Minireview

Suboptimal outcomes in patients with PKU treated early with diet alone: Revisiting the evidence

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ABSTRACT

Background: The National Institute of Health (NIH) published a Consensus Statement on the screening and management of Phenylketonuria (PKU) in 2000. The panel involved in the development of this consensus statement acknowledged the lack of data regarding the potential for more subtle suboptimal outcomes and the need for further research into treatment options. In subsequent years, the approval of new treatment options for PKU and outcome data for patients treated from the newborn period by dietary therapy alone have become available. We hypothesized that a review of the PKU literature since 2000 would provide further evidence related to neurocognitive, psychosocial, and physical outcomes that could serve as a basis for reassessment of the 2000 NIH Consensus Statement.

Methods: A systematic review of literature residing in PubMed, Scopus and PsychInfo was performed in order to assess the outcome data over the last decade in diet-alone early-treated PKU patients to assess the need for new recommendations and validity of older recommendations in light of new evidence.

Results: The majority of publications (140/150) that contained primary outcome data presented at least one suboptimal outcome compared to control groups or standardized norms/reference values in at least one of the following areas: neurocognitive/psychosocial (N=60; 58 reporting suboptimal outcomes); quality of life (N=6; 4 reporting suboptimal outcomes); brain pathology (N=32; 30 reporting suboptimal outcomes); growth/nutrition (N=34; 29 reporting suboptimal outcomes); bone pathology (N=9; 9 reporting suboptimal outcomes); and/or maternal PKU (N=19; 19 reporting suboptimal outcomes).

Conclusions: Despite the remarkable success of public health programs that have instituted newborn screening and early introduction of dietary therapy for PKU, there is a growing body of evidence that suggests neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology and maternal PKU outcomes are suboptimal. The time may be right for revisiting the 2000 NIH Consensus Statement in order to address a number of important issues related to PKU management, including treatment advancements for metabolic control in PKU, blood Phe variability, neurocognitive and psychological assessments, routine screening measures for nutritional biomarkers, and bone pathology.

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Introduction

Phenylketonuria (PKU) is a rare autosomal recessive inborn error of phenylalanine (Phe) metabolism and a form of hyperphenylalaninemia (HPA) characterized by elevated blood Phe levels as a result of reduced PAH enzyme activity caused by a mutation in the phenylalanine hydroxylase (PAH) gene [1]. Newborn screening combined with a Phe-restricted therapeutic diet implemented within the first few weeks of life and continued throughout childhood has ameliorated the most severe clinical manifestations of PKU [1]. However, three decades worth of clinical PKU experience in the US revealed that inter-clinic variations in PKU management practices lead to suboptimal outcomes in diet-treated PKU patients. These variations coupled with persisting suboptimal outcomes in the PKU populations resulted in the National Institute of Health (NIH) convening an expert panel in 2000 to develop and publish the first national Consensus Statement in the screening and management of PKU [2].

NIH Consensus and State-of-the-Science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) key questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third [2,3]. The NIH Conference Development Programs are structured around key questions [3]. Ordinarily, four to six questions are posed, including questions on the efficacy, risks, and clinical applications of a technology, plus a final one on directions for future research. These questions determine the scope and substance of the conference and the final draft of the Consensus Statement.

The 2000 NIH Consensus Statement on PKU includes recommendations such as target blood Phe ranges of 120–360 μmol/L (2–6 mg/dL) for infants through 12 years of age, 120–900 μmol/L (2–15 mg/dL) after 12 years of age and 360 μmol/L (6 mg/dL) three months pre-conception and maintained at 120–360 μmol/L (2–6 mg/dL) throughout pregnancy [2]. The positive effects of maintaining control of Phe levels lifelong through a restricted-Phe diet are recommended, but not reinforced with outcome data [2]. Questions regarding the potential for subtle suboptimal outcomes of early diet-treated PKU patient outcomes published since 2000 was screened for inclusion into one or more of the following topical headings based on the outcome(s) measured: 1) Neurocognitive/Psychosocial, 2) Quality of Life (QOL), 3) Brain Pathology, 4) Growth/Nutrition, 5) Bone Pathology and 6) Maternal PKU (Fig. 1). Diet-only treated suboptimal outcome categorization was based on the criteria of reporting at least one outcome that was suboptimal in the context of known reference values, standardized norms or relevant control population(s). To be categorized as a diet-only treated optimal outcome(s), each measured outcome reported in the publication had to be optimal in the context of known reference values, standardized norms or relevant control population(s).

