Molecular Genetics and Metabolism 137 (2022) 114–126

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Regular Article

Management of early treated adolescents and young adults with phenylketonuria: Development of international consensus recommendations using a modified Delphi approach

Barbara K. Burton [a,*,1], Álvaro Hermida [b,1], Amaya Bélanger-Quintana [c], Heather Bell [d], Kendra J. Bjoraker [e], Shawn E. Christ [f], Mitzie L. Grant [g], Cary O. Harding [h], Stephan C.J. Huijbregts [i], Nicola Longo [j], Markey C. McNutt II [k], Mina D. Nguyen-Driver [h], André L. Santos Pessoa [l], Júlio César Rocha [m,n,o], Stephanie Sacharow [p,q], Amarilis Sanchez-Valle [r], H. Serap Sivri [s], Jerry Vockley [t], Mark Walterfang [u,v,w], Sarah Whittle [x], Ania C. Muntau [y]

[a] Ann and Robert H. Lurie Children's Hospital and Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[b] Clinical University Hospital of Santiago de Compostela, University of Santiago de Compostela, CIBERER, MetabERN, Institute of Clinical Research of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[c] Metabolic Diseases Unit, Department of Paediatrics, Ramon y Cajal Hospital, Madrid, Spain
[d] Fred A. Litwin Family Centre in Genetic Medicine, University Health Network and Mount Sinai Hospital, Toronto, ON, Canada
[e] 3:1 Neuropsychology Consultants, PLLC, Minneapolis, MN, USA
[f] Department of Psychological Sciences, University of Missouri, Columbia, MO, USA
[g] Department of Psychiatry, Drexel University College of Medicine, Philadelphia, PA, USA
[h] Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR, USA
[i] Leiden Institute for Brain and Cognition, Leiden University, Leiden, the Netherlands
[j] Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA
[k] McDermott Center for Human Growth and Development, UT Southwestern Medical Center, Dallas, TX, USA
[l] Pediatric Neurology Service, Albert Sabin Children's Hospital, University of Ceará State, Fortaleza, Ceará, Brazil
[m] Nutrition and Metabolism, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Portugal
[n] CINTESIS-Center for Health Technology and Services Research, NOVA Medical School, Lisboa, Portugal
[o] Reference Centre of Inherited Metabolic Diseases, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal
[p] Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, USA
[q] Department of Pediatrics, Harvard Medical School, Boston, MA, USA
[r] Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
[s] Hacettepe University, Faculty of Medicine, Department of Pediatrics, Section of Pediatric Metabolism, Ankara, Turkey
[t] Department of Pediatrics, University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[u] Neuropsychiatry Unit, Royal Melbourne Hospital, Melbourne, VIC, Australia
[v] Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, VIC, Australia
[w] Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia
[x] Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia
[y] University Children's Hospital, University Medical Center Hamburg Eppendorf, Hamburg, Germany

ARTICLE INFO

Article history:
Received 25 April 2022
Received in revised form 16 June 2022
Accepted 23 July 2022
Available online 29 July 2022

ABSTRACT

Background: Early treated patients with phenylketonuria (PKU) often become lost to follow-up from adolescence onwards due to the historical focus of PKU care on the pediatric population and lack of programs facilitating the transition to adulthood. As a result, evidence on the management of adolescents and young adults with PKU is limited.

Methods: Two meetings were held with a multidisciplinary international panel of 25 experts in PKU and comorbidities frequently experienced by patients with PKU. Based on the outcomes of the first meeting, a set

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale; BMI, body mass index; BDNF, brain-derived neurotrophic factor; BRIEF, Behavior Rating Inventory of Executive Function; COBESO, cognition, behavior, social functioning; DEXA, dual-energy X-ray absorptiometry; GAD-7, Generalized Anxiety Disorder 7-item; HbA1c, hemoglobin A1c; HCP, Healthcare Professional; HIPAA, Health Insurance Portability and Accountability Act; IQ, intelligence quotient; Phe, phenylalanine; PHQ, Patient Health Questionnaire; PHQ-SADS, Patient Health Questionnaire – Somatic, Anxiety, and Depressive Symptoms; PKU, phenylketonuria; PSC-17, Pediatric Symptom Checklist-17; QoL, Quality of Life; TRAQ, Transition Readiness Assessment Questionnaire; TRKB, tyrosine kinase receptor 2; Tyr, tyrosine; WHO, World Health Organization.

* Corresponding author at: Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, 225 E Chicago Ave, Chicago, IL 60611, United States.
E-mail address: bburton@luriechildrens.org (B.K. Burton).

