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ACMG PRACTICE GUIDELINE

Phenylalanine hydroxylase deficiency diagnosis and management: A 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

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ABSTRACT

Purpose: To replace an existing clinical practice guideline for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency.

Methods: The PAH Deficiency Guideline Workgroup used the Grading of Recommendations Assessment, Development, and Evaluation evidence-to-decision framework to develop evidence summaries and practice recommendations based on the recent American College of Medical Genetics and Genomics systematic review.

Results: Many recommendations from the 2014 PAH practice guideline are recognized as standard of care in this evidence-based guideline. Key recommendations from the previous guideline that were not supported by strong evidence are now strongly supported; (1) treatment for PAH deficiency should be lifelong for individuals with untreated phenylalanine (Phe) levels >360 μmol/L, (2) individuals with lifelong Phe levels ≤360 μmol/L have better intellectual outcomes than those who do not, (3) achieving Phe levels ≤360 μmol/L before

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conception is strongly recommended to prevent pregnancy complications and negative outcomes for the offspring, and (4) genetic testing for *PAH* variants is recommended at birth to confirm diagnosis and guide therapy.

Conclusion: We strongly recommend lifelong maintenance of Phe ≤360 μmol/L (using plasma or whole blood) for optimal intellectual outcomes and for reduced teratogenicity, utilizing all available and necessary dietary, pharmaceutical, and patient-educational modalities.

Introduction

Phenylalanine hydroxylase (PAH) deficiency (inclusive of phenylketonuria [PKU] and hyperphenylalaninemia [HPA]), ushered in the era of treatment and screening for inborn errors of metabolism. First reported in 1934 by Asbjörn Fölling, the therapeutic effects of early institution of dietary manipulation were recognized in the 1950s but required early identification of affected children.[1] In the 1960s, PAH deficiency became the first inborn error of metabolism identified through general population screening.[2] Since then, newborn screening (NBS) for PAH deficiency has become widely available in the United States,[3] the United Kingdom,[4] and several other countries.[5,6] NBS has changed the natural history of PAH deficiency as almost all individuals with PAH deficiency in developed countries are identified after a positive NBS result. NBS allows for presymptomatic diagnosis and treatment, most commonly with dietary phenylalanine restriction, which has been successful in preventing severe neurological sequelae and intellectual disability.[7,8] This success set the stage for the expansion of NBS to include additional disorders, altering the public health landscape for rare diseases.[9]

Even with the clear successes of NBS, management of PAH deficiency continues to advance in an effort to address emerging medical and psychosocial issues. In 2014, the American College of Medical Genetics and Genomics (ACMG) published a practice guideline for the diagnosis and management of PAH deficiency.[10] The practice guideline unified the clinically based descriptions of PKU and HPA as PAH deficiency and emphasized the importance of maintaining lifelong Phe control targeting blood Phe levels in the range of 120 to 360 μmol/L, measured using plasma or whole blood. European guidelines for the management of PAH deficiency[11] were published in 2017 to unify management across multiple countries. Although recommending the same diagnostic and management principles, including lifelong Phe control, the European guidelines stratified Phe control by age, recommending levels 120 to 360 μmol/L in individuals <12 years and 120 to 600 μmol/L in individuals ≥12 years.

At the time of publication of both the American and European guidelines, dietary therapy was the mainstay of treatment, consisting of a Phe-restricted diet through use of medical foods (ie, Phe-free or low in Phe amino acid fortified formulas). Although undoubtedly successful at preventing the severe neurological and cognitive consequences of untreated PAH deficiency, there is universal acknowledgment that adherence with the prescribed diet is difficult for a number of reasons including palatability, access, and social acceptance.[12-14] In 2017, a single FDA/EU-approved medication, sapropterin HCl was available to lower Phe levels in individuals with responsive forms of PAH deficiency. Since the publications of these guidelines, a second medication, pegvaliase, has received FDA approval for individuals ≥18 years, allowing for more therapeutic options in adults.[15] Pegvaliase is approved in the European Union and Canada for ages ≥16 years.[16] Ongoing clinical trials for other novel therapeutics have the potential to add to the treatment options for individuals with PAH deficiency.

