Open Access

OBM Genetics

Review

Phenylketonuria—Past, Present, and Future Directions

Nicole A. Bailey [1, *], Laura Mackay [2]

1. Division of Neonatology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; E-Mail: Nicole.Bailey@utsouthwestern.edu
2. Division of Pediatric Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, Texas, USA; E-Mail: laura.mackay@utsouthwestern.edu

* **Correspondence:** Nicole A. Bailey; E-Mail: Nicole.Bailey@utsouthwestern.edu

Academic Editors: Shibani Kanungo, Miao He and Georgianne Arnold

Collection: Newborn Screening and Inherited Metabolic Disorders

OBM Genetics
2024, volume 8, issue 3
doi:10.21926/obm.genet.2403256

Received: May 12, 2024
Accepted: August 13, 2024
Published: August 16, 2024

Abstract

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism with an incidence that varies throughout the world. PKU is caused by loss of function variants in the phenylalanine hydroxylase gene. This loss of function leads to the accumulation of an amino acid, phenylalanine (Phe), that can reach toxic levels in the blood. PKU is managed with a medical diet and sometimes with medication. If diagnosed early and with strict dietary control, neurocognitive deficits can be prevented. There is an important need to ensure the timely diagnosis of PKU and to develop newer therapies to treat this metabolic disorder.

Keywords

Phenylketonuria (PKU); newborn screening; metabolic disorder; phenylalanine; phenylalanine hydroxylase deficiency; Fölling's disease

© 2024 by the author. This is an open access article distributed under the conditions of the Creative Commons by Attribution License, which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

1. Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder caused by elevated blood phenylalanine (Phe). If not diagnosed early and properly treated, PKU can result in severe neurological deficits and skin disorders. Currently, in the USA and in many countries worldwide, screening for PKU is achieved through newborn screening programs. PKU is mainly treated through dietary modifications including Phe restriction and phenylalanine-free metabolic formulas. In some cases, drug therapies, such as sapropterin and pegvaliase, may be used to decrease blood Phe. Additionally, gene therapy is currently being investigated as an alternative for future treatment. We are now approaching the 100th anniversary of the discovery of PKU. There have been many advancements in the treatment of PKU. Undoubtedly, there are many more milestones to come. This paper aims to describe the history of PKU, the current therapies, and the future pathways for this well described inborn error of metabolism.

2. The History of the Diagnosis of PKU

PKU is less commonly known as phenylalanine hydroxylase deficiency or Fölling's disease. Milder forms of plasma Phe elevation are often referred to as hyperphenylalaninemia. In 1934, Dr. Ivar Fölling, a Norwegian doctor, used ferric chloride to detect phenylpyruvic acid in the urine of two Norwegian siblings with intellectual disabilities [1, 2]. After discovering a connection between the urinary substance and people with intellectual disabilities, Dr. Fölling named the condition *imbecillitas phenylpyruvica* [2]. Within several years, an English geneticist, Dr. Lionel Penrose, renamed this metabolic disorder to be known as phenylketonuria because of the green characteristic appearance of phenylpyruvic acid seen in the urine of affected patients [2].

3. Epidemiology

The incidence of PKU varies throughout the world. The worldwide estimate of PKU is around 1 in 23,930 newborns [1, 3]. In the USA, 1 in 13,500-25,000 newborns has PKU while the African American population exhibits one of the lower rates of PKU at 1 in 50,000 individuals [3, 4]. In Europe, the estimate ranges from 1 in 2,700-4,500 live births in Italy and Ireland to <1 in 100,000 live births in Finland [5]. Throughout the world, Asia has the lowest rates of PKU: Thailand (1 in 227,273), Japan (1 in 125,000), Philippines (1 in 116,006), and Singapore (1 in 83,333) [1, 3]. However, China is the exception where the estimate is 1 in 15,924 [1, 3]. In contrast, the highest rates of this disorder have been seen in the following populations: Turkey (1 in 6,667), Yemenite Jews in Israel and Scotland (1 in <6,600), Arabic populations (up to 1 in 14,493), and Czechoslovakia (1 in 5,521) [3] (Figure 1).