[1] Equally contributed.

https://doi.org/10.1016/j.ymgme.2022.07.012

Keywords:
Phenylketonuria
PKU
Adolescent
Young adult
Modified Delphi
Consensus recommendations

of statements were developed. During the second meeting, these statements were voted on for consensus generation (≥70% agreement), using a modified Delphi approach.
Results: A total of 37 consensus recommendations were developed across five areas that were deemed important in the management of adolescents and young adults with PKU: (1) general physical health, (2) mental health and neurocognitive functioning, (3) blood Phe target range, (4) PKU-specific challenges, and (5) transition to adult care. The consensus recommendations reflect the personal opinions and experiences from the participating experts supported with evidence when available. Overall, clinicians managing adolescents and young adults with PKU should be aware of the wide variety of PKU-associated comorbidities, initiating screening at an early age. In addition, management of adolescents/young adults should be a joint effort between the patient, clinical center, and parents/caregivers supporting adolescents with gradually gaining independent control of their disease during the transition to adulthood.
Conclusions: A multidisciplinary international group of experts used a modified Delphi approach to develop a set of consensus recommendations with the aim of providing guidance and offering tools to clinics to aid with supporting adolescents and young adults with PKU.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism resulting from complete or partial deficiency in phenylalanine hydroxylase enzyme activity, causing an elevation of blood phenylalanine (Phe) levels when untreated [1,2]. As a result, management focuses on lifelong reduction of blood Phe through the restriction of dietary Phe intake, with or without the addition of sapropterin [3,4]. More recently, pegvaliase is an additional treatment option for patients with blood Phe levels ≥600 μmol/L aged ≥16 years in Europe and ≥ 18 years in the United States (US) [5–8]. Regardless of the treatment regimen, regular in-clinic follow-up is recommended as patients with PKU remain at risk for mental health disorders, deficits in neurocognitive functioning, and physical health manifestations [3,4,9–11]. However, during the adolescent period, clinic attendance begins to decline and there is a tendency to relax the adherence to medical nutrition therapy resulting in increasing blood Phe levels [12–14]. This lost to follow-up rate may to some extent be explained by the historical focus of PKU care on the pediatric population, with a lack of models facilitating the transition to adult care and a scarcity of specialized adolescent and young adult care centers [15,16]. Only a limited amount of literature addresses the adolescent and young adult PKU population, with current management guidelines not specifically focusing on these age groups [3,4,17]. To address this lack of guidance, an international multidisciplinary group of experts was gathered to develop a set of consensus statements on the management of adolescents and young adults with PKU, delineating strategies to prevent the deterioration of metabolic control, lapse in care, and loss to follow-up. The recommendations are intended to help clinicians and clinics provide guidance to better manage adolescents and young adults with PKU, optimizing the outcomes and quality of life (QoL) of these PKU populations.

2. Methodology

A 2-day virtual meeting was held on October 20 and 29, 2020 on the management of adolescents and young adults with PKU, covering patients aged between 10 and 24 years, the age group as defined by the World Health Organization (WHO) [18]. The first virtual meeting was attended by an international multidisciplinary panel consisting of 25 experts from Australia, Brazil, Canada, France, Germany, Portugal, Spain, The Netherlands, Turkey, and the USA. The group included 12 physicians, two dietitians, two psychiatrists, and three pediatric neuropsychologists with expertise in PKU along with one expert involved in adolescent medicine, three experts in neuroscience and neurology, one expert in transitional care, and one patient organization representative. The PKU clinical care experts had on average 20 years of experience, managing up to 2500 patients with PKU across all age ranges. The content of the virtual meeting was developed by a steering committee of three experts who also led the meeting. In the weeks prior to the scheduled virtual meetings, the panelists reviewed a set of video-recorded presentations developed by the experts and responded to pre-meeting survey questions that were discussed during the virtual meeting. Based on the outcomes of the pre-meeting activities and the virtual meeting, draft recommendations were developed which were rated in a follow-up virtual consolidation meeting (Fig. 1).

Out of the 25 experts, 22 contributed to the virtual consolidation meeting. To facilitate the virtual consolidation meeting, a secure online-platform was arranged using the virtual engagement tool, Within3 (https://www.within3.com/), aiming to work towards consensus recommendations for the management of adolescents and young adults with PKU by applying a modified Delphi approach (Fig. 1). This methodology, developed by the Rand Corporation/University of California, Los Angeles, CA, USA, has been widely used to achieve consensus on a specific issue, especially when empirical evidence is limited [19]. During the first voting round, the experts voted anonymously on the draft recommendations and provided feedback to support their opinion. During the second voting round, statements without consensus (i.e., <70% agreement) were revisited and revoted on the platform allowing discussion among the experts. Two statements that did not achieve consensus during the second voting round were revised based on the gathered feedback and anonymously revoted during an additional survey. Final consensus recommendations were developed in five areas as defined by the experts on the management of adolescents and young adults with PKU with focus on:

- General physical health
- Mental health and neurocognitive functioning
- Blood Phe target range
- PKU-specific challenges
- Transition to adult care

For the purpose of these consensus recommendations, behavioral health encompasses mental health symptoms and disorders, including psychiatric diagnoses of depression, anxiety, and attention deficit hyperactivity disorder (ADHD), while impairments in neurocognitive functioning refer to deficits in intellectual functioning, executive functioning, processing speed, adaptive functioning, and attention. Psychosocial outcomes pertain to the impact of PKU and its management on the QoL of patients and outcomes related to education, career, relationships, and socioeconomic status.

