Review

Journal of Inborn Errors of Metabolism & Screening
2017, Volume 5: 1–9
© The Author(s) 2017
DOI: 10.1177/2326409817733015
journals.sagepub.com/home/iem
SAGE

Strategies for Successful Long-Term Engagement of Adults With Phenylalanine Hydroxylase Deficiency Returning to the Clinic

Janet Thomas, MD[1], Mina Nguyen-Driver, PsyD[2], Heather Bausell, RD, LDN[3], Jane Breck, MD[4], Javier Zambrano, MD[5], and Vanessa Birardi, PharmD[5]

Abstract

Nearly half of all patients diagnosed with phenylalanine hydroxylase (PAH) deficiency, also known as phenylketonuria, are lost to follow-up (LTFU); most are adults who stopped attending clinic after the age of 18 years. To understand why adult patients with PAH deficiency disengage from their clinic, a focus group of 8 adults with PAH deficiency who had been LTFU for 2 or more years was held in March 2016. Ten clinicians observed the focus group and discussed strategies for successfully reengaging adult patients and encouraging lifelong management of PAH deficiency. Four strategies were proposed: (1) create a safe, supportive environment, (2) acknowledge patients as partners in their care, (3) develop individualized management plans, and (4) provide patients with additional resources. These strategies provide a framework to motivate change in clinical practice to meet the unique needs of adults with PAH deficiency.

Keywords

phenylalanine hydroxylase deficiency, phenylketonuria, metabolic clinic, patient outcomes, management, rare disease

Introduction

Phenylalanine hydroxylase (PAH) deficiency, also known as phenylketonuria (PKU), results in a defect in the metabolism of phenylalanine (Phe) to tyrosine due to mutations of the phenylalanine hydroxylase (*PAH*) gene with consequent reduced enzyme activity.[1,2] Early diagnosis and lifelong management are critical because without dietary or therapeutic intervention, plasma and brain Phe levels can become elevated and have neurotoxic effects, leading to severe intellectual disability.[3] PAH deficiency presents along a spectrum of severity and is associated with a range of neurocognitive and psychological symptoms, many of which can become evident even following early treatment with compromised blood Phe control. These include impairments in memory and the ability to plan and organize, decreased behavioral inhibition, depression, anxiety, and reduced IQ.[1,4-7] Symptoms related to elevated Phe and comorbid conditions can create barriers to developing interpersonal relationships and reduce the overall quality of life, creating significant social, psychological, and work-related challenges. Women with PAH deficiency are at risk of developing maternal PKU syndrome, which results in congenital abnormalities due to the teratogenic effects of elevated maternal Phe levels on the developing fetus.[1,3]

Treatment of PAH deficiency to decrease blood Phe levels can improve symptoms in children and adults.[8] Management of PAH deficiency is focused on reducing the blood Phe concentration to a target treatment range of 120 to 360 µmol/L (2-6 mg/dL) with a Phe-restricted diet, supplemented with medical foods including amino acid–based medical foods or

[1] University of Colorado School of Medicine, Aurora, CO, USA
[2] Oregon Health & Science University, Portland, OR, USA
[3] Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
[4] Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA
[5] BioMarin Pharmaceutical Inc, Novato, CA, USA

Received May 10, 2017, and in revised form July 26, 2017. Accepted for publication August 22, 2017.

Corresponding Author:
Vanessa Birardi, 105 Digital Drive, Novato, CA 94949, USA.
Email: vanessa.birardi@bmrn.com

glycomacropeptide (GMP)–based medical foods (amino acid mixtures) and modified low-protein foods, and pharmacotherapy with sapropterin dihydrochloride (Kuvan; BioMarin Pharmaceutical Inc, Novato, CA, USA).[1,9] Sapropterin dihydrochloride is a pharmaceutical form of the cofactor tetrahydrobiopterin (BH_4), which increases residual PAH activity in patients with BH_4-responsive PKU.[9]

There is clear evidence of loss of management adherence with age.[10-15] Encouraging patients with PAH deficiency to learn how to independently manage their diet and treatment during childhood prepares them to continue to do so during the transition into adulthood.[1] A support system consisting of family and friends can also contribute to successful management of PAH deficiency throughout life. Although most patients with PAH deficiency routinely visit a clinic throughout childhood, many adults become lost to follow-up (LTFU) due to a combination of individual, social, and economic factors, as recently reviewed.[12,16] Individuals with PAH deficiency are considered to be LTFU when they have been out of contact with a clinic for at least 2 years. In the United States, of the estimated 15,000 individuals diagnosed with PAH deficiency based on newborn screening between 1965 and 2010, approximately 48% are currently engaged with a PKU clinic and an estimated 52% are LTFU.[16] As a result of early treatment discontinuation that was common several decades ago,[16,17] many LTFU adults with PAH deficiency are now aged 40 years or older and may not be aware of the recommendation for PAH deficiency to be managed for life.[1]

The neurocognitive deficits associated with elevated Phe levels place a significant burden on patients with PAH deficiency as they try to adhere to a Phe-restricted diet.[16] Treatment adherence is particularly difficult for individuals who have disengaged from clinic and do not have the support of an interdisciplinary therapeutic team.[10] Despite improvements in symptoms while on a Phe-restricted diet, many patients describe a negative effect on quality of life,[8,13,18,19] and several studies report that diet compliance worsens as patients become teenagers and adults.[13,14]