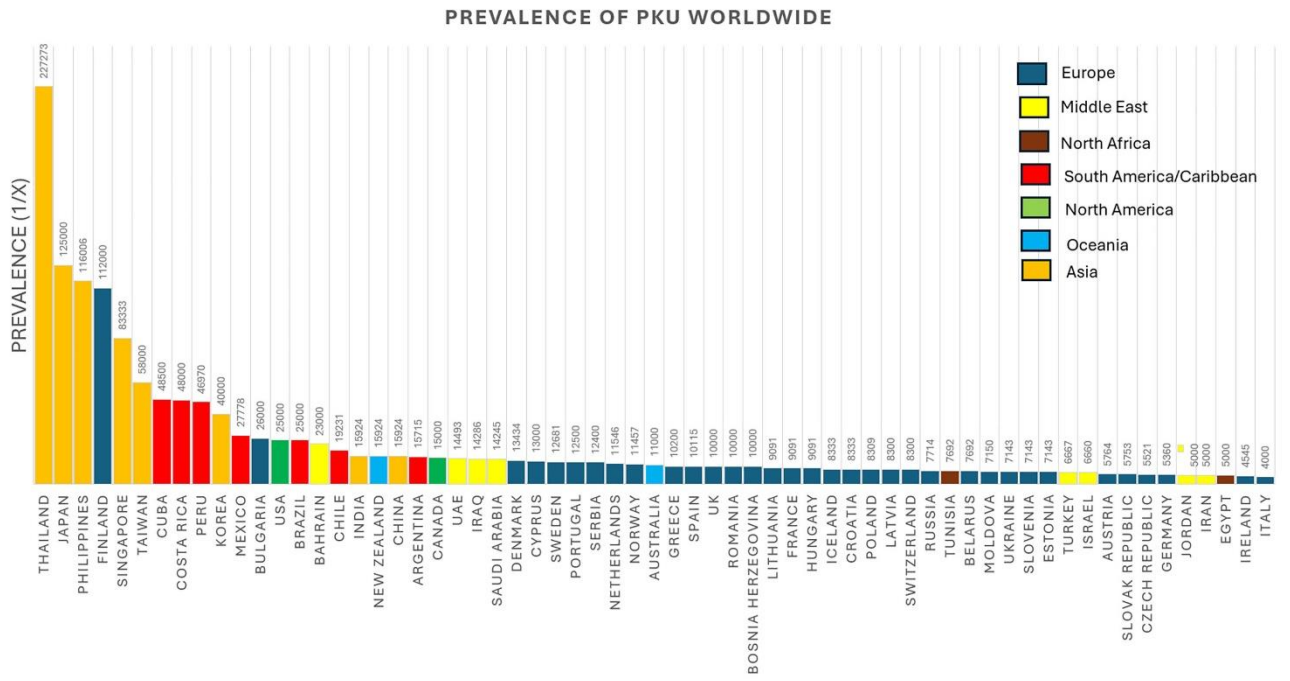

Figure 1 The prevalence of PKU worldwide [3].

4. Genetics/Pathophysiology

PKU is inherited via an autosomal recessive pattern most commonly due to pathogenic variants in the phenylalanine hydroxylase (PAH) gene located on chromosome 12 [5]. PAH is an enzyme that catalyzes the hydroxylation of Phe to tyrosine which requires molecular oxygen as a cofactor and the reduced tetrahydrobiopterin as a co-substrate [1, 5] (Figure 2). It should be noted that only 2% of hyperphenylalaninemia is due to pathogenic variants in the DNAJC12 gene or tetrahydrobiopterin deficiency, with tetrahydrobiopterin being a key cofactor in phenylalanine, tyrosine, and tryptophan hydroxylation [1, 6]. Tetrahydrobiopterin deficiency is also inherited in an autosomal recessive manner and implicated genes include *GCH1, PTS, QDPR,* and *PCBD1* [6]. To differentiate the genetic etiology of PKU, targeted genetic testing is performed.

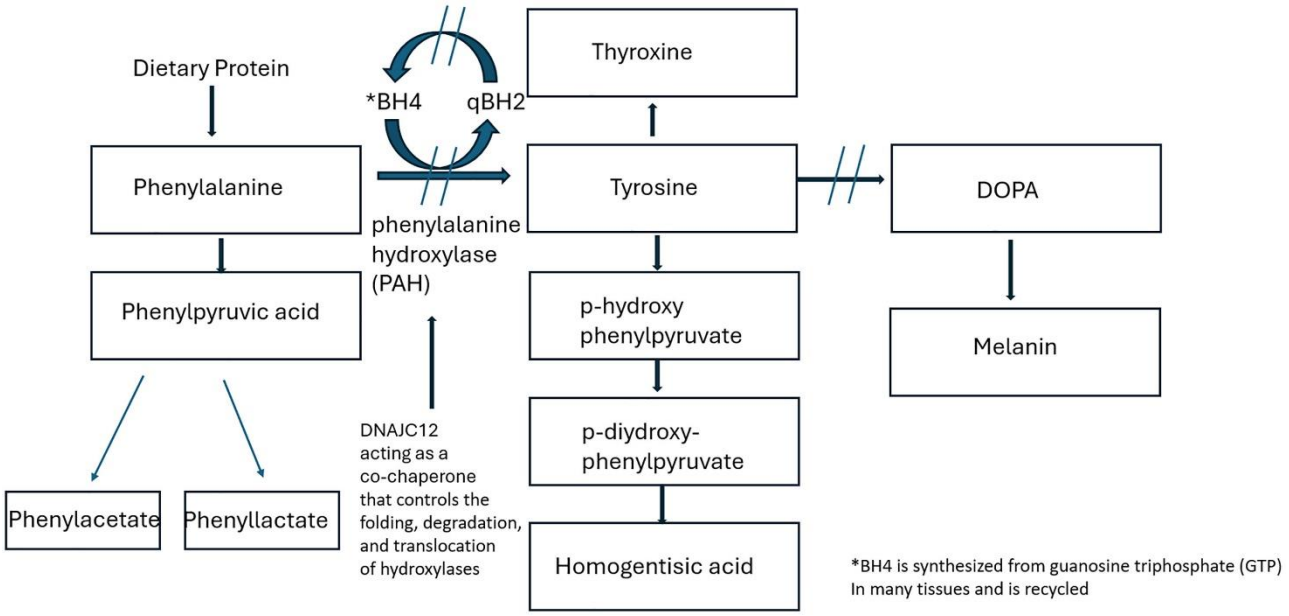

Figure 2 Metabolic pathway of PKU: Phenylalanine hydroxylase (PAH) catalyzes the hydroxylation of L-phenylalanine to L-tyrosine [1].

