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Minireview

Updated, web-based nutrition management guideline for PKU: An evidence and consensus based approach

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ABSTRACT

Background: In 2014, recommendations for the nutrition management of phenylalanine hydroxylase deficiency were published as a companion to the concurrently published American College of Medical Genetics and Genomics guideline for the medical treatment of phenylketonuria (PKU). These were developed primarily from a summary of findings from the PKU scientific review conference sponsored by the National Institutes of Health and Agency for Healthcare Research & Quality along with additional systematic literature review. Since that time, the Genetic Metabolic Dietitians International and the Southeast Regional Newborn Screening and Genetics Collaborative have partnered to create a web-based technology platform for the update and development of nutrition management guidelines for inherited metabolic disorders.

Objective: The purpose of this PKU guideline is to establish harmonization in treatment and monitoring, to guide the integration of nutrition therapy in the medical management of PKU, and to improve outcomes (nutritional, cognitive, and developmental) for individuals with PKU in all life stages while reducing associated medical, educational, and social costs.

Methods: Six research questions critical to PKU nutrition management were formulated to support guideline development: Review, critical appraisal, and abstraction of peer-reviewed studies and unpublished practice literature, along with expert Delphi survey feedback, nominal group process, and external review from metabolic physicians and dietitians were utilized for development of recommendations relevant to each question. Recommendations address nutrient intake, including updated protein requirements, optimal blood phenylalanine concentrations, nutrition interventions, monitoring parameters specific to life stages, adjunct therapies, and pregnancy and lactation. Recommendations were graded using a rigorous system derived from the Academy of Nutrition and Dietetics.

Results and Conclusion: These guidelines, updated utilizing a thorough and systematic approach to literature analysis and national consensus process, are now easily accessible to the global community via the newly developed digital platform. For additional details on specific topics, readers are encouraged to review materials on the online portal: https://GMDI.org/.

Abbreviations: ACMG, American College of Medical Genetics; AGREE II, Appraisal of Guidelines for Research and Evaluation; BH4, tetrahydrobiopterin; BMD, bone mineral disease; DRI, dietary reference intake; DXA, dual x-ray absorptiometry; EF, executive function; FFM, fat-free mass; GMDI, Genetic Metabolic Dietitians International; IMD, inherited metabolic disorder; LNAA, large neutral amino acid; MeSH, medical subject heading; MPKU, maternal PKU syndrome; MRI, magnetic resonance imaging; MSUD, Maple Syrup Urine Disease; NIH, National Institutes of Health; PAH, phenylalanine hydroxylase; PHE, phenylalanine; PI, principal investigator; PICO, population, intervention, comparison, and outcomes; PKU, phenylketonuria; QoL, quality of life; SERC, Southeast Regional Newborn Screening and Genetics Collaborative; TYR, tyrosine.

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1. Introduction

Phenylketonuria (PKU), an autosomal recessive inherited metabolic disorder (IMD), is characterized by abnormally high concentrations of blood phenylalanine (PHE) and production of phenylketones resulting from impaired phenylalanine hydroxylase (PAH) function. Also referred to as PAH deficiency, the disorder represents a continuum of impairment in enzyme function. Failure or delay in treatment can result in irreparable neurologic damage and severe developmental delay [1,2]. The main goal of PKU therapy is to maintain blood PHE concentrations within a recommended treatment range of 120–360 μmol/L and to support nutritional needs so that growth and development are within the normal range [2]. This is accomplished by restriction of dietary PHE to that required for anabolism, consumption of medical food products to ensure optimal nutrient intake, and, in some individuals, adjunct pharmacotherapy [1–3].

Widespread consensus exists regarding the importance of blood PHE control and dietary treatment [2,3]. In response to the 2013 recommendations by the National Institutes of Health (NIH) and Agency for Healthcare Research & Quality (AHRQ), the American College of Medical Genetics and Genomics (ACMG) guideline for diagnosis and medical management of PKU (ACMG Guideline) was published in 2014 in conjunction with the Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) evidence- and consensus-based recommendations for nutrition management of PAH deficiency (GMDI/SERC Recommendations) [2,3]. This guideline advances the 2014 GMDI/SERC recommendations for nutrition management of PAH deficiency by incorporating a rigorous and expanded review of the latest research, grading the body of evidence, and utilizing a web-based technology that supports global open access. This process also resulted in revised recommendations for protein requirements.

Development of this guideline is part of a multi-year project undertaken by GMDI and SERC to develop nutrition management guidelines for rare IMDs to foster optimum nutrition management of affected individuals, to reduce the uncertainty and variability in management, and to direct future research. This is the second IMD guideline published by the partnership, building on the experience of the nutrition management guideline developed for Maple Syrup Urine Disease (MSUD) [4]. The

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PKU Nutrition Management Guideline and complete evidence documentation can be accessed through both the SERC and GMDI websites: https://GMDI.org/.

2. Methods

The methodology for development of the nutrition management guidelines has been previously reported [4,5]. The rigorous, transparent, and systematic process utilizes evidence in the peer-reviewed and practice-based medical literature as well as evidence derived from Delphi survey and nominal group consensus-building processes.

2.1. Question formulation

Topics for evidence analysis were selected from areas of uncertainty and variation in practice by a PKU working group comprised of ten experienced metabolic dietitians. Six practice-based questions were identified for evidence analysis and guideline development (Table 1). Research questions were formulated in the PICO (population, intervention, comparison, and outcomes) format [6,7], and a separate systematic literature search, appraisal, and evidence analysis and summary was completed for each question.