Patients who are LTFU may be unaware that social and work problems and symptoms like depression and anxiety may be related to elevated Phe, and that returning to treatment may improve neurocognitive and psychological symptoms. Many patients may not even recognize that they are experiencing symptoms. Women with PAH deficiency who are planning to have children may not be aware of the negative effects of elevated Phe on fetal development, or they may be aware of the fetal effects and think that pregnancy is not an option for them. Because a large proportion of adult patients with PAH deficiency become LTFU, helping these individuals return to clinic and achieve lifelong management of PAH deficiency is a critical undertaking that presents a significant challenge.[1,6,8]

Aims

The aims of the current study were to better understand why adults with PAH deficiency disengage from clinic, what prompted them to reengage with a clinic, and how to encourage them to continue with lifelong management.

Table 1. Characteristics of Focus Group Participants.

Participant	Age, years	Gender	Visited Metabolic Clinic in Last 2 Years	Length of Time Away from Clinic
1	26	Male	Yes	7.5 years
2	30	Male	Yes	2+ years
3	48	Male	Yes	40 years
4	41	Female	Yes	10 years
5	36	Male	Yes	8 years
6	45	Female	No	5 years
7	26	Male	No	3 years
8	38	Female	Yes	6 years

Methods

A professionally facilitated patient focus group was held in March 2016. Recruitment for the focus group used social media and e-mail invitations sent to distribution lists from BioMarin and the National PKU Alliance to identify adults with PAH deficiency aged $\geq$18 years who had been LTFU for at least 2 years and who were not part of a clinical trial or recent market research. Eight individuals, with an average age of 36 years, participated in the focus group; of these, 6 had reengaged with a clinic and 2 had not (Table 1). The average time away from the clinic was approximately 10 years.

Ten clinicians observed the patient focus group discussion and participated in an advisory session immediately afterward. Nominations of clinicians to participate in the advisory session were solicited by BioMarin. The nominees were selected based on their experience in the management of adult patients with PAH deficiency. Nominees were invited to participate in the focus group observation and advisory session, with the goal of assembling a group of clinicians that represented various clinical settings and fields of expertise. Participating clinicians included 4 dietitians, 2 neurologists, 1 neuropsychologist, 2 biochemical geneticists, and 1 genetics nurse practitioner. The goals of the advisory session were to discuss key insights that emerged from the focus group and to develop a set of strategies for successfully reengaging LTFU adults with PAH deficiency with their clinic long-term. The issues discussed and the list of questions asked during the focus group are provided in the Supplementary Materials.

Results

Reasons for Disengagement From the Metabolic Clinic and PAH Deficiency Management

The focus group participants listed several reasons for their disengagement from the metabolic clinic (Table 2). Several participants shared a sense of abandonment or a perceived lack

Table 2. Reasons for Disengagement From the Metabolic Clinic.

Did not fully understand the practical impact of poor Phe control
Unaware of guideline recommendations to continue PAH deficiency management for life
Desire to feel "normal" by ignoring the disorder and avoiding clinic visits
Uncomfortable being treated in pediatric clinics
Pediatric clinic did not accept adult patients/no referral process in place to an adult metabolic physician or clinic
Perceived or actual lack of insurance coverage
Difficulty navigating the logistics of insurance coverage
Fear of being judged by clinicians for allowing treatment to lapse
Restrictiveness, palatability of the recommended diet
High cost of medical foods
Frequency/fear of blood testing

Abbreviations: Phe, phenylalanine; PAH, phenylalanine hydroxylase.

of support by clinicians after they had turned 18. The majority agreed it is challenging to get attention from clinics as adults unless pregnancy is a consideration, especially after a period of disengagement.

Perceived or actual lack of insurance coverage was an issue as several participants reported that their insurance providers refused to reimburse medical foods or treatment for PAH deficiency after the age of 18 years. Inadequate insurance coverage for medical foods, as well as the expense of co-pays and deductibles associated with clinic visits and lab tests, presented significant obstacles to continued management of PAH deficiency beyond childhood.

Focus group participants also described a lack of perceived value of clinic visits beyond routine assessments and expressed apathy toward independent management of PAH deficiency. Some stopped going to clinic when they departed for college or moved away from their clinic. For many participants, their parents had played a primary role in managing PAH deficiency and ensuring adherence to the diet during childhood. Consequently, these participants felt unprepared to continue treatment as adults in different environments and social situations. Participants recognized the need for greater support from family members and significant others to help manage PAH deficiency during adulthood.

Reasons for Reengagement With the Metabolic Clinic and PAH Deficiency Management

Participants returned to a metabolic clinic to search for information about new treatments, to find help with management of PAH deficiency, or to improve management of PAH deficiency during or in preparation for pregnancy. Some had acquired health insurance or had improved health-care coverage, making it affordable to return to clinic. Although some patients returned to clinic because they or their family members were concerned about the neurocognitive and psychological symptoms of PAH deficiency, other patients realized the association between their symptoms and elevated Phe only after they had reengaged with a clinic and reduced their Phe levels. Participants reported developing discomfort with the feelings and behaviors that occur when Phe levels are high and expressed fear about the potential long-term negative consequences of high Phe levels.