PAH deficiency causes elevated blood Phe and lower concentrations of tyrosine in all body tissues (including the blood), and elevated blood Phe are neurotoxic. The mechanisms for neurotoxicity are not well understood. Although, it is suspected that elevated blood Phe causes defective synapse formation, impairment of neuronal cell growth, and abnormal myelination, the latter of which continues throughout life [5, 7]. Restriction of dietary Phe lowers the risk of neurotoxicity if started within a few weeks of birth. A strong correlation between control of blood Phe in childhood and intelligence quotient (IQ) has been shown [7]. Tyrosine plays a key role in neurotransmitter synthesis (i.e. dopamine, adrenaline, and norepinephrine) and lower levels of tyrosine have been associated with attention deficit hyperactivity disorder [1]. In addition to neurotransmitter synthesis, tyrosine serves other metabolic purposes: (1) conversion to thyroxine in the thyroid gland, (2) conversion to melanin in melanocytes, and (3) complete catabolism to acetoacetate (a ketone) and fumarate (a Krebs cycle intermediate) to be used as fuel [5].

5. Clinical Presentation

One of the earlier clinical signs of PKU was a musty odor noticed in the urine or sweat. Phenylacetic acid or phenylacetate, a by-product of urinary phenylpyruvic acid, is the substance responsible for this musty odor [2]. Other clinical symptoms of untreated PKU are severe intellectual disability, epilepsy, seizures, psychiatric movement behaviors, microcephaly, generalized hypopigmentation of skin (including eyes and hair), and eczema [1, 5]. In rare cases, ocular findings such as photophobia, cataracts, corneal clouding, subluxation of the lens, pallor of the optic disc, refractive amblyopia, strabismus, high myopia, glaucoma, and bilateral vision loss have been reported [8]. Prior to the discovery of PKU, intellectual disability was a primary manifestation of this disorder. However, in the mid-1950s, medical management utilizing dietary restrictions was introduced, thus permanently changing the clinical landscape of PKU [2]. In the 1960s, newborn screening programs were initiated to detect PKU. Currently, all fifty states in the USA screen

newborns for PKU through state driven newborn screening programs. With early diagnosis and treatment initiation including dietary phenylalanine restriction, the severe neurological findings seen in the past are now rarely seen.

In rare cases, PKU may be diagnosed late or not treated due to newborn screening failures or parental non-compliance [9, 10]. In Western countries, most late-diagnosed PKU patients are immigrants from countries without a national screening program [10]. A late diagnosis or initiation of treatment may also occur due to false negative testing or in countries without treatment protocols. If inadequately treated for extended periods of time, adults with PKU may develop lower extremity spasticity, cerebellar ataxia, tremors, encephalopathy, visual abnormalities, mental health disorders such as anxiety and depression, and even dementia [5, 9-11]. Adverse effects on attention, mood, memory, and executive function can be seen in adolescents and adults with elevated Phe concentrations due to difficulty in adhering to the strict life-long dietary restrictions [5, 12, 13]. Even though dietary restrictions lower the risk of intellectual disability, attention-deficit–hyperactivity disorders and specific learning disabilities might remain higher in well-treated patients with PKU compared with individuals without PKU [5].

6. Diagnosis/Screening

With varied detection techniques, PKU is an inherited disorder that is uniformly screened for at birth in the United States. Based on Dr. Fölling's research, screening for PKU was initially done in the 1950s with the ferric chloride test which involved placing a few drops of ferric chloride on urine specimens obtained from infants [2]. However, this test was not always diagnostic shortly after birth because it takes several weeks for the diagnostic substance, phenylpyruvic acid, to appear in the urine since this is a disorder of intoxication [2]. In the 1960s, PKU screening transitioned from urine specimens to collecting a drop of blood from a neonate by a heel prick. The bacterial inhibition assay (Guthrie test), a test in which bacteria is used to measure the concentration of a substance in a sample, and fluorometric and photometric detection immunoassays were all developed for blood specimens. As of the 1990s/early 2000s, in most developed countries, tandem mass spectrometry has been used to determine the concentration of Phe and the ratio of Phe to tyrosine. This ratio will be elevated in patients with PKU. While more costly than the other tests, the tandem mass spectrometry method allows for early detection of multiple metabolic disorders [5]. It is also faster and more accurate than Guthrie's bacterial inhibition assay [2].

Screening for PKU involves placing several drops of blood from an infant's heel onto a special filter paper card (Guthrie card). The card is dried and is sent to the appropriate state designated laboratory. A standard sized punch is obtained from the card and blood is eluted from the punch [13]. The timing of screening for PKU varies among countries and regions. However, the first screening usually occurs between 24-48 hours of life to allow time for abnormal metabolites to build up after initial feedings. Some state based newborn screening programs include a second screen at age 7-14 days for enhanced detection of disorders of intoxication [14].

In the early 1960s, Massachusetts was the first state in the USA to adopt mandatory screening for PKU in newborns [14]. Mandatory testing has since expanded to all US states and to many developed countries throughout the world, with different testing menus in each country [15, 16]. For instance, Thailand, a country with one of the highest rates of PKU, initiated a mandatory and universal screening program for PKU in 1996 [17]. However, PKU screening is not available

everywhere. By 2015, in Latin America, only four countries had successfully implemented newborn screening programs at a national level that reaches 98% of newborns--Cuba in 1986, Costa Rica in 1990, Chile in 1992, and Uruguay in 1994 [16, 18]. There are many limitations to the implementation of newborn screening programs such as the shortage of resources and funding, the availability of skilled personnel, and the inability to afford the costly low Phe diet consisting of medical foods and metabolic formulas, which prohibits the expansion of newborn screening in the developing world [15]. The International Society for Neonatal Screening (ISNS) provides support for improving newborn screening worldwide [18].