2.2. Search process, critical appraisal and abstraction, and consensus input and evidence summary

The search process, critical appraisal and abstraction, and consensus input and evidence summary were previously described in the Maple Syrup Urine Disease guidelines and are outlined on the SERC/GMDI portal (https://GMDI.org/) [4]. Pub Med searches included human studies (excluding genetic studies not related to treatment) published in English from 1980 to late 2000 and from 2011 to February 2014. Studies published from 2000 through 2010 were reviewed and summarized for the National Institutes of Health (NIH) State of the Science Conference (February 2013) by dietitians who were members of the NIH Diet Management Working Group or Maternal PKU Working Group, and who were also involved in this GMDI/SERC guideline effort. The summary statement from the State of the Science Conference [1] is referenced in the guideline in lieu of individual articles used in preparation of the summary statement. Literature reviewed for the published companion ACMG Guidelines and GMDI/SERC Recommendations are similarly referenced [2,3].

Gray literature refers to resources that cannot be accessed through standard search systems. These include abstracts and presentations from scientific meetings, clinical protocols and guidelines, unpublished research, communication among experts (including list-serves), professional newsletters, and book chapters. Gray literature related to PKU was collected by work group members and was screened and prioritized for inclusion based on relevance, currency, and substantive information not available in scientific literature.

Peer-reviewed articles were assessed based on criteria for sound scientific research, and gray literature assess based on purpose, development process, clarity and relevance. Consensus input and evidence summary are also described in Frazier et al. [4].

2.3. Guideline development

The final conclusion statement and recommendations for the nutrition management of individuals with PKU in each of the six topic areas were based on synthesis of all evidence and consensus sources. These were written, reviewed, and edited by the project core group. A guideline consultant, not involved in developing the recommendations, and with input from PIs and co-PIs with domain expertise, rated each recommendation with respect to strength of the evidence behind the recommendation (strong, fair, limited, consensus) and need for clinical action (imperative [i.e., broadly applicable to individuals with PKU] or conditional [ie, applicable in specific situations]). Definitions for strength of evidence and clinical action ratings are described in Table 2.

These clinical practice recommendations, along with background and other information to support their implementation, are contained in the PKU Nutrition Management Guideline document. The final document was reviewed by an external panel using the Appraisal of Guidelines for Research and Evaluation (AGREE II). The external panel consisted of three metabolic physicians, three dietitians, and an expert in guideline development and methodology, who were not involved in the evidence analysis nor in the development phases of the PKU guideline.

2.4. Web application

A secure, web-based application was developed specifically for IMD guidelines development and is described in detail elsewhere [4]. All reference material is categorized and stored within the web-based platform. In addition, each step of the guideline development process

Table 1
Research questions in PICO format.

Nutrient intakes	For individuals with PKU, what nutrient intakes are associated with positive outcomes?
Blood PHE concentrations	For individuals with PKU, what blood phenylalanine concentrations are associated with positive outcomes?
Nutrient interventions	For individuals with PKU, what nutrient interventions are associated with positive outcomes?
Long term monitoring	For individuals with PKU, monitoring of what parameters is associated with positive outcomes?
Adjunct and newly emerging therapies	For individuals with PKU whose therapy includes adjunctive therapy or other therapy options (sapropterin or large neutral amino acids) what dietary considerations are needed for positive outcomes?
Pregnancy and lactation	For pregnant individuals with PKU what nutritional therapies are associated with positive outcomes during pregnancy planning, pregnancy, and the post-partum period including lactation?

Table 2
Recommendation Ratings and Clinical Actions/Applications.*

Strength of evidence for recommendation ratings	
Strong	The benefits clearly exceed the harms (or the harms clearly exceed the benefits in the case of a strong negative recommendation); and the quality of the supporting evidence is good. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
Fair	The benefits exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong as above. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.
Weak	The quality of evidence that exists is suspect or well-done studies show little clear advantage for one approach over another.
Consensus	Expert opinion (determined from consensus methodology) supports the recommendation even though the available scientific evidence did not present consistent results, or studies were lacking.
Insufficient evidence	There is a lack of pertinent evidence (from research and clinical practice) and/or an unclear balance between benefits and harms.
Clinical action/application	
Imperative	The recommendation is broadly applicable to the target population without conditions.
Conditional	The recommendation clearly defines a specific situation that limits its applicability.

* Adapted for this guideline from: American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics. 2004;114(3):874–877 [117].

is stored and tracked within the platform. These features assisted in the development of the current guideline and will support future updates to the guideline.

3. Results

Of 1596 identified sources that met inclusion criteria, 239 peer-reviewed and 25 gray literature sources were adjudicated to be analyzed and became part of the evidence synthesis (including 40 for nutrient intake, 26 for blood PHE concentration, 121 for nutrition intervention, 65 for monitoring, 59 for adjunctive therapies, and 30 for pregnancy). Additionally, a literature synthesis from the NIH Phenylketonuria Scientific Review Conference was incorporated [10]. Fifty physicians, dietitians, researchers, and patient advocates contributed expertise through Delphi surveys, nominal group meeting participation, and review processes. Provided in this report are recommendations, strength of the supporting evidence, relative need for clinical action, and evidence summary for each of the six research topic questions listed in Table 1. The completed online *Guideline for Nutrition Management of PKU* provides full details with links to sources, specific nutrient intake recommendations, biochemical and clinical monitoring recommendations, and resources for both professionals and families: https://GMDI.org/. A summary discussion of recommendations resulting from management topic questions follows.

3.1. Nutrient intake

3.1.1. Question

For individuals with PKU, what nutrient intakes are associated with positive outcomes?