Results

From the initial combined database of 771 articles, 150 were selected that described outcomes in a diet-only treated PKU patient population [4–153]. The 150 articles were sorted into one or more categories based on their outcomes as follows: 1) Neurocognitive/PsychoSocial (n = 60; 58 reported suboptimal outcomes [4–61], 2 reported optimal outcomes [62,63]), 2) Quality of Life (n = 6; 4 reported suboptimal outcomes [40,52,64,65], 2 reported optimal outcomes [66,67]), 3) Brain Pathology (n = 32; 30 reported suboptimal outcomes [7,8,13,37,49,68–92], 2 reported optimal outcomes [42,93]), 4) Growth/Nutrition (n = 34; 29 reported suboptimal outcomes [38,39,94–120], 5 reported optimal outcomes [121–125]), 5) Bone Pathology (n = 9; 9 reported suboptimal
outcomes [126–134]) and 6) Maternal PKU (n = 19; 19 reported suboptimal outcomes [135–153]) (Fig. 1). The total of 160 articles categorized is greater than the initial 150 article database as ten articles contained multiple outcomes that fell into more than one category [7,8,13–37,42,49,52]. The majority, 140/150 of the primary literature database, had at least one suboptimal outcome in the diet-only treated PKU population.

Limitations

The goal of this review was to identify and categorize publications since the year 2000 with primary study data on PKU population outcomes or primary statistic analysis of prior literature (meta-analyses). We did not reinterpret the quality of the findings, validity of statistical analysis or appropriateness of study design. Further, we did not analyze author compilation, interpretation of results or impact of the outcome on patient functioning of included publications as they all individually were accepted and analyzed by the independent review processes of their respective journals.

Due to the breadth of information collected in the literature search, descriptive summaries of findings in each category of this review are primarily limited to larger study populations, including meta-analyses, and studies demonstrating suboptimal outcomes in patient populations that were early and continuously treated with diet therapy alone. The inclusion of meta-analyses may be perceived as counting certain publications twice as independent data. However, we included meta-analyses as they offer new statistical interpretation of pooled study data which is invaluable in rare diseases where sample sizes of individual studies are typically small. Five meta-analyses were included in the literature search and the inherent limitations of interpreting results from pooled data are discussed within each [5,6,21,48,57].

As a qualitative review, categorization of a publication as reporting suboptimal outcomes included, where appropriate, presentation of significant statistical differences between the PKU study group and control groups on ≥ 1 study parameter analyzed. When statistical approaches were not appropriate for analysis, outcome discussions of results were considered.

Many of the selected publications have pooled the results of children, adolescents and adults, each of which has a distinct outcome profile. Some other difficulties include the challenge of recruiting an adequate number of participants to ensure statistical power due to the rarity of the disease. Selection bias may also occur when patients are recruited from the available PKU patients often within specialized clinics, typically excluding those not being regularly followed. Outcomes from the same patient population may also have been reported in different publications. Additionally, the majority of the literature reports comparisons between PKU patients and healthy control subjects but not between PKU patients on- and off-diet; thus in many instances the distinction cannot be easily made as to whether suboptimal outcomes are due to the stress and burden of the disease or due to lack of metabolic control of the disease. Furthermore, expert recommendations are only as effective as their degree of clinical incorporation with recent evidence suggesting considerable variation in PKU management from clinic to clinic despite the availability of expert recommendations [154–156]. For the purpose of this review, studies that collected patient data prior to 2000 are included as novel if published in years ≥ 2000. Likewise, non-US-based studies published in 2000 or beyond were included if information was deemed relevant to this rare disease when considering revising NIH recommendations. In regards to revising NIH guidelines, the inclusion of non-US based publications may be perceived as a study limitation in the context that there are different recommendations for optimal blood levels in different countries, particularly in children over 10 years of age and in adults.