3. Consensus recommendations

3.1. Prevention of physical health comorbidities in adolescents and young adults with PKU

The physical health comorbidities that require attention in adolescents and young adults with PKU are shown in Fig. 2. In addition to

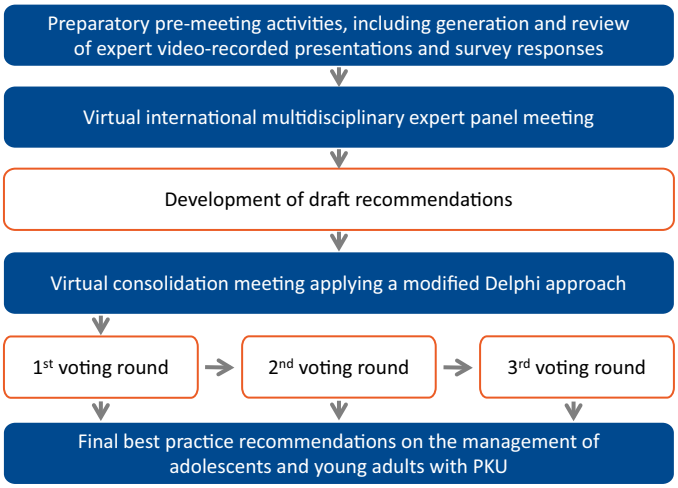

Fig. 1. Overview of the study methodology. Consensus was achieved when the percentage agreement was ≥70%.

the most frequently reported conditions, anemia, metabolic syndrome, dental and oral health issues, dyslipidemias, and precocious puberty were each identified by one of the experts. Overall, the identified comorbidities are consistent with those described in previous retrospective insurance claim-based comorbidity studies evaluating adults with PKU [9,11].

Statement #1	Consensus %
Based on evidence from retrospective insurance claims data, more attention should be given to PKU-associated comorbidities pertaining to general physical health in adolescents and young adults	95%

Due to the risk of physical health comorbidities, healthcare professionals (HCPs) should start to screen for them at an early age. Ideally, such screening should be performed every 6 months, but depending on the clinical (i.e., level of blood Phe control, treatment regimen, and compliance) and family history, once yearly screening may be appropriate, fitting better into the life of the adolescent or young adult while reducing financial barriers that may impede the implementation of frequent screening in some countries.

Statement #2	Consensus %
Screening for physical health comorbidities should be a continuous process, starting at an early age considering that these comorbidities may occur throughout life and be dependent on the level of blood Phe control	95%
Statement #3	**Consensus %**
Ideally, screening of adolescents and young adults with PKU for the presence of physical health comorbidities should be performed every 6 months	90%

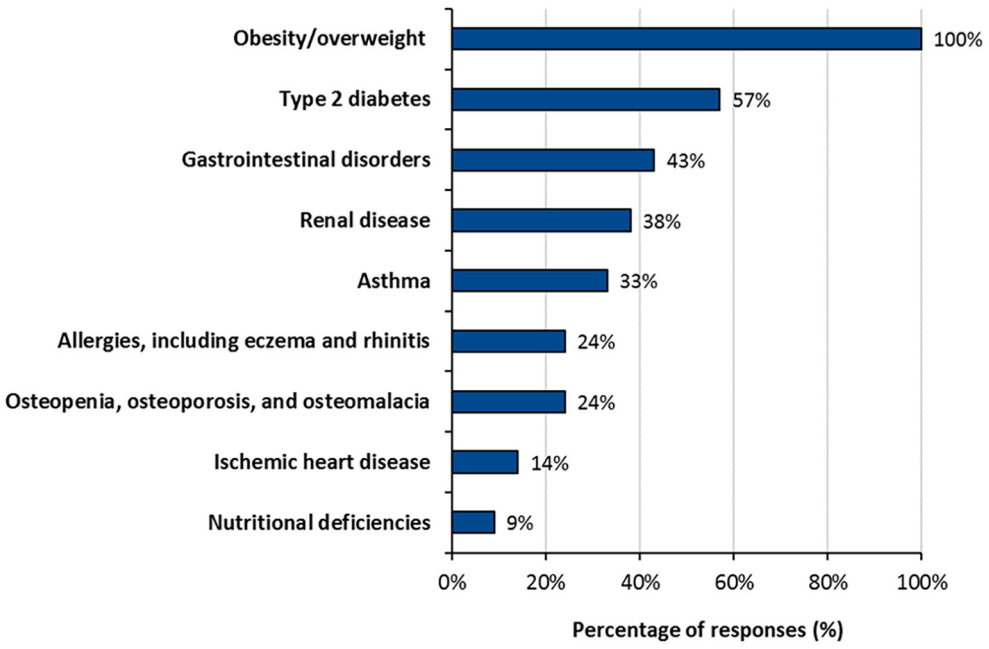

Fig. 2. Overview of the physical health comorbidities requiring special attention in adolescents and young adults with PKU as identified by the experts.
Percentage of responses reflects the number of experts who selected the physical health comorbidities that they would particularly pay attention to in adolescents/young adults with PKU.