Many of the recommendations in the 2014 ACMG practice guideline represented codification of standard of care in the field. These statements are summarized briefly below.

Diagnosis

- Additional testing is needed to identify the etiology of elevated blood Phe and should include analysis of pterin metabolism.
  - Individuals with a positive NBS result for elevated Phe must undergo additional testing to determine its etiology. This can include additional biochemical or molecular testing.
  - Analysis of blood and/or urine pterin metabolism must be included in the follow-up of a positive NBS result.
- Quantitative blood amino acids should be performed as part of the diagnostic testing for follow-up of a positive NBS, and should quantify Phe, Phe:Tyr ratio, and complete amino acid profile.
- PAH genotyping is indicated for improved therapy planning.

Management

- The risk for neurocognitive or psychological symptoms in PAH deficiency is related to age of onset of therapy, lifelong Phe levels, and adherence to treatment. Age-specific neuropsychiatric and cognitive testing is necessary to adequately assess clinical needs.
- Appropriate intellectual and mental health assessments are an important component of care for individuals

affected with PKU to provide appropriate access to psychological, educational, and community support resources.
- Any combination of therapies that facilitate improvement in blood Phe levels for a given individual is appropriate; therapies can be combined and should be individualized.
- Reduction of blood Phe, increase in dietary Phe tolerance, or improvement in clinical symptoms are all valid indications for continuation of therapy.
- Genetic counseling should be provided as an ongoing process for individuals with PAH deficiency and their families.

Maternal PAH deficiency

- Large neutral amino acids are not recommended for use during pregnancy.
- Routine prenatal care and monitoring should be supplemented by close monitoring of fetal growth and assessment for fetal congenital heart disease by a high-risk obstetrics group.

Transition to adulthood

- Key points:
  - Adult-focused treatment centers are optimal for older patients but are unavailable in many areas.
  - Transition programs for adolescents with PAH deficiency should foster independence.
- Recommendation:
  - Treatment for life mandates the need for medical insurance to provide coverage for medications and medical foods regardless of age.

This publication replaces the 2014 ACMG practice guideline,[10] with expanded scope, and reaffirms the goal of maintaining blood Phe control ≤360 μmol/L, measured using plasma or whole blood, over the life course, using an individualized combination of available therapeutic options.

Materials and Methods

Guideline workgroup composition

In 2020, the ACMG Board of Directors approved proposals that consisted of separate workgroups to (1) perform a systematic evidence review (SER) and (2) develop an evidence-based guideline (EBG) to update the existing 2014 practice guideline.[10] Consistent with the ACMG policy that EBG workgroup composition be multidisciplinary, participants were selected based on their expertise, adherence to ACMG diversity, equity, and inclusion goals, and conflicts of interest policies. For this EBG, workgroup participants included American Board of Medical Genetics and Genomics certified members specializing in clinical/biochemical genetics (W.E.S., S.A.B., B.K.B., H.J.M., J.V.), laboratory/molecular/biochemical genetics (K.B., C.B., K.L.M., C.S.), guideline methodologists (J.M., G.P.J., O.M.D.), and a patient advocate (C.B.). Guideline methodologists were nonvoting members of the EBG workgroup. Conflicts of interest were assessed according to ACMG board policy and independent review by the ACMG Conflict, Composition, Procedure Review Committee at the time of project approval by the ACMG Board of Directors and before publication. Funding for this EBG was provided internally through staff support (J.M., G.P.J., O.M.D.) by ACMG; EBG workgroup members were uncompensated for their work.

At the project outset, EBG workgroup cochairs (J.V., W.E.S.) collaborated with a staff methodologist (J.M.) to develop key questions to determine the scope for the SER based on the overarching question, "What is the optimal diagnostic and management strategy for PAH deficiency?" These questions were later revised and are presented in Supplemental Table 1. EBG and SER workgroups did not interact with one another, except for the ACMG methodologists who provided methodological assistance.