Table 3. Strategies for Reengaging Adults in Lifelong Management of PAH Deficiency.

1. Create a safe, supportive environment
   - Emphasize that it is never too late to resume treatment
   - Acknowledge the patient's decision to return to clinic for treatment
   - Remind patients that changes in symptoms will take time
   - Acknowledge any improvements in symptoms to keep patients motivated
2. Partner with patients
   - Use motivational interviewing to help patients clarify their needs and goals
   - Develop treatment plans with input from patients
   - Set patients' expectations on their role and the clinic's role in management
   - Set patients' expectations about returning to treatment as a process, and explain that change may not happen quickly
3. Develop and implement individualized solutions
   - Ask patients open-ended questions about feelings and function
   - Develop personalized management strategies based on patient needs and goals
   - Refer to the ACMG practice guidelines
   - Use the teach-back approach to confirm that patients understand their treatment plan
4. Provide additional support and resources
   - Maintain regular contact between clinic visits
   - Provide take-home resources to reinforce key concepts discussed in the clinic
   - Connect patients to outside support groups
   - Refer patients for neuropsychological support
   - Direct patients to clinical and financial support services and information

Abbreviation: ACMG, American College of Medical Genetics and Genomics; PAH, phenylalanine hydroxylase.

Strategies for Successful Long-Term Engagement of Adult Patients With PAH Deficiency

After observing the focus group discussion, the clinician advisors discussed specific strategies and clinical considerations for supporting adults with PAH deficiency who were LTFU and returned to clinic. The strategies listed in Table 3, supported by the peer-reviewed literature and clinical experiences of the advisory board members, are presented as a framework to motivate change in clinical practice to meet the unique needs of adult patients and encourage lifelong management of PAH deficiency and engagement with a metabolic clinic. Although all of these strategies aim to encourage adult patients with PAH deficiency to remain engaged with their care, individual clinics have different structures and available resources, making certain approaches more feasible than others.

Create a safe, supportive environment. It is important to create a judgment-free clinic environment.[20] Letting patients know how

important it is that they have reengaged with the clinic and acknowledging the challenges associated with managing PAH deficiency, in addition to all of their other competing priorities and responsibilities, can help patients perceive the clinic as a safe and supportive environment.[21] Adult patients may experience a range of emotions, including fear, grief, anger, denial, apathy, pressure, and even a sense of loss, and it is important to acknowledge these feelings. In addition, patients may feel overwhelmed by the number of providers they see and the volume of information received or they may feel defeated by negative feedback from providers about Phe levels outside of the target range or lack of compliance with previous treatment recommendations. Emphasize that it is never too late to start managing Phe levels, as many patients who resume therapy after discontinuation experience an improvement in symptoms as a result of their reduced Phe levels.[1] It may be helpful to remind patients that changes in symptoms may take time or in some cases, others may notice a change before the patient. Any improvement in disease management or symptoms should be acknowledged to keep patients motivated and engaged.

Partner with patients. Involving patients as partners in their own care and establishing a personal connection can occur as soon as the first visit. Patients and providers should strive to reach concordance about their care, that is, an agreement regarding the strategy of care that takes the patient's wishes and goals into account.[10,12] Motivational interviewing[22]—which involves asking patients open-ended questions about their motivations for reengaging with the clinic and restarting treatment—can help start a dialogue that will provide insight into patients' readiness to change their behavior and adhere to a lifelong management plan. Motivational interviewing can be used to guide patients as they work through feelings of ambivalence about returning to the clinic and resolve these feelings internally with encouragement from the provider, rather than in response to external directives or instructions from the provider.[23,24] It also encourages accountability for patients to adhere to the plan that they developed in partnership with their provider. Partnering with patients includes setting expectations for the patient's role and the clinic's role in management. For example, a patient might pledge to collect blood samples for measuring Phe levels on a twice-monthly basis, while the clinic agrees to provide weekly telephone follow-up on the Phe level results.

Develop and implement individualized solutions. Taking into account each patient's individual needs and lifestyle can help identify barriers to care.[1,10,25] Asking patients nonthreatening, probing, open-ended questions about how they are feeling and their level of function[20] and providing examples can help elicit meaningful responses,[10,20] as patients may have difficulty articulating their feelings or functional ability. Using a conversational approach can help establish a relationship between the clinician and patient.[26,27] The list of topics and questions in Tables 4 and 5 can help guide the discussion.

Another way to facilitate discussion is to use questionnaires adapted from existing tools or developed to fit the specific clinic's needs. Examples include the Profile of Mood States 2 (POMS 2) instrument (Multi-Health Systems Inc, North Tonawonda, NY, USA), which is used to assess mood states of individuals aged $\geq$13 years,[28] and the Brief Mental Status Exam, a cross-sectional tool for assessing multiple aspects of patient status, from mood to executive functioning.[29] The POMS instrument was recently modified for use specifically for patients with PAH deficiency (PKU-POMS).[30] Current guidelines for the management of PAH deficiency[1] recommend the Beck Depression Inventory II and Beck Anxiety Inventory, as well as the Adaptive Behavior Assessment System 3,[31] for psychological testing of adults. Ideally, patient answers to questionnaires should be discussed face-to-face to check that the written answers accurately reflect the patient's feelings and function.