The majority of studies used normal control as comparators or utilized assessment tools that have been standardized to large normative control populations. However, the potential lack of validating the various neurocognitive, psychological and QOL assessment tools for use in the PKU patient population may be considered a limitation.

The assignment of suboptimal outcomes to diet-alone therapy may be perceived as misleading as many suboptimal outcomes were related to higher blood Phe levels potentially indicating lack of dietary control in these patients. However, lack of adherence to the onerous regimen of the diet may also be a suboptimal outcome of diet-alone therapy: a sentiment echoed in the 2000 NIH guidance document recommending alternative therapies to the diet [2].

Neurocognitive and psychosocial outcomes: early-treated diet-alone therapy

In spite of early and continuous treatment, children and adults with PKU may experience cognitive symptoms as well as disturbance
in emotional and behavioral functioning [4–61]. Although early initiation of the PKU diet has eliminated severe cognitive impairment, evidence indicates that overall intellectual functioning and specific neuropsychological abilities may be suboptimal. Symptoms may cover a broad range and generally correlate with the timing and degree of exposure to elevated Phe levels. Executive function (EF) deficits, attention deficit issues, and reduced processing speed with early diet-treated PKU patients have been reported by many groups [4–61].

**Children and adolescents**

Children with PKU treated early and continuously with diet alone show overall intellectual functioning that is within the normal range, but lower than the general population and their siblings [25,48]. Evidence from the National PKU Collaborative Study, a 14-year longitudinal initiative, demonstrated that the mean lifetime Phe level was inversely correlated with results of neurocognitive tests at age 12; IQ was negatively correlated with age at initiation of diet and blood Phe levels from 4 to 10 years, and was positively correlated with the age at which they lost dietary control [13,37]. More recently, a meta-analysis involving 43 studies showed a 1.8 to 3.8 point reduction in IQ for each 100 μmol/L increase in lifetime blood Phe level [57].

In addition to suboptimal IQ, early-treated children and adolescents may demonstrate specific neuropsychological compromise and lower academic achievement [7–9,18,20,36,55]. Anastassoea et al. demonstrated that early–continuously diet-treated PKU children with well-controlled blood Phe levels had suboptimal neurocognitive outcomes as measured by full-scale IQ testing [6]. These outcomes correlated with variability in blood Phe within the recommended ranges. These results indicate the importance of the stability of blood Phe levels in relation to cognitive functioning, especially in those with classical PKU whose blood Phe levels are more prone to fluctuation based on dietary Phe intake. Executive dysfunction has also been noted in working memory, inhibitory control, conceptual reasoning, mental flexibility and organizational strategy [7,8,42]. Most recently, EF deficits in early and continuously treated PKU children were more closely associated with Phe/Tyrosine ( tyr) ratios than Phe only measures [51].

Attentional problems have been documented consistently in children with PKU [8,12,20,31,32]. Attentional problems may have a negative impact on academic progress, as well as on self-esteem and emotional development [36,55]. This can further complicate adherence to the Phe-restricted diet, determining milligrams of Phe, inhibiting impulsive food choices, and recording dietary Phe intake, as these all require well-developed EF.