SER

The results of the ACMG SER and its full methodological details have been published separately.[17] The key questions, population, intervention, comparator, outcomes, timing, and setting study inclusion and exclusion criteria are reproduced in Supplemental Table 1. The literature assessed and analyzed in the SER spanned to September 28, 2021. The full search criteria can be found in the SER.[17] Briefly, 350 studies were included in the SER. The primary goal was to identify the optimal lifespan blood Phe level for individuals with PAH deficiency. Findings showed lower blood Phe levels were consistently associated with better outcomes. Specifically, SER findings support (1) individuals who maintained a lifetime Phe level of ≤360 μmol/L had higher IQ scores, (2) achieving Phe ≤360 μmol/L before conception substantially lowered the risk of negative effects to offspring in pregnant individuals, and (3) medication helps reduce Phe levels.

Translating evidence to recommendations

Outcomes of interest were rated for practical and clinical importance by all members of the EBG workgroup from 1 (not critical to making a decision regarding the optimal patient care strategy) to 9 (critical to making a decision regarding optimal patient care). The outcomes were ranked after the SER protocol was finalized and were re-evaluated before EBG manuscript writing. ACMG methodologists presented evidence summaries for these outcomes using information obtained from the SER. The evidence summaries included certainty assessments for each outcome informed by (1) indirectness, imprecision, and inconsistency

of study results, (2) study-level risk of bias assessments, and (3) risk of publication bias in the body of evidence.

The EBG workgroup started developing recommendations using principles from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Evidence-to-Decision (EtD) framework on September 27, 2022. The workgroup finalized and voted to approve the recommendations on February 10, 2023. Since this date, additional studies and consensus statements have been published that seem to further support the developed recommendation statements. They are not included in this EBG because the articles were unable to undergo the process outlined above.

The EtD framework explicitly considered all 4 central domains (certainty of evidence, balance of benefits to harms, patients' values and preferences, and resource utilization) for moving from evidence to recommendations.[18] Each EBG workgroup voting member voted on all 12 assessment questions under the 4 central domains outlined in the GRADE EtD framework. After completion of initial voting, the methodologists led the EBG workgroup through a consensus-reaching process to attain a minimum 80% agreement on the final judgment for each domain as needed. The overall strength and direction for each recommendation were agreed upon by a minimum of 80% of all workgroup members. If consensus for a recommendation could not be achieved, a statement to this effect was documented along with the rationale.

Interpretation of recommendation statements

Based on GRADE principles, there are 2 potential strengths (strong or conditional) and directions (for or against an intervention) for a recommendation statement. Supplemental Table 2 presents 5 types of recommendation statements that could be developed by guideline workgroups, along with how they should be interpreted by patients and health care providers. Statements which are considered good practice, that is, recommendations for which the likely alternative would be unethical, counter to medical convention, or when indirect evidence unquestionably and with high confidence supports the benefit of the intervention,[19] are not required to use GRADE and are presented above as standard of care.

Peer review of the EBG

The recommendations and manuscript were approved by all members of the EBG workgroup. Internal ACMG peer review included all members of the sponsoring committee and the Board of Directors. After the internal review, a draft of the EBG was distributed for ACMG member comment (external review) for a period of no fewer than 30 business days. Comments from all stakeholders were considered; necessary revisions to the EBG and a formal response to each comment was prepared for the ACMG Board of Directors and the sponsoring committee before the final approval of the document for publication.

Recommendations

There were several topics following the 2014 ACMG guideline that were deemed to have inadequate evidence or required additional analysis and thus were addressed by the SER and the EBG, leading to the following new recommendations. For ease of presentation, recommendations for Phe levels to achieve is defined as ≤360 μmol/L throughout this document. Clinical experience suggests that there is no harm to individuals with PAH deficiency who achieve Phe levels <120 μmol/L because the lower limit of normal in unaffected individuals is 30 μmol/L. Some available pharmacotherapeutic options can place individuals at risk to develop levels below the lower range of normal and care should be taken to prevent this occurrence.