3.1.2. Recommendations

Recommendation	Strength of evidence	Clinical action
Meet the individual's recommended PHE intake (for anabolism and maintaining an appropriate blood PHE concentration) by adjusting intact protein intake.	Fair	Imperative
Provide a total protein intake (from a combination of intact protein and amino acid-based medical food) approximately 50% higher than the DRI for infants and children from birth to 4 years of age and 20–40% higher than the DRI for those over 4 years of age. The amount of medical food prescribed is based on the difference between the total protein recommendation and the intact protein allowance.	Fair	Imperative
Provide supplemental TYR if blood TYR concentrations are consistently below the normal range.	Fair	Conditional
With the exception of recommended intake for protein, PHE, and TYR, individuals with PKU should meet the same DRI for age- and gender-specific nutrient/micronutrients and energy as healthy individuals in the general population.	Weak	Imperative

3.1.3. Evidence summary

PHE is an essential amino acid found in most dietary intact protein sources. Because individuals with PKU are unable to catabolize PHE to TYR, daily intact protein intake must be limited to only the amount that provides the PHE required for anabolism. Hence, standard treatment for PKU consists of a specialized diet restricted in PHE, along with medically prescribed PHE-free or PHE-restricted amino acid-rich medical food as a primary protein source. This diet, which involves regular monitoring and adjustment of medical food and PHE intake, enables individuals with PKU to maintain plasma PHE concentrations within the recommended therapeutic range of 120–360 μmol/L throughout life [1]. See Table 3 for recommended ranges for PHE, TYR, and total protein intake by age.

Table 3
Guidelines for PHE, TYR, and protein intake for individuals with PKU.

AGE	PHE[a] (mg/day)	TYR[a] (mg/day)	Protein[b] (g/kg/day)
Infants to <4 years[a]			
0 to <3 months[c]	130–430	1100–1300	2.5–3.0
3 to <6 months	135–400	1400–2100	2.0–3.0
6 to <9 months	145–370	2500–3000	2.0–2.5
9 to <12 months	135–330	2500–3000	2.0–2.5
1 to <4 years[d]	200–320	2800–3500	1.5–2.1
After early childhood[e]			
>4 years to adult	200–1100	4000–6000	120–140% DRI for age[f]
Pregnancy and lactation[g]			
Trimester 1	265–770	6000–7600	≥70
Trimester 2	400–1650	6000–7600	≥70
Trimester 3	700–2275	6000–7600	≥70
Lactation[h]	700–2275	6000–7600	≥70

[a] Adapted from Acosta [118], recommendations for PHE and TYR intake for infants and children <4 years with more severe PKU and treated with PHE-restricted diet alone. TYR intake recommendations may require adjustment based on blood TYR monitoring.
[b] PHE recommendations for premature infants may be higher.
[c] PHE tolerance usually stabilized by 2–5 years of age [3]. Recommendations are based on size (increases with age) and growth rate (decreases with age). Individual PHE intake recommendations should be adjusted based on frequent blood PHE monitoring.
[d] Adapted from Acosta. Range of recommended PHE intake applies to spectrum of PKU severity (mild to severe).
[e] Recommended protein intake greater than the DRI is necessary to support normal growth in PKU.
[f] Recommendations are slightly higher for pregnant women ≤19 years of age.
[g] Recommended nutrient intake during lactation is same as for third trimester of pregnancy for all women.
[h] Protein recommendations for individuals consuming medical foods as the major protein source.

Because medical food, which is rich in L-amino acids that oxidize more rapidly, must be relied on for the majority of protein intake (75–85% of total protein needs), the recommendation for protein intake is increased by 50% over the dietary reference intake (DRI) for infants and 20–40% for individuals over 4 years of age to compensate [8,9]. Protein intake for infants with PKU (0–3 months of age), according to literature sources, should be at minimum 120% of the DRI [46,47], and can range up to 233% of the DRI when consuming amino acid-based medical foods, as was the case with a pre-term PKU infant [48]. Lower numbers are based on a conservative approach for infants and children between birth and four years of age. The guideline recommendation takes a moderate approach, with higher total protein requirements when less intact protein is tolerated and medical food must be relied on as the main protein source to meet anabolic and growth needs. Recommendations for protein intake presented in this guideline differ somewhat from those previously presented [2,3]. Review of subsequent evidence and consensus led to recommendations aligned more closely with age appropriate DRI, which is generally lower than the earlier RDA (1989) on which previous recommendations were based. This was found to be particularly appropriate for individuals whose intake of intact protein could be liberalized with adjunct therapy to amounts close to the DRI.

A Cochrane review concluded there is insufficient evidence to establish a TYR intake recommendation for individuals with PKU [10]. Presently, recommendations for intake are based on maintaining blood TYR concentrations within the normal range (Table 3) [3,11].

The evidence suggests that individuals who consume "complete" PHE-free medical foods (contributing all necessary nutrients other than PHE) and are adherent to their daily consumption recommendation, are not at risk for nutrient deficiencies or excesses [2,3]. Studies reporting supplementation of individuals with PKU with DHA, long chain polyunsaturated fatty acids (LCPUFA) [1,3,12–18] and selenium [19–22] have led to inclusion of these nutrients in many medical

foods available in the US and Canada. A table for classification and characterization of medical foods may be found on the Guideline website. LCPUFA sources for individuals who are deficient may be provided by fish oil to supplement both omega-3 and -6 essential fatty acids [23]. Lower bioavailability of some minerals (e.g., zinc) that are added to medical foods, as compared to their bioavailability in natural food sources, may increase the amount of supplementation recommended to meet the needs of individuals on a PHE-restricted diet [20]. There is some evidence there may be abnormalities in bone metabolism in individuals with PKU that are not directly correlated with vitamin D or calcium intake [3,20].

3.2. Blood PHE concentrations

3.2.1. Question

For individuals with PKU, what blood phenylalanine concentrations are associated with positive outcomes?

3.2.2. Recommendations

Recommendation	Strength of evidence	Clinical action
Maintain lifelong blood PHE between 120 and 360 μmol/L.	Fair	Imperative
Treatment should be initiated in individuals with PKU whose blood PHE exceeds 360 μmol/L.	Weak	Imperative

3.2.3. Evidence summary

Individuals with PKU should follow a PHE-restricted "diet for life" [2,3,24]. This includes initiating PHE restriction for those who were late-diagnosed or never treated, and re-introducing treatment for those who relaxed or discontinued PHE restriction. Doing so can improve physiological and neurobehavioral outcomes including level of cognitive disability, psychiatric symptoms, eczema, and impaired socialization [1,25,26].