Suboptimal IQ scores, EF abnormalities, and reduced processing speed place children with PKU at risk for poor academic performance. Early and continuously treated children and adolescents with PKU present with significantly more school problems as defined by students needing tutoring, repeating a class, or discontinuing their studies before completing secondary school [26]. Stemerdink and colleagues reported in a study of 30 PKU adolescents and 23 controls that PKU subjects were more hyperactive and their school performance was lower than control subjects, but they found no statistically significant difference between the 2 groups in the need to repeat classes or to require tutoring [55]. In contrast to other studies that reported school difficulties, Simon and colleagues found no differences in the level of education achieved and the distribution of highest professional qualifications between young adult PKU patients and control groups, with the exception that more than half of the female patients had not completed vocational training as compared to one-third in the general population in Germany [52]. This may be attributable to their younger age or may alternatively reflect a delayed psychosocial development. These results are confirmed by the study of Bosch et al., who reported that a higher percentage of PKU patients had attended special education classes in primary school, though the highest level of education attained was comparable in the two groups [66]. In addition, EF deficits have been associated with difficulties in forming social relationships and communicating effectively [66].

**Adults**

Studies examining the relationship between PKU treatment variables and cognitive outcome in adulthood are consistent with the pediatric literature and provide evidence of cognitive deficits despite early treatment and average IQ. Adults with PKU may demonstrate deficits in executive function, attentional problems, decreased verbal memory, expressive naming and verbal fluency [5,13,15–17,22,23,32,37,43,46–48]. Meta-analysis of neuropsychological symptoms of early and continuously treated adults with PKU indicated that patients with PKU differed significantly from controls on overall, intellectual functioning, processing speed, inhibition, and motor control [48]. Cognitive deficits in adults with PKU suggest that functioning may have been compromised during early brain development by elevated Phe levels or that specific areas of cognitive function may be more vulnerable to even slight elevation or variability in Phe levels [6].

Early-treated individuals with PKU are also at risk for social and emotional difficulties. Children and adolescents may demonstrate decreased social competence, autonomy and self-esteem [35,36,55]. Adolescents may also display low self-esteem and lack of autonomy, and may tend to develop depressed mood, generalized anxiety, phobias, decreased positive emotions, social maturity deficits and social isolation [53]. Psychosocial factors such as the burden of living with a chronic illness may also contribute to psychological and psychiatric outcomes in PKU. Not all individuals with PKU present with psychological or psychiatric symptoms and a PKU-specific psychiatric phenotype has not been identified [58]. The relationship between metabolic control and severity of symptoms suggests a biological basis of dysfunction. Longitudinal studies are required to evaluate the impact of biochemical control and emerging therapies on psychosocial functioning. Untreated or untreated emotional issues may have a significant impact on the quality of life and social status of individuals with PKU.

**Quality of life outcomes: early-treated diet-alone therapy**

Quality of life (QOL) assessment has focused primarily on adult PKU populations. However, decreased QOL has been reported for both adults and children with PKU that have been treated with diet alone [40,52,64,65]. Fewer children report positive emotions and adults report difficulties in adhering to the strict diet and subsequently report higher levels of distress [64,65].

**Children and adolescents**

Landolt et al. 2002 assessed 37 patients with PKU between 3 and 18 years of age (mean, 10.9 years) [40]. Results suggested that most dimensions of QOL in children with PKU were not different from reference values; however, they were suboptimal in their reporting of positive emotions.

**Adults**

Simon et al. investigated the QOL of 67 adult PKU patients compared to the German census on an age matched control collective [52]. The QOL of adult PKU patients measured with the Profile of Quality of Life in the Chronically Ill (PLC) revealed mean values for capacity of performance in the patient group in the same range as in the chronically ill control collective.

Studies have also shown that when adult patients return to diet and lower their blood Phe levels, they may report a subsequent improvement in QOL [64,65]. Bik-Multanowski et al. (2008) examined whether adult patients (n = 53) returning to the diet had improved QOL. Initial QOL assessment revealed severe distress in 17%, moderate
distress in 28% and positive well-being in 55% [64]. Bik-Multanowski et al. also highlighted the result that only 29 persons managed to maintain the diet for at least 3 months and only 10 participants finished the entire 9-month study protocol. In the majority of patients with severe or moderate distress, improvement of subjective well-being was observed if they managed to return to the diet, highlighting the difficulty in adhering to the onerous dietary regimen even knowing that their QOL could be improved by better control of their blood Phe levels.

