be associated with suboptimal adherence should be assessed.

Another area of potential research is the use of adherence supports for both drug and diet to optimize potentially positive outcomes. It is assumed that support at familial, social, and system levels may be helpful, and this idea should be empirically addressed.

Long-term efficacy outcomes beyond 22 weeks and safety outcomes beyond 3 years are currently unavailable, as are measures of behavioral change, cognition, and patient-reported outcomes, including quality of life. The degree to which reductions in blood Phe are associated with measurable cognitive outcomes or even patient perception of increased mental clarity is unknown. Furthermore, explicit assessment of the potential for liberalization of the diet and the subsequent nutritional effects has yet to be conducted.

Future research should comprise larger studies designed to allow subgroup analysis of the effectiveness of adjuvant pharmacologic therapy for PKU. Although the current literature does not provide evidence for effectiveness in all target patients, some benefit is seen in some patients. Whether these patients differ from the overall population in terms of genotype is an area of current research focus that has the potential to allow targeting of treatment.

A number of studies are reportedly underway to address gaps in the current literature. These include a long-term study of the effect of BH4 on neurocognitive function in young children, a study of the effect in adolescent patients with attention-deficit hyperactivity disorder, and a registry that includes pregnant women. However, we stress the importance of making data available and note that several commitment studies have been listed as completed but have yet to make findings available. These include studies on the cardiac effects of BH4. Another commitment study that is reported as fulfilled is an open-label study to study the safety and efficacy of BH4 for treating patients with hyperphenylalaninemia, yet no results have been made available. Finally, publicly funded studies to confirm and expand on reported efficacy and effectiveness data are needed.

LNAAs. The three very small studies of LNAAs cannot be considered as more than proof of concept at this time, and if further work is to occur in this area, it should be done in well-conducted RCTs of adequate size. The mechanism by which LNAAs may work should be clarified, as should the optimal target population and specific treatment goals. The current formulations that have been tested require taking many pills per day, so the formulations should be made more palatable.

Conclusion

The commonly used blood Phe target of 120 to 360 $\mu\text{mol/L}$ is supported in our meta-analysis.³ Notably, the negative association between Phe and IQ is strongest when Phe is measured at least 1 year prior to IQ testing. The Phe level obtained more than 1 year before IQ testing is likely a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship supports the principle that cognitive effects accumulate over a long time period, that concurrent measurements are poor predictors of a cognitive effect, and that control should be continued into adulthood. Review of the research on maternal PKU supports the need for dietary control as early as possible before pregnancy or in pregnancy and maintenance of Phe control to prevent poor cognitive outcomes in infants.

Dietary management remains the mainstay of treatment for PKU, and maintaining control over the lifetime is an appropriate goal. Nonetheless, there is potential to support patients in achieving their clinical goals and possibly liberalizing their diet with adjuvant therapy. BH4 has been shown in two RCTs and two open-label trials to reduce Phe levels in some patients, with significantly greater reductions seen in treated versus placebo groups.

We do not yet have the ability to predict which patients are most likely to be responders, as all participants in the trials were initially responsive in screening tests but not necessarily so in the efficacy studies. One RCT also demonstrated increased Phe tolerance using BH4 among children on restricted diets. Overall, harms associated with the drug were minor and did not occur more frequently in the treatment group than in placebo arms. To date, there are no data to directly establish the potential effects of BH4 on longer term clinically important outcomes, including cognition, executive function, and quality of life. Significant gaps in the evidence include effectiveness of the drug in a range of patients outside of the clinical trial setting. Thus, while the strength of evidence is moderate for a large positive effect of BH4 on reducing Phe levels over the short term in some groups of patients showing initial responsiveness, evidence for the effect of BH4 on longer term clinical outcomes is low and is based on indirect associations, including our meta-analysis.

In theory, supplementation of a Phe-restricted diet with LNAAs might have a beneficial effect on cognition, as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However, there is insufficient evidence to suggest that LNAAs could

be a viable treatment option for reducing Phe levels or increasing Phe tolerance.

Continued studies that include adequate numbers of participants should be conducted in both tightly controlled and nonadherent populations, and among different age groups, for both types of adjuvant therapies. In addition, data on effectiveness in various groups of patients outside the clinical trial setting are needed, including data on those individuals with variability in adherence.

Registries have been established and will provide important data, as will ongoing studies that measure additional outcomes, including behavioral and psychiatric measures. Data are not currently available to understand potential modifiers of treatment effectiveness, including genotype. Moreover, the variability in responsiveness to BH4 is unexplained.

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This executive summary is part of the following document: Lindegren ML, Krishnaswami S, Fonnesebeck C, Reimschisel T, Fisher J, Jackson K, Shields T, Sathe NA, McPheeters ML. Adjuvant Treatment for Phenylketonuria (PKU). Comparative Effectiveness Review No. 56. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. HHS 290-2007-10065-I.) AHRQ Publication No. 12-EHC035-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