Cognitive outcomes are inversely correlated to blood PHE levels with the strongest association found during critical periods of development (<age 6 years) and at levels exceeding 400 μmol/L [1,2,27].

Studies have shown that individuals with PKU perform less well on measures of executive function (EF), but performance may improve when blood PHE is below 360 μmol/L [28]. Individuals with lower blood PHE have been reported to have improved processing speed in various aspects of memory while doing mental tasks (using WAIS-III, WMC-III, & TMT A & B testing) [29]. In one study, adults with PKU who were off diet had lower reaction times than those on diet, with improved reaction times when blood PHE improved [30]. Another study showed that the ratio of blood PHE to TYR had a better association with EF than did blood PHE concentrations alone [31]. However, an analysis of 19 studies found that while blood PHE concentration correlated with various measures of EF in some studies, the degree of correlation on individual measures was inconsistent [32]. Subsequent studies have shown that individuals with PKU performed less well on measures of EF, and in two studies performance did not correlate with concurrent blood PHE [29,33]. However, one study of 20 individuals with classic PKU who underwent tests of sustained attention, memory, and ability to perform complex operations showed improved performance when blood PHE was <360 μmol/L [28].

Individuals with PKU experience more anxiety, depression, and agoraphobia than the general population, and symptoms are related to the degree of metabolic control [1]. Some who relaxed or discontinued PHE-restriction reported problems such as depression and anxiety [1], although QoL measures are shown to improve in those individuals who experienced "distress" in the form of depression when they return to a PHE-lowering diet [34].

Quality of life scores have been found to be higher for individuals with PKU who received early and continuous treatment, or who returned to treatment after a period of relaxed dietary adherence [35–37]. Individuals with PKU can exhibit lower or delayed autonomy and increased difficulty forming adult relationships or stable marriages, even when compared to individuals with similar educational levels and labor status in the general population [38]. Healthy emotional adjustment is possible when PKU is diagnosed early and is well treated [1,2,36,38]. Strict dietary treatment, specifically through childhood and adolescence, yields optimal metabolic control that may allow for normal health related QoL and psychological adjustment [39].

Many treatment centers initiate treatment at when blood PHE is 360 μmol/L or higher. However, data is inconsistent regarding the impact of untreated blood PHE concentrations of 360–600 μmol/L on cognitive and executive function, and there is disagreement on whether treatment is necessary. A study of 31 individuals with hyperphenylalaninemia (HPA) who were never treated and whose blood PHE concentrations did not exceed 600 μmol/L had normal IQ, educational achievement, and normal MRI studies; suggesting that some individuals with HPA may not need dietary treatment [40]. Blood PHE of >360 μmol/L may be considered suboptimal in an individual with treated PKU yet safe in a person with HPA because individuals with HPA have less variability in blood PHE (which is associated with better neurocognitive outcomes) [41], have a lower PHE:TYR ratio (which may have a positive prognostic value) [31], and may have lower brain concentrations of PHE. Blood PHE may not be the only determinant of the need for a PHE-restricted diet, since blood PHE can vary depending on state of health or dietary intake. Other factors such as genotype and dietary PHE tolerance should also be considered [1].

3.3. Strategies for nutrition intervention

3.3.1. Question

For individuals with PKU, which nutrition interventions are associated with positive outcome?

3.3.2. Recommendations

Recommendation	Strength of evidence	Clinical action
Choose medical foods to meet recommended nutrient intake and achieve optimal adherence. When incomplete medical foods are chosen, ensure that vitamin, mineral, energy, and/or fat intake is supplemented from other sources when necessary.	Weak	Imperative
Plan consumption of medical food throughout the day, in several well-spaced intervals, to allow optimal blood PHE concentrations and dietary PHE tolerance.	Strong	Imperative
Encourage use of breast milk, when possible, either from direct breast feeding or use of expressed breast milk, as the source of PHE (and intact protein) in infants.	Fair	Conditional
Gradually introduce solids, to replace the equivalent amount of PHE/intact protein in infant formula or breast milk, when the infant is developmentally ready (usually at 4–6 months of age).	Fair	Imperative
Minimize elevation of blood PHE during illness by treating the underlying illness, meeting protein and energy needs, and preventing dehydration and electrolyte imbalance.	Consensus	Imperative
Ensure appropriate PHE intake in individuals with PKU by having accurate data regarding PHE content of foods, and effective and convenient methods of planning and monitoring dietary PHE intake.	Weak	Imperative
Encourage all individuals to follow treatment recommendations throughout their lives; including those who have relaxed their diet restrictions and	Fair	Imperative

(*continued*)

Recommendation	Strength of evidence	Clinical action
those who have never been treated. Recognize and address individual barriers that may impede success.		
Adopt clinic procedures that enhance adherence to the nutritional recommendations of "diet for life" by providing individualized educational strategies, referrals to appropriate social service and mental health professionals, age-appropriate group activities, and a plan for transition from pediatric to adult clinical services.	Fair	Imperative

3.3.3. Evidence summary

Adherence to a nutritionally balanced diet that supports normal growth and development while maintaining metabolic control is the mainstay of PKU treatment [2]. To foster adherence to complex dietary management, nutrition intervention strategies and instruction must be tailored to the individual's or caretaker's educational level, cultural norms, experience, motivation and financial resources [42–46]. Because individuals with PKU typically meet 75–85% of their protein allowance from PHE-free medical food [1–3,47], selection of appropriate products is important for developing taste acceptance, adhering to the dietary prescription, and achieving optimal nutrient intake. Access to medical food and other modified low-protein food products may be limited by cost and third party reimbursement [3,48]. Use of incomplete medical foods may require use of vitamin, mineral, and/or fat supplements.