Brain pathology outcomes: early-treated diet-alone therapy

Brain imaging techniques used on diet-alone treated PKU patients have revealed white matter abnormalities (WMA), reduced cerebral protein synthesis, altered brain Phe concentrations, altered L-DOPA, Phe and Tyrosine (Tyr) uptake at the blood brain barrier, volume changes of grey at white matter, and altered cerebral metabolism [7,8,13,37,49,68–92].

Increased availability and advancements in brain imaging technology have been applied to the investigation of white matter abnormalities in PKU. The basis of this hypothesis is reduced myelination associated with PKU leads to aberrant brain neurosignaling and neurocognitive deficits including decreased speed of information processing. Anderson et al. assessed the relative impact of white matter abnormalities (WMA) on cognitive functions in children with early-treated PKU [8]. Children in the PKU group with extensive WMA (n = 14) displayed significant impairments across all cognitive domains. The degree of metabolic control weakly to moderately correlated with attention, executive, and memory/learning factors. Regression analysis revealed that EF and attention factors were independently related to severity of WM pathology and age, while the memory and learning factor was independently related to metabolic control and age. Children with early-treated PKU exhibit a global pattern of impairment, with a particular deficit in processing speed [8]. White matter (WM) pathology extending into frontal and subcortical regions correlates with the greatest deficits and a profile of impairment consistent with diffuse WM damage [7]. Furthermore, improvements in WM damage have been observed when patients regain metabolic control [89].

A second hypothesis known as “the dopamine depletion hypothesis” theorizes that reduced availability of neurotransmitters in the brain, especially dopamine in the prefrontal cortex thought responsible for EF, can explain some of the observed neurocognitive deficits in PKU. Landvogt et al. demonstrated that fluoro-L-dopamine (FDOPA) uptake into the brain was impaired when elevated plasma Phe levels were present and suggested that this was due to competitive inhibition at the specific large neutral amino acid (LNAA) transporter level at the blood brain barrier [76]. They also demonstrated that there is a significant reduction of decarboxylation of FDOPA reaching the brain in PKU subjects indicating dopamine synthesis pathways may be impaired.

Hoekema et al. determined the protein synthesis rate in relation to the plasma Phe concentrations in vivo in adult PKU patients by positron emission tomography (PET) brain studies [72]. Results showed a significant negative relationship between plasma Phe concentration and the cerebral protein synthesis rate in 19 PKU patients. At increased plasma Phe concentrations above 600–800 μmol/L, the cerebral protein synthesis rate is clearly decreased compared to lower Phe concentrations. These data suggest that cerebral protein metabolism in PKU adults can be abnormal due to high plasma Phe concentrations which may affect both myelin and dopamine synthesis pathways.

Growth and nutrition outcomes: early-treated diet-alone therapy

Early diet-treated PKU patients have reported deficiencies in several essential nutrients and micronutrients, increased body mass index (BMI), altered folate metabolism, plasma lipid peroxidation and other oxidative stresses [94–120].

Children and adolescents

Studies of children and adolescents following the Phe-restricted diet in adult PKU patients have revealed white matter abnormalities (WMA), reduced cerebral protein synthesis, altered L-DOPA, Phe and Tyrosine (Tyr) uptake at the blood brain barrier, volume changes of grey at white matter, and altered cerebral metabolism [7,8,13,37,49,68–92].

Bone pathology outcomes: early-treated diet-alone therapy

Imbalances in bone formation and bone resorption as measured by biomarkers, decreases in bone mass density (BMD) and alterations in appearance of permanent teeth have been reported in early diet-treated PKU patients [126–134].

Children and adolescents

Bone formation and resorption markers have been found to be significantly reduced in diet-alone treated PKU children compared to healthy controls [126,127,134]. Ambrokievicz et al. measured markers of the alteration of bone pathology present in diet-alone treated PKU children and adolescents signaling risk of bone disease as they age [127].