Recommendation 1: ACMG recommends that treatment for PAH deficiency should be lifelong for individuals with untreated Phe levels >360 μmol/L. (Strong recommendation, based on high certainty of evidence.)

The evidence supports treatment directed at lowering blood Phe be initiated as soon as possible after birth for infants with Phe levels >360 μmol/L and should be continued for life to achieve optimal outcomes. Strong evidence supports the observation that mean blood Phe levels are correlated with IQ.[17] Furthermore, loss of metabolic control with rising Phe levels in older individuals is associated with neurocognitive and neuropsychiatric symptoms, as well as frank neurologic abnormalities, including tremor and gait disturbance.[20-24] For untreated adults, Phe levels declined once treatment was resumed,[25] and individuals showed improvement in overall well-being[26] and improvements in nutritional status.[27,28] Treatment for PAH deficiency should be individualized. Personalized treatment goals should be determined through shared decision making, balancing the potential benefits of treatment against the potential harms related to adverse effects or costs of treatment. Dietary protein restriction, along with Phe-free protein supplementation with medical foods (amino acid or glycomacropeptide based), and pharmacologic therapies can all have a role depending on the needs and preferences of the individual person with PAH deficiency.

Recommendation 2: ACMG recommends maintaining Phe ≤360 μmol/L for life in individuals with PAH deficiency because it is associated with higher IQ levels. (Strong recommendation, based on high certainty of evidence.)

Across 14 studies that were meta-analyzed in the SER, significantly higher mean IQ scores, 106.38 (95% CI = 101.38-111.39), were observed in participants who maintained mean lifetime blood Phe level of ≤360 μmol/L, in contrast to the lower mean IQ scores, 101.95 (95% CI = 100.75-103.15), reported in studies in which participants'

mean lifetime blood Phe levels were >360 μmol/L ($P < .01$).[17] A variety of neurocognitive and psychiatric outcomes can develop later in life if well-controlled Phe levels are not maintained during adolescence and adulthood.[20-23,29] With loss of metabolic control, there is an increased risk for a lower quality of life.[30,31] In particular, there is a negative impact on executive functioning that can result in lower overall education attainment and socioeconomic status.[30,31] These factors can exacerbate the difficulty individuals experience in adherence to treatment in an effort to maintain metabolic control.[12,13]

Recommendation 3: ACMG recommends achievement of maternal Phe levels ≤360 μmol/L in individuals with PAH deficiency before conception to prevent negative gestational outcomes or negative outcomes for the offspring. (Strong recommendation, based on high certainty of evidence.)

Individuals who achieved Phe control (Phe ≤360 μmol/L) by the time of conception were 93% less likely to have a child with a microcephaly, congenital anomalies (including congenital heart defects [CHD]), a lower-than-average IQ, and/or behavioral issues compared with pregnancies in which Phe control was not attained until after conception, if at all (OR = 0.07, 95% CI = 0.04-0.14; $P < .0001$).[17] Clinical studies of maternal PAH deficiency continue to support the guidelines for strict management of maternal Phe levels before and during pregnancy to prevent potential teratogenic effects of elevated Phe in the fetus.[32-35] Elevated Phe levels before and during the first trimester of a pregnancy can lead to an increased risk of congenital malformations, including microcephaly, poor fetal growth, and CHD.[36-38] In addition to diet therapy, the availability of new treatments makes the goal of achieving Phe levels ≤360 μmol/L more achievable. Given the importance of lifelong maintenance of Phe ≤360 μmol/L and the increased likelihood of poorer gestational and newborn outcomes when preconception maternal Phe levels are not well controlled (ie, Phe > 360 μmol/L), clinicians treating individuals with PAH deficiency who are in the reproductive age group should preemptively counsel them about the importance of maintaining Phe ≤360 μmol/L.