The amount of recommended dietary PHE and prescribed medical food must be individualized based on factors such as current blood PHE concentrations, age, growth, and protein and energy needs. The diet prescription should be monitored and modified frequently during childhood in order to assure sufficient PHE, protein, and calories required for growth are provided.

Medical food products vary in completeness of nutrient composition (vitamin, mineral, carbohydrate, and fat content) as well as in formulation and extent of third party reimbursement. Based on these factors, as well as personal preference, choice of medical food may affect compliance with therapy. A classification table for medical foods, including description of nutrient profile, protein to energy ratio, and physical form (e.g., powder, gel, capsule, bar) can be found within the full GMDI Nutrition Management Guideline for PKU.

Numerous studies have shown that increasing the number of times medical food is consumed over a 24-hour period improves both blood PHE and dietary PHE tolerance [49–52]. General clinical consensus (Delphi and gray literature) supports a minimum of three, well-spaced, intervals when consuming medical food. Glycomacropeptide (GMP), an intact protein from whey that is naturally low in PHE (1.8 mg PHE/gram of protein), can be incorporated into medical food products (with supplementation of some limiting free amino acids) and may facilitate adherence [53].

Breast milk is an appropriate source of intact protein and PHE for infants with PKU [3]. Good metabolic control has been shown using either expressed breast milk or feeding at the breast [54–56] and various strategies have been offered. These include alternating feedings between medical food bottles and direct breast feeding, mixing expressed breast milk and medical food in a bottle for each feeding, and feeding a bottle of medical food followed by ad lib breast feeding at each feeding. If infant formula is used as the intact protein source, it should be supplemented with DHA and ARA [3]. In infants with PKU, no significant difference in blood PHE levels was observed when medical food and regular infant formula/breast milk was given in alternating feedings [49].

Most infants with PKU, like those in the general population, gain appropriate developmental skills to accept solid foods between 4 and 6 months of age [57]. In order to keep dietary PHE intake consistent and maintain good blood PHE control, the intact protein from either breast milk or regular infant formula should be gradually removed from the formula mix and replaced with an equivalent amount of PHE from appropriate solid foods [3,57]. If an infant >12 months of age cannot meet all the recommended PHE intake with solid food, additional PHE can be provided from precise amounts of soy or cow's milk rather than infant formula [57].

No specific studies evaluating dietary treatment for individuals with PKU during illness have been reported. However, clinical practice and expert consensus obtained as part of this guideline's evidence review [1,3] prioritized treatment of the underlying illness. At the same time, recommendations are to minimize protein catabolism and encourage anabolism by providing adequate energy through a combination of medical foods and protein-free fluids. This spares endogenous protein, prevents dehydration, and protects electrolyte balance. Successful use of a total parenteral nutrition solution that included a PHE-free module has been reported in two recent cases of individuals who were unable to be fed enterally [58,59]. Adequate energy and fluid intake can be accomplished with sweetened beverages, PHE- free foods, or protein-free medical foods [60]. If medical food is refused, it should be reintroduced as soon as possible, first using 1/2 strength if full strength is not well tolerated (gray literature and Delphi consensus) [61].

Knowledge about the PHE content of foods and ability to track and plan daily PHE intake is necessary for treatment adherence sufficient to achieve appropriate blood PHE concentrations, as well as adjust PHE intake when blood PHE is elevated [3].

In the U.S., an estimated 77% of adults with PKU between the ages of 25–45 are not adherent to dietary treatment [62] even though most individuals report improvement in many aspects of their lives when PHE restriction is implemented or maintained [63,64]. Continuous and individualized education, community support, and removal of barriers to access to care and essential medical food products are important in helping individuals with to PKU maintain lifelong treatment.

Barriers to adherence include limited access to age-appropriate and disease specific medical and dietary care, failure to understand basic diet management or believe in its effectiveness [65], stress and time constraints of menu planning and record keeping [66], poor acceptance of medical food, maintenance of diet in school/work or other social situations [48,67,68], lack of social support, infrequent monitoring and clinic visits [65], and psychosocial problems that may develop with high blood PHE concentrations [2,3,65].

To combat these barriers, educational tools and strategies must be individualized based on the needs and abilities of the family or individual affected by PKU [42–46]. Clinics have reported various strategies that improve individual adherence, including; home visits [69], home delivery of medical food products [70], integration of metabolic clinic and mental health services [27,71], inclusion of social services in the metabolic team [44], and simplification of dietary PHE tracking [72,73]. Studies indicate that there is no one successful strategy, but educational tools and supportive activities must be adapted [67] to individual needs. In addition, the metabolic team should encourage individuals with PKU and their care-givers to seek social support for best outcomes.

While most education is directed toward parents and other caregivers when the child with PKU is young, gradual transfer of responsibility for management should begin early, and age specific educational activities are important [74]. Transition of the individual with PKU from a pediatric- to an adult-centered program [2,3] assures continued attention to medical, psychosocial, educational, and vocational needs [1,75]. Maintaining adolescents and young adults with PKU on dietary therapy requires a well-designed plan for transition. Adolescents and young adults have identified the need to learn more practical skills for diet management, and coping skills for integrating the diet into a normal lifestyle [76]. Peer support groups and activities can be helpful [77]. Important components of successful transition have been found to be continuous contact with the clinic and coordination between the pediatric and adult healthcare providers [75].

3.4. Monitoring nutrition intervention

3.4.1. Question

For individuals with PKU, monitoring of which parameters is associated with positive outcomes?