Table 1
Proposed assessments to screen for physical health comorbidities and their respective frequency.

Assessment	Frequency
• Blood phenylalanine and tyrosine	Monthly
• Physical exam, including vitals	Every 6 months
• Anthropometrics	
• Nutritional intake assessment	
• Other plasma amino acids	Every 6 months to once yearly
• Allergy history (including eczema and rhinitis)	
• Micronutrients, including vitamins B12, D, folate, and zinc	Yearly
• Lipid panel, including cholesterol panel	
• DEXA scan	Initial scan earliest at age 12, findings determine frequency of repeating

BMI: body mass index; DEXA: dual-energy X-ray absorptiometry.

Proposed assessments to screen for physical health comorbidities and their respective frequency are shown in Table 1. Ideally, full plasma amino acid profile needs to be assessed every 6 months to once yearly, whereas blood Phe, tyrosine (Tyr) levels, and Phe/Tyr ratios should be evaluated monthly [20,21]. Comprehensive metabolic panel, hemoglobin A1c (HbA1c), thyroid levels, body composition analysis, and dental examination are additional assessments that can be performed if there is a clinical reason for concern.

The management of physical health comorbidities depends on the underlying cause of the clinical manifestations which can be related to elevated blood Phe levels and/or long-term adherence to a Phe-restricted diet with supplementation of synthetic amino acids [9,22,23]. Regardless of the underlying cause, management of physical health comorbidities should focus on prevention through regular follow-up, preferably by a multidisciplinary team knowledgeable about PKU and its physical health manifestations, considering that the etiology can be complex and multifactorial.

Statement #4	Consensus %
Preventative measures, i.e., healthy diet, exercise, sleep hygiene, and weight management, are important to discuss with adolescents/young adults with PKU	95%
Statement #5	**Consensus %**
Management of physical health comorbidities should look beyond simply focusing on blood Phe as some can be part of a complex series of pathophysiological reactions	81%

3.2. Managing the mental health and neurocognitive implications of PKU in adolescents and young adults

3.2.1. Mental health and neurocognitive implications

Generally, impairments in neurocognitive functioning and mental health disorders can be prevented by starting treatment from diagnosis at newborn screening throughout early childhood [24–26]. However, sustaining metabolic control beyond childhood remains challenging for many adolescents and young adults increasing the risk for comorbidities that can impact psychosocial outcomes, despite early treatment [12,13,20,24–28]. Of the potential mental health disorders, anxiety and depression are identified by the experts as the most common and important disorders requiring special attention in early treated adolescents and young adults with PKU.

Statement #6	Consensus %
Adolescents and young adults with PKU are at higher risk for mental health disorders and impairments in neurocognitive functioning than their non-PKU peers	100%
Statement #7	**Consensus %**
The way mental health and neurocognitive problems are expressed may be age dependent. During a consultation, it is important to ask neutral/open-ended/appropriate questions reflecting the age and developmental level of the patient	95%
Statement #8	**Consensus %**
Anxiety, depression, and impaired executive functioning are the most important comorbidities related to mental health and neurocognitive functioning requiring special attention in adolescents and young adults with PKU	76%

The focus on anxiety symptoms and depressed mood is not surprising as they often have onset during adolescence and are generally common among patients with metabolic disorders [29–32]. In adolescents and young adults with PKU, the etiology of internalizing mental health problems can be related to both the burden of illness and the consequences of elevated blood Phe levels disturbing monoaminergic neurotransmitter levels in the brain [2]. Additionally, elevated blood Phe levels can affect myelination through altered protein and cholesterol synthesis, inducing white matter abnormalities that contribute to the development of executive functioning difficulties, which are one of the most common deficits experienced by early treated patients with PKU, especially those with classical disease [2,33–35]. Although anxiety, depression, and impaired executive functioning were deemed most important by the expert panel, screening should not be limited to these three areas of concern. Assessment of neurocognitive impairments in processing speed, sustained attention, fine motor skills, and expressive language, as well as other possible mental health conditions, such as panic attacks and psychosis, should also be considered [2,34,36–43].

3.2.2. Predictors of mental health disorders and impairments in neurocognitive functioning

It is well established that poor control of blood Phe during childhood (i.e., blood Phe >360 μmol/L) correlates with a decrease in intelligence quotient (IQ) test scores and cognitive outcomes later in life [13,44,45]. This finding is extended by the cognition, behavior, social functioning (COBESO) study, demonstrating an inverse correlation between social-cognitive functioning and historical blood Phe levels for adolescents with PKU [36]. Although neurocognitive outcomes of patients with good metabolic control during early life are generally comparable to those of healthy controls, higher-order executive functioning skills (e.g., planning and problem-solving abilities) remain sensitive to elevations in blood Phe during adolescence and young adulthood [24–26,46]. Each neurocognitive outcome, however, can be affected differently by historical, lifetime, and/or concurrent blood Phe levels with unexplained inter-individual variability to Phe vulnerability [24–26,47].