While newborn screening is a screening test and is not diagnostic, suspicion of PKU based on newborn screening should be confirmed with plasma amino acids and molecular testing. Plasma amino acids showing a phenylalanine level persistently greater than 130 µmol/L (>2 mg/dL) with an abnormal phenylalanine to tyrosine ratio along and biallelic pathogenic variants in PAH gene are diagnostic for PKU [19]. Phenylalanine level at diagnosis and known genotype/phenotype correlation aid in distinguishing benign hyperphenylalaninemia that will not require medical intervention and mild hyperphenylalaninemia vs. mild PKU, moderate PKU, and classic PKU. Hyperphenylalaninemia is defined as pretreatment blood Phe of 360-600 µmol/L or 6-10 mg/dL, mild PKU is 600-900 µmol/L or 10-15 mg/dL, moderate PKU is 900-1200 µmol/L or 15-20 mg/dL, and classic PKU is >1200 µmol/L or >20 mg/dL [20].

7. Prenatal Diagnosis of PKU

In families that already have a PKU-affected child, prenatal testing is another pathway to screen for the disorder in the fetus. Currently, the most common methods for prenatal testing are chorionic villus sampling and amniocentesis [21]. Additionally, pre-conception expanded carrier screening enables couples at risk of having an affected child to be identified with the downstream ability to pursue in vitro fertilization with pre-implantation genetic testing for monogenic disorders (PGT-M) and/or prenatal diagnostic genetic testing on the spontaneously conceived fetus. Non-invasive prenatal testing (NIPT) is also being investigated as a first-tier screening technique for PKU in high-risk couples [21, 22].

8. Management

The dietary management of PKU involves: (1) restriction of foods high in Phe such as meat, dairy, and eggs (2) supplementation with a Phe-free amino acid mixture and (3) consumption of low-protein medical food products [1, 5]. First introduced seven decades ago, a Phe-restricted diet remains the primary treatment for PKU [5, 23]. During infancy, breastfeeding is often possible in combination with a Phe-free medical formula [5, 23-25]. In older children and adults, l-amino acids (without Phe) and glycomacropeptide (GMP), an intact protein that is low in Phe, have been used as a protein source [23]. In addition, tyrosine, essential fatty acids, vitamins, and minerals may need to be supplemented in the diet to meet nutritional requirements [19, 23]. Many patients experience problems with the taste of amino acid mixtures, but dietary formulations continue to improve [5]. There is also a significant issue with compliance related to social aspects surrounding food such as meals at school or at social gatherings, especially in adolescence.

Although the Phe-restricted diet is still the primary course of treatment, two drugs are available that decrease the blood Phe concentration [5]. In 2007, the Food and Drug Administration (FDA)

approved sapropterin dihydrochloride. This medication is a tetrahydrobiopterin (BH4) synthetic analogue which can decrease blood Phe by converting phenylalanine to tyrosine. Some patients with milder forms of PKU or hyperphenylalaninemia can forego or decrease protein restriction and metabolic formula while on sapropterin dihydrochloride [5, 26]. However, only 25-50% of patients respond to this treatment, and those with classic PKU are usually non-responders [5, 26]. In 2018, the FDA approved pegvaliase, an injectable pegylated Phe ammonia lyase [5], for use in adults. Pegvaliase is very effective in lowering Phe concentrations in most patients which allows patients to be managed without severe dietary restrictions [5, 27]. However, pegvaliase has many side effects such as anti-pegvaliase antibodies, skin reactions, arthralgia and, very rarely, anaphylactic responses [5]. The antibody response may take several months to overcome before the pegvaliase becomes effective [5]. Additionally, pegvaliase is currently only approved for affected individuals who are 16 years old or older.

9. Monitoring of PKU

Infants whose blood Phe exceed 600 µmol/L (10 mg/dL) require treatment [19]. While standard of care for treatment centers in North America is to initiate treatment at a Phe level of 360 µmol/l (6 mg/dL) or higher, some outside treatment centers do not initiate treatment because the evidence regarding clinical outcome in untreated patients with blood Phe between 360 and 600 µmol/L (6-10 mg/dl) is mixed [19]. Treatment for infants with blood Phe between 120 and 360 µmol/L (2-6 mg/dL) is not recommended, although these individuals should be followed closely at least for the first 2 years of life, at puberty, and prior to pregnancy to ensure blood Phe remain <360 µmol/L (<6 mg/dL) [19].

According to the American College of Medical Genetics (ACMG), blood Phe in all patients should be maintained in the range of 120-360 µmol/l (2-6 mg/dL) [19, 23, 28]. From birth to one year of age, blood Phe should be monitored at least weekly with increased monitoring during periods of rapid growth and transitions of diet, such as with the introduction of solid foods [19]. Between 1 year of age and until age 12 years, biweekly to monthly sampling is recommended, based on Phe level stability and compliance [19, 28]. Monthly testing may be adequate in adolescents and adults who are well controlled [19]. Given the close association between blood Phe and patient outcomes, blood Phe provides the best measure of a patient's adherence to treatment [28].

The European PKU guidelines vary slightly from the American guidelines. These guidelines were created to achieve consistency in the medical management of PKU across Europe. The European guidelines suggest that patients up to age 12 should maintain blood Phe in the range of 120-360 µmol/l (2-6 mg/dL) [29]. Patients older than 12 years of age should maintain blood Phe between 120-600 µmol/l (2-10 mg/dl) [29].