Adults

Osteopenia and osteoporosis has been detected in the adult PKU population [131,134]. The decrease in peak BMD in adult PKU patients may be explained by long-standing dietary deficiency in protein, calcium, vitamin D or trace elements, or a primary defect in bone turnover inherent to the disease itself [134]. Further studies are needed to elucidate the cause of low bone density in PKU patients that have only been treated with diet.
Maternal PKU outcomes: early-treated diet-alone therapy

Abnormally high and prolonged intrauterine Phe levels in expectant PKU mothers are teratogenic to the developing fetuses and can manifest in a myriad of symptomology with varying degrees of severity dependent upon timing and extent of Phe exposure [135–153]. Symptoms of untreated or late-treated maternal PKU can include developmental delay, microcephaly, congenital heart disease, low birth weight, craniofacial dysmorphism, and neurological abnormalities including neurocognitive deficits [135–153].

The Maternal Phenylketonuria Collaborative Study detailed the outcomes of maternal PKU offspring over an 18 year period, assessing the efficacy of a Phe-restricted diet in preventing the morbidity associated with this disorder. A total of 382 women with PKU and other forms of HPA were enrolled and completed 572 pregnancies. Optimal full-scale IQ outcomes occurred when maternal blood Phe levels between 120 and 360 μmol/L were achieved by 8 to 10 weeks of gestation and maintained throughout pregnancy [139]. Additionally, the Maternal PKU Collaborative Study demonstrated that timing of Phe exposure, specifically when metabolic control is not attained until 8–10 weeks, may determine congenital heart defects (CHD), microcephaly, and cognitive and behavioral outcomes in the offspring [142,150,151]. Furthermore, the longer the time taken to obtain maternal metabolic control the worse the outcomes [151]. Maillot et al. further suggests that the offspring of mothers with PKU with well-controlled blood Phe levels pre- and post-conception are still at risk if blood Phe variations occur within that range [144]. However, women with PKU who are aware of the risks of MPKU still have significant challenges in controlling maternal blood Phe levels. These include access to medical care, unplanned pregnancies, financial constraints, demographics, psychosocial issues, and the rigors of adhering to the strict PKU diet before and during pregnancy especially if pregnancy-related nausea and vomiting are present [136]. Thus, evidence suggests optimal fetal outcomes occur when blood Phe levels are controlled between 120 and 360 μmol/L prior to and throughout pregnancy without fluctuations [139,144].

Discussion

NIH Consensus Statements provide evidence based recommendations on how to best manage patients to ensure optimal patient outcomes and often define the standard of care for a specified pathology over a period of several years. However, that the NIH recognizes that recommendations become out of date and are labeled for “Historical Purposes” after 5 years suggests NIH support for readdressing historical guidelines such as those for PKU [3]. The assertion that expert recommendations become rapidly outdated is supported by a recent systematic review of the PKU literature assessed the need for PKU management practices according the patients’ needs may be of considerable value in updated recommendations. These can include individually tailored blood Phe target levels, the use of newer motivational tool, is the development of a portable Phe monitoring device [161–163]. Another recommendation could call for the routine screening of PKU patients of all ages for nutritional deficiencies, bone density, cognitive dysfunction, emotional well-being and psychosocial problems. Clearly not all PKU patients are equal in terms of risks for abnormalities including neurocognitive de-

1. Have interventions (diagnostic or therapeutic) been superseded or replaced by other interventions?
2. Has new evidence altered the relation between benefits and harm?
3. Have outcomes not considered at the time of the original guideline become important or have outcomes considered important now become unimportant?
4. Is there evidence that current performance is optimal and the guideline is no longer needed?