3.4.2. Recommendations

Recommendation	Strength of evidence	Clinical action
Monitor dietary records to assess adequacy of nutrient intake in supporting appropriate growth and nutritional status. If intake is suboptimal, modify individual dietary recommendations and counseling to improve adherence.	Strong	Imperative
Monitor age-specific anthropometrics.	Fair	Imperative
Routinely monitor clinical indicators and biochemical markers for deficiency or excess of nutrients whose intake may not be optimal in an individual on a PHE-restricted diet (PHE, TYR, protein, iron and vitamin D).	Strong	Imperative
Monitor clinical indicators and biochemical markers when indicated by circumstances such as rapid growth, pregnancy, poor compliance with management recommendations, or consumption of an incomplete medical food.	Fair	Conditional
Monitor neurocognitive development.	Fair	Imperative
Assess quality of life using age- and disorder-specific instruments when possible.	Weak	Conditional

3.4.3. Evidence summary

Regular monitoring of clinical and nutritional status to determine adequacy of nutrient intake, and to guide modifications in the dietary prescription, is central to management of individuals with PKU. Monitoring dietary intake of PHE, TYR, protein, and energy intake along with blood PHE concentration is important to assess adherence and assure appropriateness of dietary therapy recommendations. When incomplete medical foods are consumed that have a very high protein:energy (Kcal) ratio, or that are carbohydrate- or fat-free, adequate energy intake must be provided from the rest of the diet for protein sparing. Very low fat intake can result in essential fatty acid deficiency [3]. Fats and sugars, that contain negligible PHE and are considered "free" foods, may be over-consumed. It also should be noted that assessment of adequate intake through monitoring of blood TYR can be complicated by large diurnal variation during a 24 hour period [3,11].

Nutrients at risk for being low in individuals on a PHE restricted diet (iron, vitamin D, vitamin B_{12}, folate, zinc, selenium, and essential fatty acids) should be monitored via dietary assessment and biochemical markers throughout life [2,3,55]. Routine (every 6–12 months) laboratory evaluation of iron status, including complete blood count and ferritin, is recommended [1], along with 25-OH vitamin D, which has been shown to be lower in individuals with PKU [78]. For those non-adherent to diet therapy, B_{12} status can suffer, thus blood levels should be measured along with serum methylmalonic acid or plasma homocysteine to differentiate and diagnose functional B_{12} deficiency [79]. Abnormally low blood concentrations of DHA and ARA have been reported in children [80], adolescents, and adults with PKU [81,82]. Laboratory analysis of other at-risk nutrients can be evaluated as needed based on the individual's clinical status, adherence to medical food and dietary restrictions, and age associated risk factors.

Monitoring individual growth and adjusting the dietary prescription accordingly is key for positive outcome [47]. Poor linear growth and small head circumference have been reported as a consequence of strict adherence to the restrictive dietary therapy required to achieve blood PHE concentrations within recommended treatment range. However, individuals with strict dietary adherence until 10 years of age also were reported to achieve weight, height, and head circumference appropriate for age [83]; and normal growth patterns and body composition have been reported when individuals with PKU are compared to the healthy population [83,84]. Normal linear growth in childhood has been noted with slightly higher weight for age until at least 4 years [83].

In individuals with PKU, overweight and obesity has been historically reported to exceed the expected prevalence rate compared to the general population [47,83,85]. More recent studies of growth and body composition, and specifically fat-free mass (FFM), found no significant difference between individuals with PKU and controls, and a significant positive correlation between FFM and intact protein intake [84]. Higher blood PHE was associated with increased weight, particularly in females [83], and prevalence of overweight and obesity was found to correlate with poor metabolic control [86]. Mean body fat was reported to increase with body weight, which was significantly higher in individuals with PKU than in controls [87].

Neurocognitive and neuropsychiatric outcomes are significantly correlated with blood PHE concentrations and level of treatment [27]. Developmental progress should be assessed periodically to identify neurocognitive deficits and offer appropriate therapies [2]. Quality of life or adjustment scores were found to be higher for individuals with PKU who received early and continuous treatment, or who had early treatment and then returned to treatment after a period of relaxed dietary adherence [35–37]. Optimal metabolic control resulting from early dietary treatment and strict adherence, specifically through childhood and adolescence, may allow for normal health-related QoL and psychological adjustment [39].

The Monitoring Nutritional Management of PKU table available on the Guideline website provides frequency recommendations by age group for the above areas of monitoring and assessment plus additional detail on biochemical and bone density testing and timing of nutrition visits.

3.5. Nutrition intervention with alternative or adjunctive therapies

3.5.1. Question

For individuals with PKU whose therapy includes adjunctive therapy or other therapy options (sapropterin or large neutral amino acids [LNNA]), what dietary considerations are needed for positive outcomes?

3.5.2. Recommendations

Recommendation	Strength of evidence	Clinical action
When treatment with sapropterin (pregnancy class C) is appropriate, combine with diet therapy to improve blood PHE and/or clinical status, and develop individualized therapy plans to provide best outcome.	Strong	Conditional
Conduct a PHE challenge to determine maximal dietary PHE tolerance when sapropterin response brings blood PHE to within control range, or to clarify a sapropterin response when historical blood PHE is already within control range.	Strong	Conditional
Modify dietary therapy in individuals responsive to sapropterin to accommodate increased PHE tolerance. Liberalization should reflect increased PHE/-intact protein intake, decreased medical food intake, and vitamin/mineral supplementation as appropriate. Monitor nutritional status and educate individuals regarding modified dietary recommendations.	Strong	Conditional
Individualize and closely monitor sapropterin therapy when used in special populations, such as: infants and young children, pregnancy, and late- or untreated adults.	Weak	Conditional

(*continued*)

Recommendation	Strength of evidence	Clinical action
Consider LNAA supplementation in adults with PKU who are unable to achieve metabolic control with diet or other adjunctive therapy. LNAA therapy is not recommended for use in infants, young children, or women who are pregnant or may become pregnant.	Weak	Conditional
When LNAA therapy is chosen, provide 20–30% of total protein intake from LNAA supplements, and the remaining 70–80% from intact dietary protein. Total protein intake should meet DRI requirements (0.8 g/kg/day). Monitor adequacy of protein intake and plasma amino acids to prevent essential amino acid deficiencies.	Weak	Conditional

3.5.3. Evidence summary

Sapropterin dihydrochloride is a pharmaceutical form of tetrahydrobiopterin (BH4), that functions as an activating cofactor when residual PAH activity is present, even though BH4 concentrations are normal for individuals with PKU [2]. Thirty to 50% of patients with PKU who are given sapropterin respond with a plasma PHE decrease of at least 20% after one month of treatment [88].