Statement #9	Consensus %
Uncontrolled blood Phe, especially during infancy and childhood, is the most apparent predictor of the development of *neurocognitive* issues later in life. Management should consider the genetic, social, and environmental factors behind uncontrolled blood Phe that may contribute to the etiology of the neurocognitive comorbidities experienced by adolescents and young adults with PKU	95%

A correlation between symptoms of anxiety and depression with concurrent blood Phe levels and fluctuations in blood Phe can also be seen, although evidence-based research on how blood Phe specifically impacts underlying causes of mental health conditions in adolescent and young adults with PKU remains limited and conflicting [20,24,34]. In addition, many variables, including family size and support, genetic background, age at diagnosis, access to and quality of PKU care, socioeconomic status, and comorbid learning disabilities, can indirectly influence blood Phe control and thus should be considered in PKU management. Another factor that should not be neglected is the burden of living with a chronic disease, requiring lifelong treatment [34]. Adolescence is a developmental period that is particularly sensitive to external factors, such as stress, that may impact brain development and increase the incidence of mental health disorders [48,49]. It is unknown if adolescent brain development in PKU is affected differently by any of these external factors, but stress related to burden of illness and treatment may contribute to the development of anxiety symptoms and depression independent of blood Phe control, especially in patients who do not closely adhere to their medical nutrition therapy [24]. While it is not surprising that mental health disorders, such as anxiety, are associated with adverse psychosocial outcomes in adulthood, such as reduced life satisfaction, familial and social impairment, educational underachievement, and poor adjustment at work [50], neurocognitive impairment can compromise a patient's mental health as well [51].

Statement #10	Consensus %
Additional studies should address the degree to which the burden of illness (including the burden of treatment) and blood Phe control contribute to the mental health disorders and impairments in neurocognitive functioning experienced by adolescents/young adults with PKU	90%
Statement #11	**Consensus %**
Elevated blood Phe levels and fluctuations in blood Phe during adolescence and young adulthood are the most apparent predictors of the development of *mental health* disorders. Management should consider the genetic, social, and environmental factors behind uncontrolled blood Phe that may contribute to the etiology of the mental health disorders experienced by adolescents and young adults with PKU	87%
Statement #12	**Consensus %**
Screening or assessment to identify neurocognitive issues that may create difficulties in cognitive function, school performance, behavioral regulation, and social-emotional interactions as well as screening for mental health concerns should begin early in life. These challenges, if not recognized early in life, may be compounded over time, resulting in more severe expression of mental health issues and poor clinical and/or daily functioning outcomes	77%

Besides the burden of illness, parenting style has been widely described to influence adolescent brain development and mental health outcomes [52–54]. In chronic diseases such as PKU, authoritarian (controlling and supervising) or permissive (lack of monitoring, non-punitive, and allowing children to regulate their own activities without setting limits) parenting styles may negatively influence adherence to treatment and subsequent blood Phe control [55,56]. However, caring for a child with PKU can be demanding and stressful and parental mental health concerns should not be ignored, ensuring parents and caregivers are able to support their adolescent/young adult with PKU management [57,58].

Statement #13	Consensus %
Parenting skills leading to compromised metabolic control can be an early predictor of the development of mental health issues later in life	82%

3.2.3. Screening and management of mental health disorders and impairments in neurocognitive functioning

Brief, validated, easily accessible screening tools are available for medical providers working in busy clinical settings allowing for monitoring of symptoms associated with mental health disorders in adolescents and young adults with PKU. The advantage of these tools is that they do not need interpretation by a (neuro)psychologist/psychiatrist and can help the metabolic team with identifying symptoms. This is especially relevant when access to (neuro)psychological/psychiatric support is limited, helping the treating physician to objectively screen patients for mental health concerns. The proposed tools are intended to help the metabolic team determine if a more in-depth assessment by a mental health professional, such as a (neuro)psychologist or psychiatrist is needed. If such support is not an option, access to social workers or other mental health counselors should be explored provided they have the expertise to assess the mental health of patients with PKU. If none of these services are available, alternative therapeutic services and consideration of self-help resources, such as free or low cost web-based self-care materials, videos, apps, online courses or community forums from professional organizations (e.g., regional or national psychological or psychiatric associations), yoga, physical activities, and meditation, should be encouraged while continuing to pursue mental health services [59,60].

Statement #14	Consensus %
Optimal PKU management should involve improved access to (neuro) psychological and/or psychiatric support, especially for patients with PKU presenting with mental health and/or neurocognitive issues flagged by the metabolic team	86%
Statement #15	**Consensus %**
Continuous monitoring of mental health disorders and impairments in neurocognitive functioning can be improved by using quick, valid, reliable, multilingual, and easy to download screening tools	81%

Table 2 provides an example of some of the brief screening tools currently available online, and at no cost, for use by HCPs in busy metabolic clinics. These questionnaires are general screening tools with items not restricted to concerns specific for PKU. For example, the Patient Health Questionnaire (PHQ), used to evaluate Somatic, Anxiety, and Depressive Symptoms (PHQ-SADS), includes questions about somatic symptoms/concerns that could be particularly concerning to some patients with PKU (e.g., stomach pain, nausea/gas/indigestion, having little energy)

Table 2
Brief, validated, publicly-available, and multilingual screening tools.