Information from the feelings and function assessments can be combined with an assessment of current management approaches to implement individualized solutions that address a patient's specific needs and goals. Practical planning tools, such as calendars or reminder systems, may be helpful. For example, a patient with the goal to improve the Phe control that has identified difficulty in remembering tasks may be

Table 4. Discussion Topics and Potential Questions for Assessing Feelings.

Topics	Potential Questions
• Anxiety	• Did you feel anxious before coming to the clinic today? • How often do you feel nervous or worried? • How does feeling nervous or worried affect your daily life? • What makes you feel anxious?
• Depression	• Do you take any medications for depression? • How often do you feel down or sad?
• Stress	• How often do you feel stressed? What do you think is causing you to feel stress? • How often do you have headaches? What do you think is causing the headaches? • How are you sleeping? When was the last time you had a nightmare?
• Difficulty concentrating	• Do you find yourself having a hard time focusing on a task? What is most challenging about having a conversation?
• Irritability/moodiness	• How often do you lose your temper? Give me an example of when you have lost your temper. • Would you describe yourself as moody or irritable? What things do other people say or do that make you upset?
• Fear	• How often have you felt afraid? What makes you feel that way? • Do you avoid going to certain places? Describe a situation where you avoided going somewhere.
• Desire for normalcy	• How is your life different because of PKU? How does this make you feel?

Table 5. Discussion Topics and Potential Questions for Assessing Function.

Topics	Potential Questions
• Following through with tasks • Completing sequential tasks	• Tell me about your hobbies. • How difficult do you find tasks like managing your bank account or keeping track of schoolwork?
• Decision-making skills • Success at school, college completion	• What do you like most about college? What is the most difficult part of college?
• Ability to learn new things • Ability to transition/comfort with change	
• Challenges with memory	• How often do you lose or forget things?
• Focusing or sustaining attention for an extended period of time	• Do you like to read? Have you read any interesting books lately?
• Driving ability	• How do you commute to work or school? • Do you frequently get lost while driving?
• Holding a job	• What type of job would you like to have? • What do you like most about your job? What do you like least? • What are your job goals?
• Relationships with friends, family, spouse, and children	• Are you married? Divorced? Are you or have you been in an extended relationship? • Are you able to maintain long-term friendships? • What are some things you like to do with friends? • How many close friends do you have?
• Barriers to attending clinic	• Are you able to easily get to and from your clinic visits? • Are there things you dislike about coming to the clinic? • Is it difficult to stay on your treatment plan? How does this make you feel? • How do you feel about providing blood samples? Do you have a fear of needles?

willing to set up automated e-mail or text message reminders to submit blood spots periodically and before scheduled appointments. Patients who find it a burden to record the 3-day dietary Phe intake in diaries prior to clinic visits may be able to provide pictures of their food instead or use online websites to record Phe or protein intake.

For many patients, repetition and consistency are critical when discussing PAH deficiency and management, and a teach-back approach can confirm the patient understands what has been discussed and is prepared to be an active partner in his or her own plan of care.[20,32]

Approaches to the dietary management and treatment of PAH deficiency change over time based on new research discoveries and advances in medicine and may be different from the approaches that patients used when they were last engaged with a clinic. The latest and previous guidelines recommend that management of PAH deficiency be maintained throughout life[1,33] and that therapeutic approaches should be individualized to meet each patient's goals. In addition to dietary treatment approaches, clinicians should consider offering a trial of sapropterin dihydrochloride to patients,[1] even if past adherence to diet has not been demonstrated. Sapropterin dihydrochloride can help lower Phe in responsive patients, which can reduce symptoms and help them better manage PAH deficiency.[34]

When creating personalized solutions, consider patient lifestyle, comorbidities (including identification of the specific provider who is addressing these), level of daily activity, and insurance status. Flexibility in establishing Phe concentration targets based on the recommended range of 120 to 360 μmol/L (2-6 mg/dL), as well as establishing dietary protein targets and providing a selection of medical foods, special low-protein foods, and convenience formulas (ready to drink, bars, capsules, premeasured pouches, etc), may help patients feel empowered. Remind women of childbearing age that it is important to manage PAH deficiency; guidelines recommend that preconception Phe levels should be 120 to 360 μmol/L (2-6 mg/dL).[1]

Provide additional support and resources. Regular contact outside of scheduled visits can maintain engagement with patients.[35] Follow-up calls or e-mails after each clinic visit can help assess a patient's perspective on how helpful the clinic visit was, reinforce topics discussed, or answer any questions that may have arisen. Be sure to confirm the patient's desired frequency and preferred mode of communication (eg, contact directly or via a family member by phone, e-mail, or text) and identify other individuals who may be contacted if a patient is unreachable. Health Insurance Portability and Accountability Act forms will be needed to communicate with family members or caregivers. Some patients may require more intensive support during the initial months of returning to treatment, and others may benefit from attending clinic visits with a partner or a family member.[36]

Providing take-home resources can help reinforce concepts discussed during the clinic visit. Topics might include symptoms associated with high blood Phe levels, how to count protein and Phe in foods, how to collect and send blood samples for Phe testing, instructions for food preparation or prescribed medications, details about the different types of medical foods and special low-protein foods available, and tips for coping with and managing PAH deficiency. Consider providing materials in the format that best matches each patient's method of learning and level of health literacy, including printed materials, videos, and online resources (see Table 6).