The ACMG guideline considers it appropriate to offer sapropterin to every individual with PKU who may benefit from a response [2,89,90]. Response is commonly determined by a trial period of up to 4 weeks with a daily dose of 20 mg/kg, which provides best efficacy, and blood PHE monitoring at regular intervals [2,3,91]. Diet, medical food intake, and other lifestyle characteristics (level of exercise, etc.) should remain unchanged during the trial. A decrease of blood PHE >20–30% from baseline is most commonly cited as indicating response, but clinical judgment is an important factor when determining beneficial outcomes [2,3,89]. Rapidity of blood PHE decrease varies from within 24 h to a slower response seen only after 2–4 weeks or more [92,93].

Response to sapropterin can facilitate an increase in dietary PHE tolerance from minimal amounts, to 3–4 times baseline intake, to discontinuation of restriction in some cases. When the amount of intact protein sufficient to meet DRI levels is tolerated and energy needs are met, there is reduced dependence on medical food [94,95]. However, some dietary PHE restriction often needs to be retained [2,3], and recommendations usually call for retaining some medical food to maintain taste acceptance and a source of PHE-free protein should protein needs exceed tolerance of intact protein (e.g., during pregnancy, infection, and rapid growth) [3,96,97]. Other benefits of sapropterin response may include decreased blood PHE in individuals unable to attain this with diet therapy alone, nutritional advantages of increased intact protein intake, reduced blood PHE fluctuation, improvement in clinical and neurocognitive status, and improvement in quality of life resulting from relaxation of diet restriction [2].

Even with sapropterin, regular monitoring continues to be required to track blood PHE control, nutrient adequacy, and normal growth and health maintenance [95,97]. Vitamin and micronutrient supplements may be needed if medical food is decreased or discontinued [3]. Re-education for adherence to a more liberalized PHE/intact protein intake is essential [2,3,96,97].

U.S. labeling for sapropterin restricts use in children <4 years of age, but recent studies show safety and efficacy in young children and infants [21,98,99]. European protocols include BH4 loading tests in infants with subsequent sapropterin therapy in responsive individuals regardless of age, and European labeling of sapropterin requires no age restriction [1]. U.S. clinics commonly recommend establishing the caregiver's proficiency in diet management and the infant or young child's acceptance of medical food before offering sapropterin therapy. Determining response to sapropterin in 2–4 year olds and adjusting therapy accordingly may have the benefit of improved metabolic control along with possible nutritional benefit of more natural protein during rapid growth and development [1,98].

Large neutral amino acids (LNAAs) inhibit the passage of blood PHE into the brain through competition for carrier sites at the blood brain barrier. Supplementation with LNAAs has been described as effective in improving neurocognition in adults with PKU [100,101], although studies are limited, typically with small sample sizes or case studies with varying protocols. In a six month study of 6 adults consuming LNAAs, there was no improvement in blood PHE, but there were increases in blood TYR, decreases in brain PHE, and the subjects reported "feeling better" [102]. LNAA supplements have demonstrated some efficacy in non-pregnant adults and adolescents who have been unsuccessful in adherence to other dietary treatments for PKU [1,103]. LNAAs are not recommended for use in infants and young children as effect on growth has not been studied [3].

Clinical use of LNAA therapy varies widely and there is insufficient experience to describe best prescriptive protocol. Most reports recommend providing 20–30% of the DRI protein requirement (0.8 g/kg/day) from LNAAs, and the remaining 70–80% from intact dietary protein [103,104]. LNAA products differ significantly in formulation (specific LNAAs included and proportional amounts, vitamin and minerals) so must be evaluated for individual patient needs. Plasma amino acids should be monitored monthly to ensure nutritional adequacy, and vitamin and mineral supplements may be needed [3]. Efficacy of LNAA therapy is difficult to assess, as blood PHE concentrations are not a useful marker. Changes in white matter on MRI have been reported as indicators of LNAA efficacy [105].

3.6. Nutrition intervention before, during, and after pregnancy

3.6.1. Question

For women with PKU, what nutritional therapies are associated with positive outcomes during pregnancy planning, pregnancy, and the postpartum period (including lactation)?

3.6.2. Recommendations

Recommendation	Strength of evidence	Clinical action
Maintain blood PHE between 120 and 360 μmol/L before, during, and after pregnancy.	Strong	Imperative
Monitor weight gain, dietary intake, and biochemical parameters to ensure nutrient adequacy and metabolic control during pregnancy.	Fair	Imperative
Prescribe a diet that meets nutritional needs of pregnancy and promotes adequate weight gain.	Fair	Imperative
Avoid LNAA monotherapy during pregnancy.	Consensus	Imperative
Use of sapropterin should be evaluated during pregnancy on a case-by-case basis, and may be appropriate especially in women with moderate or mild forms of PKU who are not able to maintain blood PHE in the recommended treatment range for pregnancy.	Consensus	Imperative
Facilitate access to psychosocial support as necessary to maintain dietary therapy in pregnancy.	Consensus	Conditional
Encourage women with PKU to maintain dietary therapy after pregnancy and to breast-feed their infants.	Weak	Imperative
Modify PKU therapy and collaborate with other care-givers to support nutritional and metabolic needs of women with multiple pregnancies, gestational diabetes, and other special circumstances.	Insufficient evidence	Conditional