Screening tool	Symptoms
PSC-17 (17-item parent-report forms for children/adolescents <18 years of age only) [62] and PSC-17 Youth Form (self-report forms for youth/adolescents 11–17 years of age) [63]	General mood, attention, and conduct problems
PHQ-SADS [64]	Co-occurrence of somatic, anxiety, and depressive symptoms
PHQ 4-item screening questionnaire [65]	Depression and anxiety
ASRS symptoms checklist [66]	Inattention, impulsivity, and/or hyperactivity

ASRS: Adult ADHD Self-Report Scale; PHQ: Patient Health Questionnaire; PHQ-SADS: Patient Health Questionnaire – Somatic (15-item somatic symptom questionnaire), Anxiety (GAD-7 & anxiety attacks), and Depressive Symptoms (PHQ-9); PSC-17: Pediatric Symptom Checklist-17; PSC-Y-17: Youth Pediatric Symptom Checklist-17 (17-item PSC & PSC-Y validated screening forms adaptive from 35-item PSC screening questionnaires normed for use in medical clinical settings to detect youth with impairment in psychosocial functioning).

while also including topics with questions about sexual intercourse and menstrual cramps that can impact the QoL for some adolescents and young adults but are not specifically related to the pathogenesis of PKU. For some of these screening tools, different and even briefer versions are available, all downloadable on the PHQ website [61].

Besides the proposed use of public domain screening tools, there are other informant rating scale measures, such as the Behavior Rating Inventory of Executive Function (BRIEF), a copyright-protected executive functioning assessment tool available for purchase. Although the time needed to complete the full BRIEF is limited to 10-15 min, its completion and analysis is not always compatible with busy clinical settings. Therefore, an abbreviated 10-item version was recently proposed as an initial screen [67,68]. With regards to the adult self-report version, the 10-item subset of questions showed a high sensitivity and specificity (both >90%) to differentiate impaired from unimpaired patients based on their performance on the full BRIEF. When this initial screening is positive, the entire BRIEF should be completed to understand the spectrum and severity of deficits in executive functioning. It is recognized that results obtained on screening tools, such as the BRIEF, may reflect the impact of limited self-awareness, which can be present in some patients with PKU due to the neurocognitive impairments, complicating self-assessment of symptoms [69,70]. In such situations, alternate versions of the BRIEF are available, permitting perspectives from another informant (e.g., spouse, parent or caregiver), while rating scales could also be combined with more objective performance-based tasks.

Statement #16	Consensus %
The Behavior Rating Inventory of Executive Function (BRIEF) is an informant validated rating scale used to assess executive functioning deficits in adolescents and young adults with PKU	88%

In addition, the expert panel recommends to perform early screening of fine-motor speed or visual-motor skills, using measures such as the Purdue Pegboard, Nine-Hole Peg, and Bruininks-Oseretsky Test of Motor Proficiency. Although more research is needed and there remains much uncertainty, impairments in these skills could be a first indication of the presence of underlying biochemical and/or structural brain disruptions in patients with PKU and indirectly impact other areas of development, such as learning and independent living skills [38–40,46,71–73].

Statement #17	Consensus %
Impairment in fine motor skills may be an early predictor of neurocognitive issues later in life as well as a marker of white matter abnormalities and reduced neurotransmitter levels	83%

It is generally accepted that management of PKU needs to be lifelong with focus on maintaining or re-establishing metabolic control throughout childhood and beyond. The benefits of re-establishing metabolic control have been well-described with studies showing how white matter abnormalities are at least partially reversible by reducing blood Phe levels thereby improving executive functioning skills [74–76]. Similarly, symptoms of anxiety, depression, and inattention can be improved when reducing blood Phe levels by either resumption of dietary management or pharmacological treatments [77–79]. Besides focusing on blood Phe, adolescents/young adults benefit from developing general coping strategies, such as exercise and meditation, to aid in the management of mental health issues, especially when achieving metabolic control is challenging or when the issues are independent of blood Phe control [80].

Statement #18	Consensus %
Depending on the extent of elevated or uncontrolled blood Phe during childhood, lowering of blood Phe levels in adolescents and young adults may be associated with improvements in executive functioning and psychosocial outcomes	82%

If symptoms of anxiety and depression are experienced by adolescents and young adults with PKU, pharmacological treatment can be explored, albeit evidence around their use in PKU is limited. Despite elevated blood Phe levels, patients can experience an effect of reuptake inhibitors and benefit from taking antidepressant drugs mediating their effects by brain-derived neurotrophic factor (BDNF) through tyrosine kinase receptor 2 (TRKB) neurotrophin receptors [81]. However, when possible, high blood Phe should be addressed before the onset of severe symptoms and before initiating pharmacological treatment as their use can be associated with side effects.