This systematic review of the PKU literature assessed the need for new NIH recommendations and convening a NIH Consensus Development Conference on the screening and management of PKU in light of new evidence. Based on this approach, the NIH recommendation for obtaining a target blood Phe level between 120 and 900 μmol/L after 12 years of age may be considered invalid with potential improved outcomes reported upon stricter Phe control [5,57]. Although evidence suggests that the NIH blood Phe target ranges are otherwise primarily valid, it is clear from the evidence that diet-alone therapy still burdens the PKU population with significant suboptimal outcomes, especially as individuals age. Expert recommendations are only effective if they are followed and it is clear that a large percentage of all age groups of PKU patients find adherence to metabolic control through diet-alone difficult [37,159,160; Fig. 2].

Above all, the data suggest the potential for development of questions (Fig. 3) that would provide structure for a revised NIH Consensus Statement on PKU management. These questions would form the basis of developing new evidence-based recommendations to address the suboptimal outcomes persistent in the PKU population. One such recommendation might address the need to control blood Phe variability over time through more frequent blood Phe monitoring; maintaining consistent blood Phe within target ranges demonstrates improved patient outcomes [6]. An advancement that has the potential to control blood Phe variability, in addition to being an important motivational tool, is the development of a portable Phe monitoring device [161–163]. Another recommendation could call for the routine screening of PKU patients of all ages for nutritional deficiencies, bone density, cognitive dysfunction, emotional well-being and psychosocial problems. Clearly not all PKU patients are equal in terms of risks for suboptimal outcomes and the potential benefits of individually tailored PKU management practices according the patients’ needs may be of considerable value in updated recommendations. These can include individually tailored blood Phe target levels, the use of newer medications, follow up appointment scheduling and strategies to improve treatment adherence, more detailed nutritional assessments, blood tests, and neurocognitive functioning assessments.

Lastly, updated recommendations should address the use of new therapies with demonstrated potential benefits in the PKU population.
such as enhancing control of blood Phe levels in those who find dietary adherence difficult or want less dependence on dietary restrictions and medical foods. New alternative treatment options are currently available including sapropterin dihydrochloride (sapropterin, Kuvan®) and large neutral amino acid therapy (LNAA) [50,164–177]. Sapropterin is a cofactor of PAH that can increase endogenous PAH activity and subsequently lower blood Phe levels and increase dietary Phe tolerance in a subset of the PKU population identified as responders [164–174]. All subtypes of PKU based on clinical severity have shown response to sapropterin therapy. However large and small population studies have demonstrated that response rates correlate with disease severity, with milder forms of PKU having a higher response frequency [173,178]. Efforts are underway to identify genotype-phenotype relationship to sapropterin response and the only current method is a trial period on sapropterin therapy with evaluation of pre- and post-sapropterin blood Phe levels or Phe tolerance [167,168,173]. Evidence suggests that LNAA therapy works by inhibiting Phe transport from the gut to the blood stream and from the blood stream to the brain through a common amino acid transporter mechanism [50,175–177]. Unlike sapropterin, there appears to be no genotype influence to LNAA response. However, LNAA therapy is considered a “medical food,” which precludes formal clinical trial evaluation on its safety and efficacy for PKU. Thus, while LNAA products are deemed “safe” for consumption, there are no guarantees of effectiveness for treating PKU whereas sapropterin achieved regulatory approval based on positive safety and efficacy results from large controlled clinical trials.

Research is ongoing into other new PKU therapy approaches such as glycomacropeptide (GMP) proteins, which may create more palatable low-Phe foods and promote better long-term adherence [166]. Additional efforts include enzyme replacement and gene therapy which may enable PKU patients to have an unrestricted diet without worrying about high blood Phe levels [166].