3.6.3. Evidence summary

High maternal blood PHE is a fetal teratogen resulting in a maternal PKU (MPKU) syndrome that includes microcephaly, low birth weight, congenital heart disease, and intellectual disability in children born to mothers with untreated PKU during pregnancy [1,106]. The NIH

Consensus Statement in 2001 recommended maternal blood PHE be maintained between 120 and 360 μmol/L before conception and during pregnancy to prevent MPKU syndrome [107]. The American College of Obstetricians and Gynecologists likewise recommends strict dietary PHE control prior to conception [108]. A blood PHE of 360 μmol/L is the threshold at which cognition in the offspring begins to be impaired [1]. The relationship between maternal blood PHE and birth defect incidence, along with cognitive outcome in the offspring is linear at blood PHE >360 μmol/L [106]. Women who achieved metabolic control by 10 weeks gestation were likely to remain in good control through the pregnancy and had children with normal birth outcomes [2]. Children born to mothers who were treated prior to pregnancy had the best outcomes [106]. Recommendations for a lower limit of blood PHE during pregnancy varies. While in the US this limit has historically been 120 μmol/L [107], in Europe and Australia a lower limit of 60–100 μmol/L is recommended [109,110]. The ACMG guidelines now recommend 60 μmol/L as a safe lower limit for blood PHE in MPKU [2].

Monitoring of a woman with PKU by a metabolic team before and during pregnancy is critical to outcome of the pregnancy, since treatment must be frequently modified to ensure adequate nutrition is being provided [109]. A schedule of monitoring assessments was derived from the NIH Working Group for the NIH Consensus Review [1, 3]. Because of hemodilution associated with pregnancy, some parameters, including plasma amino acids, normally decrease during pregnancy.

Recommended dietary PHE intake during pregnancy depends on inherent PHE tolerance prior to conception and into the first trimester with a range of 225–770 mg/day (Table 3). By the second trimester, PHE tolerance increases due to increased protein synthesis in the mother and the fetus [109,111]. PHE tolerance during lactation is approximately the same as during the third trimester, taking into account protein requirements [2]. Tolerance for dietary PHE increases rapidly in pregnancy, especially in conjunction with periods of rapid maternal weight gain, thus avoiding hypophenylalaninemia is important [112], and substantial increases in PHE intake (25–50%) may be required [113]. Adequate protein and energy intake is needed to prevent catabolism and to support proliferation of maternal reproductive tissues, as well as fetal growth and development. Protein needs increase by 50% during pregnancy [1]. Increased protein needs are met through the use of medical foods, since intake of intact protein is limited [1].

Energy requirements during pregnancy increase in the same amounts as those for women without PKU [114]. Adjustments in energy intake should be made as necessary to promote weight gain goals for pregnancy [115]. For pregnant women with PKU, additional modified low protein foods, fats, and simple carbohydrates are used to meet increased energy needs, especially when intact protein is very limited and/or when medical food has a high protein:energy ratio [1,3].

LNAAs should be avoided in pregnancy, as blood PHE is not lowered sufficiently to prevent fetal PHE toxicity, and effects on human fetal growth and neural system development are unknown [1,2,100].

Sapropterin use in pregnancy has not been evaluated in controlled trials. Case reports document successful outcomes with sapropterin therapy that is initiated both before and after conception [1,116]. Recognizing FDA designation of sapropterin as a Category C drug for pregnancy, the ACMG guideline concludes that, given the known adverse effects of elevated maternal blood PHE on pregnancy outcomes, and because sapropterin may be effective in lowering blood PHE, its use should be considered on a case-by-case basis [1–3].

Adherence to PKU therapy has been shown to improve in adults who have a social support system, an understanding of the benefits of treatment, access to appropriate care along with medical foods and modified low-protein foods, and a belief that treatment for PKU is manageable. Special support is often needed to secure access to the medical foods and/or modified low protein foods required for adequate treatment of PKU during pregnancy. Specialized educational programs, camps, and other support programs may improve adherence and quality of life [3].

Despite the fact that PHE content of breast milk is higher than normal, women with PKU may safely breastfeed their infants. If the infant also has PKU, breast milk can be used in combination with PHE-free medical food. It is recommended that women with PKU should continue a PHE-restricted diet after pregnancy, and especially during the postpartum period [3].

4. Discussion and conclusion

4.1. Discussion

These recommendations for PKU management represent the best available published evidence, as well as clinical practice expertise systematically derived using Delphi surveys and a nominal group meetings. The platform used to support and document the development of the guideline provides an accessible, robust, and thorough foundation for existing evidence. The results of this systematic and comprehensive guideline development process inform best practices within the field, and the electronic platform will enable clinicians and researches to continue to efficiently build on these practices. Despite the plethora of PKU information available, there remains the need for well-designed studies using clinical data, patient registries, and clinical trials to resolve uncertainties and increase the validity of the recommendations. These PKU nutrition management guidelines will be updated as warranted by developments in PKU research and clinical practice.

4.2. Conclusion

Via the dynamic and systematic process for development of these guidelines, the current knowledge of nutrition management for individuals with PKU has been evaluated and synthesized into practice recommendations based on best available evidence and consensus of experts. It is hoped that these recommendations will lead to greater harmonization of care, stimulate much needed further research, and encourage outcomes studies within and across centers.

Conflict of interest statement

Rani H. Singh, PhD, RD, has served on the global medical advisory board for Nutricia and has received payment.

Amy Cunningham has received compensation for faculty participation at Metabolic University, which is supported by Nutricia, and a stipend for speaking at the Abbott Nutrition Metabolic Conference. She participates on advisory boards for BioMarin Pharmaceutical, for which she receives travel funding and stipend support. She functions as project coordinator of research studies for which the Hayward Genetics Center receives grant funding from BioMarin Pharmaceutical.

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