10. PKU and Pregnancy

Maternal PKU syndrome describes the teratogenic effects in the offspring of mothers with PKU which include intellectual disabilities, behavioral disorders, microcephaly, intrauterine growth restriction, facial dysmorphic features, and congenital heart disease, mainly malformations in the left chambers [19, 30-32]. The association of intellectual disability in the offspring of mothers with PKU was first mentioned in a 1937 survey [33]. In the early 1960s, a series of publications confirmed this association [33]. In the mid-1960s, additional features of phenylketonuric pregnancies were

described such as microcephaly, intrauterine growth restriction, and congenital heart disease [33]. By the early 1980s, a study published by Lenke and Levy established the frequencies of the teratogenic effects relative to maternal blood Phe [34]. This study provided baseline data for the Maternal PKU Collaborative Study (MPKUCS).

In 1984, the National Institute of Child Health and Human Development sponsored the MPKUCS in the United States to determine fetal outcomes with improved control of maternal Phe concentrations during pregnancy [30]. Later, Canada and Germany were also included in this study. It was a prospective, longitudinal study that compared outcomes of neonates born to the following: controls, mothers with PKU controlled at various timepoints during pregnancy, and mothers with untreated PKU [30, 35]. The primary outcome variables were microcephaly, intrauterine growth restriction, congenital heart disease, and intellectual disabilities [35]. The study concluded that intervention with a Phe-restricted diet reduced the morbidity for untreated pregnancies in women with PKU if blood Phe is adequately controlled by 6-10 weeks after conception [35].

Due to advancements in medicine, many women with PKU are entering the childbearing age, but the percentage of mothers achieving the therapeutic goal by the 8th week of pregnancy is only 50% [36]. Untreated maternal PKU during pregnancy results in elevated blood Phe in the fetus which may be teratogenic [31]. The risk of microcephaly increases by 5–18% when Phe remains elevated by the 10^{th} week of gestation and increases up to 67% if levels are not controlled before week 30 of gestation [19, 31]. It has also been shown that the intelligence quotient (IQ) of children exposed to high concentrations of maternal Phe (>750 µmol/l) (>12 mg/dl) during pregnancy was low (mean IQ 56) [30]. When the average exposure to blood Phe during pregnancy was less than 360 µmol/l (6 mg/dl), the offspring had normal cognitive development (mean IQ 105) [30].

Phe crosses the placenta by active transport, which increases blood Phe in the fetus from 70% to 80% over the mother's blood levels [30]. Due to fetal immaturity up until 26 weeks gestation, the fetus needs the mother's PAH enzyme function to achieve the hydroxylation of Phe [28]. However, as metabolic demands increase and the liver of the fetus begins to produce PAH normally, the mother's blood Phe will drop requiring an increased Phe intake to ensure blood Phe remain within the safe range (120 and 360 µmol/L or 2-6 mg/dL) [5]. By the end of the pregnancy, the mother's daily Phe requirements may double or even triple [5]. If maternal blood Phe fall below range (<120 µmol/L or <1-2 mg/dL), the growth and development of the fetus are at risk [5, 37].

Maternal genotype does not predict the extent of increased Phe tolerance during pregnancy [36]. Maternal Phe tolerance is empiric, relying on the frequent assessment of Phe in maternal blood in response to graded (50 mg) doses of Phe intake [36]. Consequently, mothers with PKU should pursue a regimen that maintains their blood Phe within the goal range of 120 and 360 µmol/L (2-6 mg/dL) before, during, and after pregnancy [1, 7, 19, 23, 30, 32]. The regimen may include a Phe-adjusted diet and/or pharmacological therapy. Maternal blood Phe should be followed closely especially during critical time periods of organogenesis [30]. Monitoring body weight and caloric intake changes are also critical in preventing of catabolic states which might increase Phe levels and impair metabolic control [36]. It is recommended that total weight gain is maintained in the range of 2 kg during the first trimester and 0.5 kg/week during the second and third trimester [36].

While neither FDA approved nor contraindicated, pegvaliase and sapropterin dihydrochloride may be considered during pregnancy only after assessing benefits and risks [20, 38]. Among metabolic specialists, the teratogenic risk of uncontrolled maternal PKU far outweighs the unknown risk to the fetus. While there is a paucity of data regarding the use of sapropterin or pegvaliase

during pregnancy, neither medication is known to cause anatomic defects in the fetus. More data is needed to assess long-term cognitive, behavioral, and neurodevelopmental outcomes in children exposed to these medications in utero [38-40].

According to the American Academy of Pediatrics, all women with PKU before and after conception should have access to genetic counseling [30]. Mothers should be counseled about the risks to the fetus. Maternal PKU patients should also be offered anatomy scans, fetal growth scans, and fetal echocardiography to detect fetal abnormalities [30]. Along with the above recommendations, the American College of Obstetricians and Gynecologists also recommends that a maternal fetal medicine specialist is involved in the care of these patients [32].

11. Novel Therapies

In addition to cofactor therapies like sapropterin and enzyme replacement therapies like pegvaliase, multiple other methods to lower blood Phe are currently being researched. Other novel therapies that are under investigation include other cofactor and enzyme therapies, gene editing, gene therapy, microbe therapy, mRNA therapy, and red blood cell therapy.