Statement #19	Consensus %
When considering anxiolytics and/or antidepressants, blood Phe levels should be addressed first, as high blood Phe reduces neurotransmitter levels	95%
Statement #20	**Consensus %**
Antidepressants can help manage depression in adolescents and young adults with PKU	87%
Statement #21	**Consensus %**
Anxiolytics can help manage anxiety in adolescents and young adults with PKU	86%

3.3. Blood Phe target range during adolescence and young adulthood

Currently, the US guidelines for the management of patients with PKU recommend maintaining blood Phe levels between 120 and 360 μmol/L for patients of all ages, while the European guidelines recommend blood Phe concentrations below 600 μmol/L for patients aged 12 years and older [3,4]. A growing body of evidence supports the stricter recommendation by the US guidelines as poorer social-cognition and executive functioning and more severe mental health outcomes have been reported in adolescents and young adults with blood Phe levels above 240–360 μmol/L [36,82–84]. However, some findings have been equivocal, with a recent study focused solely on neurocognitive endpoints supporting the less strict European guidelines though highlighting that Phe sensitivity is prone to individual differences [85]. Due to conflicting and lacking evidence, there was some disagreement among the experts on the blood Phe target range in the adolescent and young adult PKU population. Nevertheless, the consensus of this panel recommends maintaining blood Phe levels below 360 μmol/L without specifying the lower end of the target range.

Statement #22	Consensus %
Based on more recent evidence, available after the publication of the US and EU guidelines, adolescents and young adults with PKU should aim to maintain blood Phe levels below 360 μmol/L	74%

These experts acknowledged, however, that it is extremely difficult for most patients with classical PKU to achieve these levels by dietary management alone, which is reflected by a declining number of patients achieving metabolic control during the transition to adolescence and young adulthood [12–14]. Additionally, adherence to the medical nutrition therapy is often a double-edged sword that can prevent some of the PKU-associated comorbidities while being associated with

poorer emotional well-being due to its restrictive nature [86]. Therefore, the blood Phe target range should only be reconsidered when treatment options become available that can both substantially lower blood Phe levels while also improving patient-centered outcomes. Pegvaliase could be such treatment that is able to reduce blood Phe levels while often allowing for diet normalization under the appropriate dietetic support [87]. However, its impact on patient-centered outcomes has not been established, and pegvaliase is not yet available in all countries [8,78,88].

Statement #23	Consensus %
Achieving blood Phe levels below 360 μmol/L with dietary management may be challenging for adolescents and young adults with PKU. Further research is needed to understand the full impact of the restrictive diet on adolescent development and mental health	100%
Statement #24	**Consensus %**
The recommended blood Phe target range should be reconsidered when new treatment options become available that improve blood Phe levels and/or patient-centered outcomes	79%

3.4. Strategies to manage the challenges faced by adolescents and young adults with PKU

Although the majority of adolescents and young adults with PKU do not want to be treated differently than their non-PKU peers, they face various PKU-specific challenges on top of the ones generally experienced by adolescents/young adults (Table 3).

One of the PKU-specific challenges identified by the experts was disordered eating which is supported by a retrospective comorbidity study demonstrating a higher prevalence of eating disorders in the PKU population compared to the general population [9].

Statement #25	Consensus %
In PKU, feelings of guilt about not adhering to the medical nutrition therapy rather than an altered body image may result in a specific type of disordered eating, requiring tailored management	86%

Nevertheless, evidence is limited and eating disorders are believed to be underdiagnosed and/or unrecognized in adolescents/young adults with PKU due to inadequate screening and lack of validated eating disorder questionnaires specific for PKU [89]. Generally, mid-puberty is the age of onset of eating disorders, and the adolescent age range would be the ideal timing to start screening for disordered eating [90]. Because validated eating disorder questionnaires are not specific to PKU, the expert panel developed a list of possible questions to help screen for disordered eating patterns (Table 4). This list could be a first step towards facilitating screening for disordered eating in PKU, however, it requires validation in future studies.

Table 3
Overview of PKU-specific challenges faced by adolescents and young adults and solutions to overcome these.

Challenges
- The need to fit in and be accepted by others along with peer pressure
- Anger resulting from the inability to accept their chronic medical condition
- Feelings of guilt when not adhering to the dietary restrictions
- Feelings of shame about their disease and management resulting in social isolation
- Risk for maternal PKU
- Low self-esteem and confidence
- Concerns about the long-term impact of PKU
- PKU-associated mental health and neurocognitive issues
- Disordered eating

Solutions
- Education
- Access to (neuro)psychological/psychiatric and/or social work support
- Support from PKU and non-PKU peers
- Practice on how to react in social situations that are relevant for adolescents/-young adults with PKU

Table 4
List of possible questions to screen for eating disorders or disordered eating in adolescents/young adults with PKU.

1. Do you ever worry about your weight, thinking that you might weigh too much or too little?
2. Have you ever felt that you needed to use other behaviors to manage your food intake, like exercise, restricting what you eat, or even vomiting or laxatives?
3. Have you ever felt guilty about what you eat?
4. Would you say that thoughts about food dominate your life?
5. Do you worry that you have lost control over how much you eat (forbidden foods)?
6. Has your weight significantly changed during the last 6 months?
7. Are you satisfied with your eating patterns?
8. Do you have problems eating with or in front of others?