Table 6. Resources and Support Groups for Patients With PAH Deficiency.

Canadian PKU and Allied Disorders (CANPKU)	http://www.canpku.org
The European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU)	http://www.espku.org
How Much Phe	http://www.howmuchphe.org
Mental health resources	https://www.cdc.gov/mentalhealth/ https://www.nimh.nih.gov/index.shtml
Mid-Atlantic Connection for PKU and Allied Disorders (MACPAD)	http://www.macpad.org/
National Organization for Rare Disorders	http://www.rarediseases.org
National PKU Alliance (NPKUA)	http://www.npkua.org
National PKU News	http://www.pkunews.org
NPKUA Adults With PKU Back to Care Program	http://www.adultswithpku.org/Back-to-Care
PKU Board	http://www.pkuboard.info
PKU Metabolic Diet app	www.metabolicdietapp.org

Abbreviations: Phe, phenylalanine; PAH, phenylalanine hydroxylase; PKU, phenylketonuria.

Patients may need support to cope with comorbidities. Psychiatric symptoms, including anxiety and agoraphobia,[1,37] can interfere with patients' ability to attend clinic, and poor inhibition skills can make it difficult to avoid certain foods. Certain patients may benefit from referral to a community health center, social worker, or behavioral therapist (particularly when a neuropsychologist is not part of the clinic staff) who can conduct neuropsychological assessments and help patients manage aspects of PAH deficiency beyond diet and treatment.[1,10,16,38] Because the impact of elevated Phe levels is not readily apparent, neurocognitive or neuropsychological assessments can help patients understand the connection between high Phe levels and symptoms, and the results of these assessments may motivate them to remain on treatment and keep Phe levels within target range.

It may help to provide patients with practical approaches and resources to overcome obstacles to treatment and management, including engaging their family and friends; connecting them to online groups and support blogs; providing information about national support and advocacy networks, as well as state and local support groups (Table 6); and introducing them to other adult patients or mentors with PAH deficiency. Also consider linking patients to clinical and financial support services and information; for example, information about medical foods and treatments that are covered by their insurance plan. Direct them to organizations that may be able to offer financial support, such as the National Organization for Rare Disorders or other 501(c)(3) organizations, formula manufacturers, and local and state PKU support groups. Hospital-based clinics may have a financial office or social worker who can help patients navigate insurance questions and find support.

Clinical Considerations to Support Adult Patients With PAH Deficiency in Their Return to Care

Consider developing a formal protocol for clinic visits for adults with PAH deficiency who have been LTFU and have returned to the clinic to restart treatment. It can also be helpful to have a team or referral process in place to provide comprehensive care.[39] Although patients can be optimally managed in any clinic with a physician/geneticist and a dietitian on staff,[10] a clinic team might also include a social worker, case manager, genetic counselor, and/or neuropsychologist. If a physician or geneticist is not part of the clinic, another prescribing provider (eg, a nurse practitioner) on the team may be required if medication prescriptions are needed. Smaller clinics can build mechanisms for referring patients to community clinics that can address patients' health needs outside of those provided by the metabolic clinic (eg, behavioral services, counseling, other management of comorbidities).[16] To ensure coordinated patient care, provide literature and resources to clinicians unfamiliar with PAH deficiency.

Discussion

Addressing the Unique Needs of Adult Patients With PAH Deficiency Who Have Been LTFU

Adult patients with PAH deficiency who were LTFU but have returned to the metabolic clinic represent a population with specific characteristics and needs. While the focus group was limited in size, many of the experiences shared by the participants were consistent with those reported in the literature.[1,25,40] Patients may struggle to adhere to a diet or treatment for lowering Phe because of underlying neurocognitive deficits, including poor planning and organizational skills, which may be caused by prolonged elevations of Phe.[1] Adults with PAH deficiency may find themselves trapped in a "cycle of decline" in which high Phe levels negatively affect executive function, thereby impairing their ability to adhere to the diet or treatment, schedule and attend clinic visits, or understand their insurance coverage, all of which can contribute to the ability to manage PAH deficiency successfully.[1,6,16,20,41] The presence of psychological issues, such as anxiety, depression, and phobias, can also interfere with adherence to treatment for PAH deficiency, in addition to reducing quality of life.[6,41]

Although many adult patients with PAH deficiency decide to return to care because they want to improve job performance or relationships by reducing symptoms related to high Phe levels,[10,20] other patients may not be aware of the connection between high Phe levels and symptoms or that reducing Phe levels can improve their symptoms. Patients returning to clinic may be particularly sensitive to clinicians' comments regarding perceptions of inadequacy of care while they were out of clinic. Patients may be concerned about how clinicians will react to a history of poor adherence to diet, failure to maintain Phe levels within the target range, poor compliance with Phe monitoring,

attending clinic less frequently than recommended, and/or poor management of comorbidities during the time they were LTFU. It is important to emphasize to patients that it is never too late to return to treatment and that once they do, they will begin to see improvements in their symptoms.