Sepiapterin, also known as PTC923, is an oral drug that is a natural precursor of BH4 which has a higher capacity to enter cells than the current therapy, sapropterin [5]. In clinical trials, sepiapterin has been shown to be significantly more effective than sapropterin in reducing blood Phe [41]. CDX-6114 is a modification of the orally administered enzyme phenylalanine ammonia lyase (PAL) that converts Phe in the gastrointestinal tract to ammonia and cinnamic acid. Clinical trials have shown the potential of CDX-6114 to benefit patients with PKU by removing Phe from protein in the gastrointestinal tract before it is absorbed, thereby lowering blood Phe [42].

Phenylalanine hydroxylate (PAH) stabilizers have also been developed that stabilize the mutant PAH molecule into the active tetrameric form [43]. This protein stabilization leads to an increase in active PAH protein and lowers blood Phe in murine models [43]. PAH stabilizers, designed for convenient oral administration, have not been investigated in the setting of a clinical trial [43].

Gene correction therapy using CRISPR–Cas-associated base editors, which enable existing genes to be removed and/or new ones added, has shown to be effective in providing sufficient PAH activity (>20% of normal) in mice to restore physiological blood Phe concentrations [5]. When CRISPR technology and mRNA were delivered into mice via lipid nanoparticles to correct PAH gene variants, blood Phe normalized within 48 hours [44].

Gene therapy in mice has also been achieved using adeno-associated viruses (AAVs) and lentiviruses. AAVs, either designed for in vivo editing or gene transfer, have been shown to increase PAH activity in mice [5, 45]. AAVs have the added benefit of not integrating into the host genome and limit the potential for insertional mutagenesis [5]. However, the lack of genomic integration can result in loss of efficacy over time and the viral vector also induces an immune response, preventing the possibility of re-administration [5]. There is one active clinical trial, NCT04480567, studying the effect of adenoviruses in PKU patients [46]. Lentiviral gene therapy allows for genomic integration of the PAH gene, providing a stable source of enzyme [5]. All patients can receive this treatment since there is no pre-existing immunity to lentiviral vectors [5]. However, the possibility of insertional mutagenesis causing leukemia is a serious concern [5]. American Gene Technologies is a company that is currently developing gene therapy for PKU using a lentivirus [47].

SYNB1618 is an investigational oral drug being evaluated for the treatment of PKU. SYNB1618 is a genetically modified probiotic involving the Escherichia coli Nissle strain that can metabolize Phe in the gut after oral administration [48]. SYNB1618 was designed to be co-administered with a second strain (SYNB1934) with enhanced activity of phenylalanine ammonia lyase [46]. Recently data from a clinical trial show that treatment with both strains resulted in significant reductions in plasma blood Phe in patients with PKU [48].

The pharmaceutical company Moderna is currently developing an mRNA treatment for PKU. The mRNA therapy would deliver messenger RNAs encoding PAH to liver cells, using lipid nanoparticles, so the body can temporarily produce the PAH enzyme [5]. The benefit of mRNA therapy is that it would prevent an immune response, but it would have to be administered frequently [5]. Animal studies in methylmalonic acidemia, arginase deficiency, citrin deficiency, acute intermittent porphyria, Fabry disease, and galactosemia have demonstrated efficacy of this approach [5]. Currently, this therapy is at the investigational stage and has not yet been studied in a clinical trial [49].

Engineered red blood cells expressing phenylalanine ammonia lyase have also been investigated. In mice, it was shown that mature red blood cells loaded with phenylalanine ammonia lyase and then transfused to a murine model of PKU reduced Phe concentrations [5, 50]. A clinical trial was underway in 2019 but has since been discontinued by the sponsor [51].

12. Conclusion

Since it is well known that diagnosing and treating PKU early lowers morbidity, everyone should have access to testing and treatments. Unfortunately, newborn screening and therapies for PKU are not available worldwide. Screening for PKU during the immigration process from countries without a universal screening program may be one solution. Providing cost-effective screening technology to developing nations is another solution. If tandem mass spectrometry is not available, then the older but reliable methods to screen for PKU could be used in these countries. Phe-free metabolic formulas, low protein medical foods, and medications to treat PKU should become more accessible in developing nations as well. In the more industrialized countries, the availability of screening and treatments for PKU is not an issue. However, significantly protein restricting one's diet and/or taking metabolic formula and medications to control blood Phe over an affected individual's lifetime has become a necessary inconvenience. Application of novel therapies that can efficiently lower blood Phe or even cure the disease can ease this burden.

PKU is not yet curable, but it is treatable. A PKU-affected individual can be treated with a Phe-restricted diet and/or medications. Since the days of Dr. Fölling, the diagnosis and management of PKU have come a long way. Hopefully, novel treatments will become available soon so that PKU ultimately becomes a curable metabolic disorder.

Author Contributions

Nicole A. Bailey: Concept, design, method, writing of complete manuscript, critical review for important intellectual content. Laura Mackay: Contribution of writing of manuscript, critical review for important intellectual content.

Funding

No funding was secured for this study.

Competing Interests

There are no competing interests to declare.