Recommendation 4a: ACMG recommends pregnant individuals with PAH deficiency maintain Phe levels ≤360 μmol/L for the duration of pregnancy and postpartum time, including the use of medical foods, dietary compliance, or medical treatment to provide optimal maternal and infant outcomes. (Strong recommendation, based on high certainty of evidence.)

Clinical studies of maternal PAH deficiency support the importance of strict management of maternal Phe levels before and during pregnancy to reduce adverse gestational outcomes (including spontaneous abortions, fetal demise/still birth, and preterm delivery), as well as the teratogenic effects of elevated Phe on the fetus.[39,40] Persistently elevated Phe levels during pregnancy lead to an increased risk of congenital malformations, including microcephaly, poor fetal growth, and CHD, as well as intellectual disability collectively termed Maternal PKU Syndrome.[32,39] The landmark Maternal Phenylketonuria Collaborative Study provided evidence to support that optimal fetal outcomes occur when blood Phe levels are controlled between 120 and 360 μmol/L before and throughout pregnancy without fluctuations.[41,42] As elaborated under recommendation 3, it is important to maintain Phe ≤360 μmol/L, as good maternal Phe control was associated with a significantly lower likelihood of the offspring developing microcephaly, congenital anomalies (including CHD), lower-than-average IQ, and/or behavioral issues compared with offspring born to mothers with poorer Phe control.[17] The availability of new treatments and interventions makes the goal of consistent Phe levels ≤360 μmol/L more achievable.

Recommendation 4b: ACMG conditionally recommends the use of sapropterin in pregnant individuals with PAH deficiency to prevent negative gestational outcomes or negative outcomes for the offspring. (Conditional recommendation, based on moderate certainty of evidence.)

Sapropterin has been demonstrated to be well tolerated during pregnancy in both the mother and the fetus and can be used by individuals who are responsive after a discussion of the benefits and risks.[43] Nonpregnant individuals who responded to sapropterin treatment were often able to increase natural protein (Phe) intake, relax adherence to a low-Phe diet, and reduce consumption of medical foods.[17] Notably, treatment adherence was measurably higher in those on sapropterin than those on a low-Phe diet alone. Adverse effects are generally mild. Data from the Maternal Phenylketonuria Observational Program (MOMS) subregistry demonstrated that use of sapropterin during pregnancy was associated with lower and more consistent mean Phe levels and fewer incidents of gestational Phe levels measuring >360 μmol/L.[43] The National Institute for Health and Care Excellence in the UK approved sapropterin for use during pregnancy based on the known teratogenicity of uncontrolled maternal Phe levels.[44] Information regarding sapropterin use during pregnancy and lactation should be reviewed before prescribing (US Prescribers Information).[45]

Recommendation 4c: ACMG cannot recommend nor discourage the use of pegvaliase in pregnant individuals with PAH deficiency to prevent negative gestational outcomes or negative outcomes for the offspring. (No recommendation, due to insufficient evidence.)

Clinical trials conducted on the use of pegvaliase excluded pregnant individuals. Thus, there are very limited data on the risks of continuation of pegvaliase during pregnancy. One case report of a healthy infant born to a mother who continued pegvaliase treatment during pregnancy has been published.[46] However, significant adverse effects have been reported with use of pegvaliase that could affect pregnancy risks. Studies on a larger patient population are warranted and a registry for pregnancies exposed to pegvaliase is

collecting available observational data (PALomino Pregnancy Observational Safety Study). Information regarding pegvaliase use during pregnancy and lactation should be reviewed before prescribing (US Prescribers Information).[47] Given the limited evidence on pegvaliase during pregnancy, ACMG makes no recommendation for the use of pegvaliase during pregnancy at this time.

Recommendation 4d: ACMG recommends individuals with PAH deficiency be encouraged and supported to breastfeed, if desired, including when babies have PAH deficiency. (Strong recommendation, based on high certainty of evidence.)