Development of personalized management plans, created in partnership with the patient and which take into account the patient's specific needs and challenges, can help encourage adult patients with PAH deficiency to stay engaged. Motivational interviewing with open-ended and nonjudgmental questions to help patients identify their own treatment needs and goals can be particularly useful. Phone-based motivational interviewing has been shown to improve feelings of self-efficacy in patients with PAH deficiency (N = 31, age 7-35 years),[24] and motivational interviewing in various settings has been shown to improve treatment adherence and self-management behaviors across multiple chronic diseases.[23,42] It is important to note, however, that motivational interviewing may be challenging for adult patients with PKU who have high Phe levels and may not be aware of the effect on their functioning; these patients may benefit from repeated follow-up visits with resources and educational materials provided to support a gradual understanding of their functioning.

Despite their willingness to return to clinic, many patients may be unprepared to independently manage PAH deficiency as adults.[40] They may have entered adulthood with a lack of coping skills, an inability to prepare meals or medical foods, and inadequate education about PAH deficiency and its treatment. Adults who have been LTFU may also be unaware of their options for insurance coverage or other forms of support for managing PAH deficiency. Patients may benefit from learning specific practical coping skills for how to manage PAH deficiency. Adults with PAH deficiency returning to the metabolic clinic also present with a variety of past management experiences and differences in the length of time they have been away from clinic. They may benefit from education on the basics of PAH deficiency and also on new approaches and treatment options for managing the disorder.

The teach-back method has been shown to improve disease understanding, adherence, self-efficacy, and self-care skills in patients with chronic diseases[32] and may be particularly helpful for adult patients with PKU who have returned to clinic after being LTFU, as they may be experiencing neurocognitive symptoms related to elevated Phe. Using this approach, providers can immediately gauge the level of understanding patients have regarding PAH deficiency itself, their specific treatment plan, insurance coverage issues, and practical self-care strategies. Education provided in the clinic can be further reinforced with between-visit phone calls and/or e-mails. Both telephone-based follow-up and educational support tools have been shown to improve adherence to dietary advice in patients with various chronic diseases.[35] Most studies on the effect of engagement strategies on outcomes are for chronic diseases, although prospective studies are needed to assess the impact of these strategies specifically for adults with PAH deficiency.

Improving Insurance Coverage to Achieve Optimal Outcomes Among Adults With PAH Deficiency

Although the ACMG guidelines recommend that all appropriate approaches be used to help patients manage PAH deficiency,[1] access barriers may limit the care that patients can actually receive. Through the Affordable Care Act, patients are eligible for coverage under their parents' medical insurance until the age of 26. Yet individuals with PAH deficiency-related neurocognitive impairments may be unaware of the details of their coverage or may be unable to complete the paperwork required to receive Medicaid coverage. For patients without coverage, the expense of medical foods or insurance co-payments may preclude them from receiving this critical component for the management of PAH deficiency.

Insurance coverage for pharmacological treatments and medical foods varies by state. In some states, private health insurance may cover prescribed pharmacological treatments but not the cost of medical foods or special low-protein foods. Currently, 16 states have mandated Medicaid payer coverage. For adult patients with PAH deficiency, only 7 states mandate insurance coverage of medical formula. Currently, 37 states have private payer mandates for coverage of medical foods and/or special low-protein foods; of these, 8 states require private payer coverage of only medical foods and 1 requires coverage of only special low-protein foods. In addition, private payer mandates in 15 of the 37 states have dollar caps and age limits.[16,43]

The need for improved insurance coverage for medical foods is well recognized; the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children has issued several reports on improving insurance coverage of medical foods for the treatment of inherited metabolic disorders.[44,45] As part of the National Defense Authorization Act for 2017, Congress recently authorized TRICARE, the health-care program of the Military Health System, to provide coverage for medical foods.[46] Recently, the Medical Nutrition Equity Act (MNEA) was drafted with the goal of requiring all insurance plans to cover medical foods for both children and adults with PAH deficiency.[47] Advocacy groups are currently seeking support for MNEA from individual members of Congress to successfully introduce the bill. Clinicians are powerful patient advocates and can help generate awareness of the need for improved coverage for medical foods for adult patients with PAH deficiency.

Conclusion

Adult patients with PAH deficiency who return to clinic after having been LTFU represent a population with unique characteristics that requires individualized approaches to encourage consistent, lifelong care. It is important these patients have a positive initial experience as they return to the metabolic clinic, and clinicians can build partnerships that will help their patients stay engaged in their care over the long-term. A key objective is to help patients understand that high Phe levels can

lead to symptoms that interfere with the ability to adhere to diet and treatment, schedule and attend clinic visits, and take part in activities of everyday living, but that these symptoms can be improved when Phe levels are lowered with treatment.[1,6,20,41] To reduce the number of patients who are LTFU, adolescents and their parents should be counseled on how to develop the skills needed to transition successfully to independent care as adults. More work is needed to understand the most effective strategies for encouraging LTFU patients to return to clinic, to address the lack of adult services in pediatric metabolic clinics as well as to educate insurance providers, medical directors, and state insurance commissions about the need to cover services and medical foods for adults with PKU.