**Conclusion**

The evidence demonstrates that significant suboptimal outcomes exist in the PKU population treated with diet-alone and suboptimal outcomes are present in all age ranges (Fig. 4). Although many of the recommendations within the 2000 NIH Consensus Statement on PKU

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![Late-Treated or Untreated Maternal PKU: Offspring Outcome(s)](image)

- **Infants**
  - increased infant risk for mental retardation, microcephaly and/or congenital heart disease [135-153]

- **Children/Adolescents**
  - white matter abnormalities [7,8,73,78,89,92]
  - brain volume abnormalities [92]
  - intracerebral accumulation of a hydrophilic metabolite [85]
  - reduced erythrocyte-membrane ACHE activity [86]
  - deficits in cognitive functioning/abilities** [4,45]
  - linear growth impairment [98,103,105]
  - reduced head circumference [106]
  - overweight [94]
  - elevated total homocysteine levels [106,115,117]
  - increased plasma lipic peroxidation [102,118]
  - low antioxidant status [116,118]
  - reduction of long-chain polyunsaturated fatty acid (LCPUFA) status [38,39,99-101,114,119]
  - higher rates of internalizing problems and/or psychiatric treatment [35,36,43,53,58]
  - increased behavioral problems, learning difficulties or reduced school achievement [11,14,26,53,56]
  - reduced positive emotions [40]
  - vitamin B(12) and/or vitamin B(6) deficiency [115]
  - reduced markers for bone formation [126,129,132]
  - reduced peak bone mass/bone density [133]
  - reduced zinc levels [103]
  - reduced selenium levels [104]
  - iron deficiency [95, 97]
  - reduced carnitine levels [120]

- **Adults**
  - white matter abnormalities [13,37,49,69,70,73,75,77-79,82,87,86,91]
  - grey matter abnormalities [70,82]
  - brain volume abnormalities [69,71,82,83]
  - decreased cerebral functional connectivity [68]
  - deficits in cognitive functioning/abilities** [5,13,15,17,19,21,23,37,44,46,50,57,68,70,73]
  - reduced cerebral protein synthesis rate [72]
  - increased body mass index (BMI), overweight [110]
  - increased brain phenylalanine levels [74,80,81,88]
  - elevated cholesterol/HDL ratios [111]
  - reductions of long-chain polyunsaturated fatty acids (LCPUFA) [111,119]
  - reduced cerebral glucose metabolic rates [96]
  - imbalances of cerebral energy metabolism [84]
  - intracerebral accumulation of a hydrophilic metabolite [85]
  - vitamin B(12) and/or vitamin B(6) deficiency [107,113]
  - behavioral problems [37,53,55]
  - reduced achievement [37,55]
  - increased agitation [65]
  - reduced positive emotions, delayed autonomy [52]
  - increased anxiety and depressiveness [84]
  - reduced cerebral fluoro-L-dopamine uptake [78]
  - reduced bone formation [128,130,132,134]
  - reduced peak bone mass/bone density [131]
  - elevated total homocysteine levels [107]
  - altered folate metabolism [109]
  - reduced platelet serotonin levels [112]
  - increased Plasma lipid peroxidation [118]
  - low antioxidant status [118]
  - reduced carnitine levels [120]

- **Seniors**
  - TBD (early-treated patients through newborn screening are now in their 40s; therefore, long-term repercussions of diet management are still under debate)

*Includes early-treated PKU patients who may or may not be adhering to dietary treatment.

**Deficits in cognitive functioning/abilities in PKU were too many to list in entirety; examples include but are not limited to measures of IQ, executive functioning, information processing speed, visual evoked or event-related potentials, selective and sustained attention, flexible attention, inhibition, verbal memory, recognition memory, and/or expressive naming verbal fluency.

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**Fig. 4.** Suboptimal outcomes exist in all age groups of PKU.
may still be valid, the literature supports the formulation of new recommendations. However, the NIH rarely revisits Consensus Statements and only does so when newly available data warrant a second conference. One such rare instance occurred in 2002, when the 1997 NIH Consensus Statement on the Management of Hepatitis C was revisited based primarily on the introduction of new therapeutic advances in the time frame since its original publication [3,179–182]. Similarly, the availability of the new evidence in this systematic literature review coupled with treatment advancements such as the availability of sapropterin provides support for a new NIH Consensus Development Conference to revisit PKU management strategies to optimize patient outcomes.

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