Reference

1. Elhawary NA, AlJahdali IA, Abumansour IS, Elhawary EN, Gaboon N, Dandini M, et al. Genetic etiology and clinical challenges of phenylketonuria. Hum Genom. 2022; 16: 22.
2. Centerwall SA, Centerwall WR. The discovery of phenylketonuria: The story of a young couple, two retarded children, and a scientist. Pediatrics. 2000; 105: 89-103.
3. Hillert A, Anikster Y, Belanger-Quintana A, Burlina A, Burton BK, Carducci C, et al. The genetic landscape and epidemiology of phenylketonuria. Am J Hum Genet. 2020; 107: 234-250.
4. Sumaily KM, Mujamammi AH. Phenylketonuria: A new look at an old topic, advances in laboratory diagnosis, and therapeutic strategies. Int J Health Sci. 2017; 11: 63-70.
5. van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria. Nat Rev Dis Primers. 2021; 7: 36.
6. Opladen T, López-Laso E, Cortès-Saladelafont E, Pearson TS, Sivri HS, Yildiz Y, et al. Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH_4) deficiencies. Orphanet J Rare Dis. 2020; 15: 126. Erratum in: Orphanet J Rare Dis. 2020; 15: 202.
7. Rovelli V, Longo N. Phenylketonuria and the brain. Mol Genet Metab. 2023; 139: 107583.
8. Hopf S, Nowak C, Hennermann JB, Schmidtmann I, Pfeiffer N, Pitz S. Saccadic reaction time and ocular findings in phenylketonuria. Orphanet J Rare Dis. 2020; 15: 124.
9. Rosini F, Rufa A, Monti L, Tirelli L, Federico A. Adult-onset phenylketonuria revealed by acute reversible dementia, prosopagnosia and parkinsonism. J Neurol. 2014; 261: 2446-2448.
10. van Wegberg AM, Trefz F, Gizewska M, Ahmed S, Chabraoui L, Zaki MS, et al. Undiagnosed phenylketonuria can exist everywhere: Results from an international survey. J Pediatr. 2021; 239: 231-234.
11. Jaulent P, Charriere S, Feillet F, Douillard C, Fouilhoux A, Thobois S. Neurological manifestations in adults with phenylketonuria: New cases and review of the literature. J Neurol. 2020; 267: 531-542.
12. Bilder DA, Noel JK, Baker ER, Irish W, Chen Y, Merilainen MJ, et al. Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria. Dev Neuropsychol. 2016; 41: 245-260.
13. Jahja R, van Spronsen FJ, De Sonneville LM, van der Meere JJ, Bosch AM, Hollak CE, et al. Long-term follow-up of cognition and mental health in adult phenylketonuria: A PKU-COBESO study. Behav Genet. 2017; 47: 486-497.
14. Arnold GL. Newborn screening for inborn errors of metabolism. OBM Genet. 2023; 7: 197.
15. Al-Bari AA. Current scenario and future direction of newborn screening and management program for phenylketonuria in Bangladesh. J Inborn Errors Metab Screen. 2022; 10: e20210024.
16. Borrajo GJ. Newborn screening for phenylketonuria: Latin American consensus guidelines. J Inborn Errors Metab Screen. 2016; 4: e160034.

17. Wilaiwongsathien K, Wattanasirichaigoon D, Rattanasiri S, Aonnuam C, Tangshewinsirikul C, Tim-Aroon T. Parental awareness, knowledge, and attitudes regarding current and future newborn bloodspot screening: The first report from Thailand. Int J Neonatal Screen. 2023; 9: 25.
18. Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, et al. Current status of newborn screening worldwide: 2015. Semin Perinatol. 2015; 39: 171-187.
19. Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, Frazier DM, et al. Phenylalanine hydroxylase deficiency: Diagnosis and management guideline. Genet Med. 2014; 16: 188-200.
20. Camp KM, Parisi MA, Acosta PB, Berry GT, Bilder DA, Blau N, et al. Phenylketonuria scientific review conference: State of the science and future research needs. Mol Genet Metab. 2014; 112: 87-122.
21. Peng D, Ganye Z, Gege S, Yanjie X, Ning L, Xiangdong K. Clinical application of non-invasive prenatal diagnosis of phenylketonuria based on haplotypes via paired-end molecular tags and weighting algorithm. BMC Med Genom. 2021; 14: 294.
22. Duan H, Liu N, Zhao Z, Liu Y, Wang Y, Li Z, et al. Non-invasive prenatal testing of pregnancies at risk for phenylketonuria. Arch Dis Child. 2019; 104: F24-F29.
23. Singh RH, Rohr F, Frazier D, Cunningham A, Mofidi S, Ogata B, et al. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. Genet Med. 2014; 16: 121-131.
24. MacDonald A, van Wegberg AM, Ahring K, Beblo S, Bélanger-Quintana A, Burlina A, et al. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis. 2020; 15: 171.
25. Kalvala J, Chong L, Chadborn N, Ojha S. Breast feeding in infants diagnosed with phenylketonuria (PKU): A scoping review. BMJ Paediatr Open. 2023; 7: e002066.
26. Somaraju UR, Merrin M. Sapropterin dihydrochloride for phenylketonuria. Cochrane Database Syst Rev. 2015. doi: 10.1002/14651858.CD008005.pub4.
27. Scala I, Brodosi L, Rovelli V, Noto D, Burlina A. Management of patients with phenylketonuria (PKU) under enzyme replacement therapy: An Italian model (expert opinion). Mol Genet Metab Rep. 2024; 39: 101065.
28. Jurecki ER, Cederbaum S, Kopesky J, Perry K, Rohr F, Sanchez-Valle A, et al. Adherence to clinic recommendations among patients with phenylketonuria in the United States. Mol Genet Metab. 2017; 120: 190-197.
29. Van Wegberg AM, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet J Rare Dis. 2017; 12: 162.
30. Committee on Genetics. Maternal phenylketonuria. Pediatrics. 2008; 122: 445-449.
31. Ugalde-Abiega B, Stanescu S, Belanger A, Martinez-Pardo M, Arrieta F. New challenges in management of phenylketonuria in pregnancy: A case report. J Med Case Rep. 2023; 17: 465.
32. Rink B, Dukhovny S, Timofrev J. Management of women with phenylalanine hydroxylase deficiency (phenylketonuria) ACOG Committee Opinion, Number 802. Obstet Gynecol. 2020; 135: E167-E170.
33. Levy HL. Historical background for the maternal PKU syndrome. Pediatrics. 2003; 112: 1516-1518.
34. Lenke RR, Levy HL. Maternal phenylketonuria and hyperphenylalaninemia. An international survey of the outcome of untreated and treated pregnancies. N Engl J Med. 1980; 303: 1202-1208.