Acknowledgments

The authors thank the focus group participants for their time and valuable insights. They also acknowledge the contributions of the clinician advisory board members, Kendra Bjoraker, PhD, Melanie Colville, RD, Mitzie Grant, PhD, Laura Jeffers, RD, Julie Johnston, RD, and Natalie Owen, NP. Note that the authors also served on the advisory board. Medical writing assistance was provided by Jill Cantelmo, DPhil, MSc, and Stacey Tobin, PhD, at The Access Group.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Janet Thomas, MD, has served as an advisory board member and has received clinical trial support from BioMarin Pharmaceutical Inc. Mina Nguyen-Driver, PsyD, has served as a neuropsychology advisory board member and has received consulting fees from BioMarin Pharmaceutical Inc. Heather Bausell, RD, LDN, has served as an advisory board member and received consulting fees from BioMarin Pharmaceutical Inc. Jane Breck, MD, has served as an advisory board member and received consulting fees from BioMarin Pharmaceutical Inc. Javier Zambrano, MD, and Vanessa Birardi, PharmD, are employees and stockholders of BioMarin Pharmaceutical Inc.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article. Funding for this article was provided by BioMarin Pharmaceutical Inc.

Supplemental Material

Supplementary material for this article is available online.

References

1. Vockley J, Andersson HC, Antshel KM, et al; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16(2):188-200.
2. Pey AL, Martinez A. The phenylalanine hydroxylase system. In: Blau N, ed. *PKU and BH_4. Advances in Phenylketonuria and Tetrahydrobiopterin*. Heilbronn, Germany: SPS Verlagsgesellschaft; 2006:67-91.
3. Matalon KM. Dietary recommendations in the USA. In: Blau N, ed. *PKU and BH_4. Advances in Phenylketonuria and Tetrahydrobiopterin*. Heilbronn, Germany: SPS Verlagsgesellschaft; 2006:220-231.
4. Jahja R, Huijbregts SC, de Sonneville LM, et al. Mental health and social functioning in early treated Phenylketonuria: the PKU-COBESO study. *Mol Genet Metab*. 2013;(110 suppl):S57-S61.
5. Jahja R, van Spronsen FJ, de Sonneville LM, et al. Social-cognitive functioning and social skills in patients with early treated phenylketonuria: a PKU-COBESO study. *J Inherit Metab Dis*. 2016;39(3):355-362.
6. ten Hoedt AE, de Sonneville LM, Francois B, et al. High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial. *J Inherit Metab Dis*. 2011; 34(1):165-171.
7. Weglage J, Fromm J, van Teeffelen-Heithoff A, et al. Neurocognitive functioning in adults with phenylketonuria: results of a long term study. *Mol Genet Metab*. 2013;(110 suppl):S44-S48.
8. Waisbren SE, Noel K, Fahrbach K, et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Mol Genet Metab*. 2007; 92(1-2):63-70.
9. Kuvan [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; 2015.
10. Demirkol M, Giżewska M, Giovannini M, Walter J. Follow up of phenylketonuria patients. *Mol Genet Metab*. 2011;(104 suppl): S31-S39.
11. Jurecki ER, Cederbaum S, Kopesky J, et al. Adherence to clinic recommendations among patients with phenylketonuria in the United States. *Mol Genet Metab*. 2017;120(3):190-197.
12. MacDonald A, Gokmen-Ozel H, van Rijn M, Burgard P. The reality of dietary compliance in the management of phenylketonuria. *J Inherit Metab Dis*. 2010;33(6):665-670.
13. Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? *Lancet*. 2002; 360(9326):55-57.
14. Wappner R, Cho S, Kronmal RA, Schuett V, Seashore MR. Management of phenylketonuria for optimal outcome: a review of guidelines for phenylketonuria management and a report of surveys of parents, patients, and clinic directors. *Pediatrics*. 1999; 104(6):e68.
15. Ahring K, Bélanger-Quintana A, Dokoupil K, et al. Blood phenylalanine control in phenylketonuria: a survey of 10 European centres. *Eur J Clin Nutr*. 2011;65(2):275-278.
16. Berry SA, Brown C, Grant M, et al. Newborn screening 50 years later: access issues faced by adults with PKU. *Genet Med*. 2013; 15(8):591-599.
17. Schuett VE, Gurda RF, Brown ES. Diet discontinuation policies and practices of PKU clinics in the United States. *Am J Public Health*. 1980;70(5):498-503.
18. Cotugno G, Nicoló R, Cappelletti S, Goffredo BM, Dionisi Vici C, Di Ciommo V. Adherence to diet and quality of life in patients with phenylketonuria. *Acta Paediatr*. 2011;100(8):1144-1149.
19. Simon E, Schwarz M, Roos J, et al. Evaluation of quality of life and description of the sociodemographic state in adolescent and young adult patients with penylketonuria (PKU). *Health Qual Life Outcomes*. 2008;6:25.