Babies without PAH deficiency can readily metabolize Phe in breastmilk, and reports of breastfeeding vs bottle feeding in babies born to PAH-deficient mothers have demonstrated similar outcomes in success of breastfeeding and blood Phe levels in the babies. Thus, mothers with PAH deficiency receiving nutritional support and continued diet therapy can safely breastfeed infants unaffected by PAH deficiency.[48-50]

Infants with PAH deficiency can also safely breastfeed, in conjunction with use of medical foods and appropriate monitoring of Phe levels. Seventeen studies reported findings related to breastfeeding infants with PKU, which included normal physical and neurological development overall. Typical difficulties experienced during breastfeeding (breastmilk supply, breast milk pumping, nipple confusion) were not unique to nursing infants with PKU, other than during the initial Phe washout period right after diagnosis. In a study conducted in the UK, the age at infant weaning from breastfeeding was slightly earlier for infants with PKU (4.3 months as compared to 5.1 months).[51]

Recommendation 5: ACMG strongly recommends confirmatory molecular genetic testing in individuals with PAH deficiency. (Strong recommendation, based on high certainty of evidence.)

Biallelic variants in *PAH* resulting in reduced PAH enzyme activity are the most common cause of elevated blood Phe.[52] In addition to confirming a biochemical diagnosis and allowing for carrier screening of at-risk family members, molecular results may also be used to inform clinical management. Over the last two decades, numerous studies have elucidated the functional effects of *PAH* variants on residual enzyme function, the severity of the PAH deficiency, and the response to BH4 treatment.[53] Although mostly variants of uncertain significance, more than 3350 *PAH* variants have been recorded in the Phenylalanine Hydroxylase Gene Locus-Specific Database (PAHvdb) (biopku.org). The ClinVar database maintained at the National Institutes of Health contains 766 pathogenic or likely pathogenic *PAH* variants including 416 missense, 132 frameshift, 78 nonsense, and 76 splice site variants. The Clinical Genome Resource (ClinGen) phenylketonuria variant curation expert panel[54] reviewed the majority of these variants (ClinVar 3 stars review status) and developed *PAH*-specific variant interpretation guidelines based on the established ACMG-AMP standards and guidelines for interpretation of sequence variants.[55] Routine molecular diagnostic testing to confirm NBS results is likely detecting many additional *PAH* variants.

PAH variant analysis is not required for initial treatment of babies with elevated Phe levels identified by NBS, which is based on measuring blood Phe levels and exclusion of cofactor BH4 deficiency using biochemical analysis.[56] However, formal confirmation of the diagnosis of PAH deficiency can only be achieved through molecular analysis. Additionally, although individuals with similar variant *PAH* genotypes can have disparate phenotypes, a genotype of known significance is clearly an important clinically available predictor of the severity of PAH deficiency and the potential for biopterin response.[10,52,53] The SER workgroup reviewed 16 studies reporting genotype-phenotype associations in individuals with PAH deficiency.[17] This study identified an association of specific alleles with PAH deficiency severity based on the Database of Patients and Genotypes Causing HPA/PKU including BH4-Responsive Phenotypes (BIOPKU), which included a prediction of the higher allelic phenotype value of the 2 *PAH* alleles in each person. Although several exceptions to this observation were found, individuals with severe or classic PAH deficiency were overall less responsive to biopterin treatment than those with mild or HPA disease. These results are consistent with the variable genotype-phenotype associations and the genetic and environmental factors contributing to an individual's total plasma Phe level.[52,57] Limitations of the study included that not all articles reviewed had reported complete genotypes for both alleles and that results for sapropterin/BH4 responsiveness were only available from 9 of the 16 studies.

PAH genetic testing can inform individual clinical diagnosis and personalized treatment options and should be offered to all individuals at risk for developing elevated Phe levels due to PAH deficiency. In addition to improving patient care, universal *PAH* genetic testing will also advance understanding of the molecular underpinnings of PAH deficiency, the study of genotype-phenotype associations in other inborn metabolic disorders, and the development of personalized treatment approaches for these diseases. *PAH* genetic testing, expert variant curation, data management, and sharing are important cornerstones for advancing patient care.