35. Koch R, Friedman E, Azen C, Hanley W, Levy H, Matalon R, et al. The international collaborative study of maternal phenylketonuria: Status report 1998. Eur J Pediatr. 2000; 159: S156-S160.
36. Caletti MT, Bettocchi I, Baronio F, Brodosi L, Cataldi S, Petroni ML, et al. Maternal PKU: Defining phenylalanine tolerance and its variation during pregnancy, according to genetic background. Nutr Metab Cardiovasc Dis. 2020; 30: 977-983.
37. Teissier R, Nowak E, Assoun M, Mention K, Cano A, Fouilhoux A, et al. Maternal phenylketonuria: Low phenylalaninemia might increase the risk of intra uterine growth retardation. J Inherit Metab Dis. 2012; 35: 993-999.
38. Feillet F, Ficicioglu C, Lagler FB, Longo N, Muntau AC, Burlina A, et al. Efficacy and safety of sapropterin before and during pregnancy: Final analysis of the Kuvan® Adult Maternal Paediatric European Registry (KAMPER) maternal and phenylketonuria developmental outcomes and Safety (PKUDOS) PKU-MOMs sub-registries. J Inherit Metab Dis. 2024; 47: 636-650.
39. Bier C, Dickey K, Bibb B, Crutcher A, Sponberg R, Chang R, et al. Outcomes in 14 live births resulting from Pegvaliase-treated pregnancies in PKU-affected females. Mol Genet Metab. 2024; 141: 108152.
40. Boyer M, Skaar J, Sowa M, Tureson JR, Chapel-Crespo CC, Chang R. Continuation of pegvaliase treatment during pregnancy: A case report. Mol Genet Metab Rep. 2021; 26: 100713.
41. Bratkovic D, Margvelashvili L, Tchan MC, Nisbet J, Smith N. PTC923 (sepiapterin) lowers elevated blood phenylalanine in subjects with phenylketonuria: A phase 2 randomized, multi-center, three-period crossover, open-label, active controlled, all-comers study. Metabolism. 2022; 128: 155116.
42. Fazio TN, Healy L, Heise T, Inwood A, Manolikos C, Rahman Y, et al. Pharmacodynamics, safety, tolerability and pharmacokinetics of a single oral dose of an engineered phenylalanine ammonia-lyase in patients with phenylketonuria. Mol Genet Metab Rep. 2023; 37: 101012.
43. Agios. Connected through the science of cellular metabolism [Internet]. Cambridge, MA: Agios Pharmaceuticals, Inc.; [cited date 2024 March 29]. Available from: https://agios.com/rare-diseases/our-science/.
44. Brooks DL, Whittaker MN, Said H, Dwivedi G, Qu P, Musunuru K, et al. A base editing strategy using mRNA-LNPs for in vivo correction of the most frequent phenylketonuria variant. Hum Genet Genom Adv. 2024; 5: 100253.
45. Brooks DL, Whittaker MN, Qu P, Musunuru K, Ahrens-Nicklas RC, Wang X. Efficient in vivo prime editing corrects the most frequent phenylketonuria variant, associated with high unmet medical need. Am J Hum Genet. 2023; 110: 2003-2014.
46. National Library of Medicine. AAV gene therapy study for subjects with PKU [Internet]. Bethesda, MD: National Library of Medicine; 2021 [cited date 2024 March 29]. Available from: https://clinicaltrials.gov/study/NCT04480567.
47. American Gene Technologies. Phenylketonuria (PKU) Cure Program [Internet]. Rockville, MD: American Gene Technologies; [cited date 2024 March 29]. Available from: https://www.americangene.com/pipeline/phenylketonuria-pku/.
48. Vockley J, Sondheimer N, Puurunen M, Diaz GA, Ginevic I, Grange DK, et al. Efficacy and safety of a synthetic biotic for treatment of phenylketonuria: A phase 2 clinical trial. Nat Metab. 2023; 5: 1685-1690.
49. Moderna. Research-mRNA pipeline [Internet]. Cambridge, MA: Moderna; [cited date 2024 Aug 15]. Available from: https://www.modernatx.com/en-US/research/product-pipeline.

50. Rossi L, Pierigè F, Carducci C, Gabucci C, Pascucci T, Canonico B, et al. Erythrocyte-mediated delivery of phenylalanine ammonia lyase for the treatment of phenylketonuria in BTBR-Pahenu2 mice. J Control Release. 2014; 194: 37-44.
51. Rossi L, Pierigè F, Aliano MP, Magnani M. Ongoing developments and clinical progress in drug-loaded red blood cell technologies. BioDrugs. 2020; 34: 265-272.