20. Gentile JK, Ten Hoedt AE, Bosch AM. Psychosocial aspects of PKU: hidden disabilities–a review. *Mol Genet Metab*. 2010; 99(suppl 1):S64-S67.
21. Burton BK, Leviton L. Reaching out to the lost generation of adults with early-treated phenylketonuria (PKU). *Mol Genet Metab*. 2010;101(2-3):146-148.
22. Tuccero D, Railey K, Briggs M, Hull SK. Behavioral health in prevention and chronic illness management: motivational interviewing. *Prim Care*. 2016;43(2):191-202.
23. Teeter BS, Kavookjian J. Telephone-based motivational interviewing for medication adherence: a systematic review. *Transl Behav Med*. 2014;4(4):372-381.
24. Viau KS, Jones JL, Murtaugh MA, Gren LH, Stanford JB, Bilder DA. Phone-based motivational interviewing to increase self-efficacy in individuals with phenylketonuria. *Mol Genet Metab Rep*. 2016;6:27-33.
25. Pietz J, Fätkenheuer B, Burgard P, Armbruster M, Esser G, Schmidt H. Psychiatric disorders in adult patients with early-treated phenylketonuria. *Pediatrics*. 1997;99(3):345-350.
26. Caldwell KL, Gray J, Wolever RQ. The process of patient empowerment in integrative health coaching: how does it happen? *Glob Adv Health Med*. 2013;2(3):48-57.
27. Lawson KL, Jonk Y, O'Connor H, Riise KS, Eisenberg DM, Kreitzer MJ. The impact of telephonic health coaching on health outcomes in a high-risk population. *Glob Adv Health Med*. 2013; 2(3):40-47.
28. Heuchert JP, McNair DM. *POMS 2: Profile of Mood States*, Second Edition. Tonawanda, NY: Multi-Health Systems, Inc; 2012.
29. Barnhill JW. The psychiatric interview and mental status examination. In: Hales RA, Yudofsky SC, Roberts LW, eds. *The American Psychiatric Publishing Textbook of Psychiatry*. 6th ed. Arlington, VA: American Psychiatric Publishing; 2014.
30. Bacci ED, Wyrwich KW, Gries KS, et al. An adaptation of the profile of mood states for use in adults with phenylketonuria. *J Inborn Errors Metab Screen*. 2016;4:1-11.
31. Harrison P, Oakland T. Adaptive Behavior Assessment System, Third Edition (ABAS-3). San Antonio, TX: Pearson; 2015.
32. Ha Dinh TT, Bonner A, Clark R, Ramsbotham J, Hines S. The effectiveness of the teach-back method on adherence and self-management in health education for people with chronic disease: a systematic review. *JBI Database System Rev Implement Rep*. 2016;14(1):210-247.
33. Singh RH, Rohr F, Frazier D, et al. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. *Genet Med*. 2014;16(2):121-131.
34. Longo N, Arnold GL, Pridjian G, et al; Phenylketonuria Demographics, Outcomes and Safety Registry. Long-term safety and efficacy of sapropterin: the PKUDOS registry experience. *Mol Genet Metab*. 2015;114(4):557-563.
35. Desroches S, Lapointe A, Ratté S, Gravel K, Légaré F, Turcotte S. Interventions to enhance adherence to dietary advice for preventing and managing chronic diseases in adults. *Cochrane Database Syst Rev*. 2013(2):CD008722.
36. Dwarswaard J, Bakker EJM, van Staa A, Boeije HR. Self-management support from the perspective of patients with a chronic condition: a thematic synthesis of qualitative studies. *Health Expect*. 2016;19(2):194-208.
37. Waisbren SE, Levy HL. Agoraphobia in phenylketonuria. *J Inherit Metab Dis*. 1991;14(5):755-764.
38. Trefz FK, van Spronsen FJ, MacDonald A, et al. Management of adult patients with phenylketonuria: survey results from 24 countries. *Eur J Pediatr*. 2015;174(1):119-127.
39. Camfield CS, Joseph M, Hurley T, Campbell K, Sanderson S, Camfield PR. Optimal management of phenylketonuria: a centralized expert team is more successful than a decentralized model of care. *J Pediatr*. 2004;145(1):53-57.
40. Bilginsoy C, Waitzman N, Leonard CO, Ernst SL. Living with phenylketonuria: perspectives of patients and their families. *J Inherit Metab Dis*. 2005;28(5):639-649.
41. Bilder DA, Burton BK, Coon H, et al. Psychiatric symptoms in adults with phenylketonuria. *Mol Genet Metab*. 2013;108(3):155-160.
42. Lundahl B, Moleni T, Burke BL, et al. Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. *Patient Educ Couns*. 2013;93(2): 157-168.
43. Data on file. Internal report July 29, 2016. BioMarin Pharmaceutical Inc.
44. Berry SA, Kenney MK, Harris KB, et al. Insurance coverage of medical foods for treatment of inherited metabolic disorders. *Genet Med*. 2013;15(12):978-982.
45. US Department of Health and Human Services. *Secretary's Advisory Committee on Heritable Disorders in Newborns and Children: 2013 Annual Report*. http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/reportsrecommendations/reports/heritdisordersnewbornschildrenannualrpt13.pdf. Published 2013. Accessed February 24, 2017.
46. National Defense Authorization Act for Fiscal Year 2017. Public Law No: 114-328 (December 23, 2016).
47. Medical Nutrition Equity Act. National PKU Alliance website. http://npkua.org/Take-Action/Medical-Nutrition-Equity-Act. Accessed February 24, 2017.