Implementation considerations

With the expanding number of pharmacological therapeutics, a blood Phe ≤360 μmol/L can be achieved through individualized medicine. However, it is also important to acknowledge that despite the presence of effective therapies, existing research priorities and the high cost of implementing personalized treatment approaches limits equitable access to effective therapies for many individuals with PAH deficiency.[58]

Research priorities

PAH deficiency is one of the longest-studied and longest-treated inborn errors of metabolism. Many states in the United States have now been screening for PAH deficiency for close to 60 years and it is one of the few rare disorders that has more than 1 approved pharmacologic treatment. However, gaps in knowledge and the need for additional research remain.

As the initial cohort of treated individuals with PAH deficiency enters their senior years, it is uncertain how PAH deficiency will influence the aging process. Blood Phe is the current gold standard for monitoring treatment, but little is still known on what happens when Phe crosses the blood-brain barrier. Point-of-care blood Phe testing could improve PAH deficiency clinical management with more timely results and shed new light on how blood Phe levels fluctuate during the day. Research also shows abnormalities in both the white and gray matter of the brains in people with PAH deficiency.[59,60] Even with early and continuous treatment, individuals with PAH deficiency experience cognitive and neurologic disruptions, including a slight decrease in overall IQ and impairments in executive function, processing speed, and emotional regulation.[61] These research findings mirror the patient experience as data become available through the National PKU Alliance's PKU Patient Registry. Overall, 64% of registry participants reported experiences with anxiety, and 52% reported a history of depression. Of the registry participants with a history of anxiety and/or depression, 38% reported treatment for an emotional/behavioral disorder. Interventions included medication and psychotherapy. There is a need to better measure, quantify, and improve the impact of executive dysfunction, anxiety, and depression given the widely reported neurologic disruptions among those with PAH deficiency. More research is needed to better understand these issues.

In addition, individuals with PAH deficiency suffer a wide variety of other comorbidities ranging across a number of organ systems.[62] The etiology for many of the comorbid conditions warrant more investigation, and additional research to ascertain if they are related to elevated blood Phe levels or the requisite Phe-restricted low-protein diet.[57]

Looking to the future, better tools, strategies, and treatments are still needed to optimize care for the individual and improve long-term outcomes. There are now more new therapies under investigation for PAH deficiency than ever. Multiple modalities are now in or preparing clinical trials, including gene therapy (Clinicaltrials.gov [NCT04480567, NCT06332807]), mRNA therapy (NCT06147856), Phe uptake receptor blocker (NCT05781399), sepiapterin chaperone therapy (NCT06302348), and multiple diet and dietary supplement studies. It is safe to predict that there will be multiple options for treatment of PAH deficiency in coming years. Current and future therapies should be evaluated not only for their ability to lower Phe but also for the ability of individuals with PAH deficiency to consume more natural protein and to enhance the quality of life for affected individuals and their families.

Economic considerations

PAH deficiency poses a significant economic burden at both the individual and societal levels. The primary concern stems from the lifelong management of PAH deficiency, which necessitates adherence to a strict low-Phe diet and specialized medical foods. The cost of these dietary restrictions, including the purchase of low-protein foods and specialized formulas, can be substantial for individuals and their families. Moreover, the need for regular monitoring through blood tests, clinic visits, and consultations with health care professionals adds further financial strain and time burden, contributing to the overall economic impact of PAH deficiency.[63]

Health care coverage for PAH deficiency plays a crucial role in mitigating the economic burden on affected individuals and their families and is essential for ensuring access to comprehensive care and management strategies. Without adequate coverage, individuals with PAH deficiency can face significant financial barriers to accessing essential treatments and services.[64] In many countries, health care coverage for PAH deficiency is provided through public health insurance programs or private insurance plans. Public insurance programs, such as Medicaid in the United States, often cover the costs of medical foods and essential medical services for individuals with PAH deficiency.[65] However, coverage policies and reimbursement mechanisms vary, leading to disparities in access to care and out-of-pocket expenses (Supplemental Table 3).[66] Private insurance plans usually offer coverage for some PAH deficiency-related expenses, but coverage terms and limitations differ depending on the specific plan and provider.[63] In a nationally representative sample of US administrative claims data, 64% of individuals with PAH deficiency had exclusive provider organization/preferred provider organization as their insurance type.[67] Mean total medical and health care costs per person per month were $1060 and $2123, respectively.[67] Fifty percent of health care costs were attributed to outpatient prescriptions.[67]

Challenges related to health care coverage for PAH deficiency include limitations on coverage for certain treatments or services, as well as restrictions on the types and brands of medical foods that are eligible for reimbursement.[11] Additionally, individuals often encounter difficulties in obtaining coverage for emerging therapies or novel treatment approaches, such as enzyme substitution therapy or gene therapy.[11] These challenges highlight the need for ongoing advocacy efforts to improve health care coverage policies and ensure equitable access to innovative treatments for PAH deficiency.

The economic burden of PAH deficiency on health care systems underscores the importance of cost-effectiveness analyses and evidence-based decision making in determining

coverage policies and reimbursement structures. By evaluating the long-term benefits and cost savings associated with early intervention and comprehensive management of PAH deficiency, policymakers can make informed decisions regarding health care coverage that optimize health outcomes and resource allocation.[68] Collaborative efforts between health care providers, patient advocacy groups, and policymakers are essential for addressing the complex health care coverage needs of individuals with PAH deficiency and improving access to high-quality care.[68]

Conclusion

The evidence strongly supports lifelong maintenance of blood Phe ≤360 μmol/L to obtain optimum intellectual outcomes in all individuals with PAH deficiency, including neonatal outcomes in maternal PAH deficiency, utilizing all available and necessary dietary and pharmaceutical modalities available. Additionally, evidence continues to strongly support the conclusion that lifetime Phe levels correlate with intellectual outcome. Standard of care dictates that personalized treatment goals for individuals who are untreated should be determined through shared decision making, balancing benefits (amelioration of symptoms, normalizing protein intake, improved behavior, and/or psychologic symptoms) with harms/difficulties of treatment (eg, adverse effects of treatment, inability to adhere to treatment, and costs of treatment). Complete reversal of symptoms might not be feasible or realistic for every individual. Achievement of maternal Phe levels ≤360 μmol/L before conception and maintained below this level through pregnancy is strongly recommended to prevent negative gestational outcomes and negative outcomes for the offspring. The use of sapropterin in pregnancy is conditionally recommended, but insufficient data are available to make a recommendation regarding pegvaliase at this time. Genetic testing for *PAH* variants is strongly recommended at birth to confirm diagnosis and guide therapy. These conclusions are based on high certainty of evidence from a companion SER.

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Conflict of Interest

The funding and support listed here did not support development of this document unless included in the acknowledgments section. Susan A. Berry is a member of the Board of Directors of the National PKU Alliance. Barbara K. Burton has received consulting fees and honoraria for speaking engagements from BioMarin Pharmaceutical, consulting fees from PTC Therapeutics and Jnana Therapeutics and funding for conducting clinical trials in PAH deficiency from BioMarin, Jnana Therapeutics, Homology Medicines, and Synlogic. Kim L. McBride has received research funding from BioMarin Pharmaceutical, Homology Medicines, and Ultragenyx, received speaker fees from Ultragenyx, and serves on a data monitoring board for Sanofi. Jerry Vockley has received research funding from BioMarin Pharmaceutical, Jnana Therapeutics, Homology Medicines, and PTC Therapeutics for participation in clinical trials on PAH deficiency. All other authors report no conflicts of interest.

Additional Information

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