Education is essential to manage the PKU-specific challenges faced by adolescents and young adults. Although parents require ongoing education beginning with fundamental knowledge about PKU, it is important that patients with PKU are included in the educational process as early as possible. Education should include how blood Phe levels can affect physical, neurocognitive, emotional, psychosocial, and mental well-being. Additionally, education should stimulate the adolescent/young adult to contact the metabolic clinic and focus on cooking skills, metabolic food preparation, monitoring protein intake, and maintaining Phe tolerance, ensuring that patients are able to independently follow a healthy diet when becoming adolescents/young adults. Although PKU management should not be sex-specific, female patients with PKU should be progressively educated on maternal PKU starting with raising awareness on the risks related to high blood Phe levels during pregnancy followed by advising on medical nutrition therapy and self-monitoring, emphasizing the importance of planning pregnancy. The age to start maternal PKU education should be individualized depending on the readiness of the patient and should be a joint effort between the patient, parents, family members, partner, social support, non-PKU medical providers, and the metabolic team, taking into consideration cultural beliefs. One-on-one counselling remains the mainstay of maternal PKU education but can be supported with group sessions with the multidisciplinary team, genetic counselling, written and/or electronic educational materials, peer mentoring and support groups, social media groups, web-based learning modules, and mobile applications if available.

Statement #26	Consensus %
The age to start maternal PKU education should be individualized depending on the onset of reproductive capacity, cultural differences, and the level of developmental, cognitive, behavioral, and emotional maturity	100%
Statement #27	**Consensus %**
The mainstay of education about maternal PKU is one-on-one counselling adapted to the developmental level of the patient, explaining in an age-appropriate format the risks of maternal PKU and how these can be prevented	100%

Ideally, access to (neuro)psychological/psychiatric support should assist adolescents with identifying, understanding, and reporting of PKU-specific challenges (Table 3), offering individualized recommendations on managing these challenges. Although there is no replacement for mental health services for patients with identified needs, psychosocial support from PKU peers, e.g., through PKU camps, virtual social events, etc., can at least in the short-term help to improve metabolic control by providing individuals an opportunity to participate in supportive PKU-related educational activities potentially reducing

perceived social isolation [91]. In addition to PKU camps, which may be very specific to certain regions or countries, HCPs should consider encouraging involvement in local, regional, national and international PKU patient/family advocacy and social support organizations, introducing adolescents and young adults to national/international patient registries [92,93]. Besides support from PKU peers, patients can benefit from non-PKU peer support, although some adolescents and young adults with PKU may not disclose to others and may avoid eating in with others or eating in public due to potential feelings of anxiety or feelings of being ashamed of their disease. In addition, patients with PKU of all ages, but particularly vulnerable adolescents and young adults, can benefit from having the opportunity to learn about and practice strategies that help promote feelings of empowerment and self-efficacy that can be used in both familiar and unfamiliar environments where they may experience peer pressure and feel the need to 'fit in'. For example, a role-play approach involving behavioral rehearsal, self-monitoring, goal setting, and training in problem-solving skills with emphasis on initiation and inhibition (i.e., how to say no) could be provided by parents, PKU peers, or even members of the PKU team. These types of activities can be used to teach adolescents with PKU how to react in social situations, such as dining out, helping to avoid indulging and increased risk-taking behavior, a hallmark of the adolescent period [94].

Statement #28	Consensus %
Some of the PKU-specific challenges can be overcome by support from PKU and/or non-PKU peers (e.g., PKU camps), education of both parents and patients, and (improved) access to (neuro)psychological/-psychiatric and/or social work support	95%
Statement #29	**Consensus %**
To overcome challenges related to the need to fit in and peer pressure, adolescents with PKU should practice how to react in social situations leading to risky behaviors	86%

3.5. Transition to adulthood

3.5.1. Developing strategies to prevent loss to follow-up

Adherence to medical nutritional therapy, monitoring of blood Phe, and in-clinic follow-up decline over time, resulting in blood Phe levels above clinic-recommended target ranges in many adolescents and young adults with PKU [12,13].

Statement #30	Consensus %
Decreased adherence to dietary restrictions may result from a combination of developmental behaviors, perceived social pressures, shift in management responsibility from parents to teens, incomplete knowledge and understanding of treatment regimens and future health risks, fatigue from PKU care, and fluctuating mood	81%

Key factors identified by the expert panelists as contributing to loss to follow-up in patients with PKU from adolescence onwards are shown in Fig. 3. Increasing demands in life and lack of motivation were considered the most relevant factors impacting lapse in care by this panel of experts. Insurance and financial issues are more relevant in countries where reimbursement is not guaranteed, and can contribute, in part, to decreased adherence to medical nutritional therapy. However, decreased adherence to medical nutritional therapy does not necessarily equate to lapse in care, as many of these patients continue to be seen in PKU clinics. Four strategies aiming to prevent an increase in the lost to follow-up rate are presented below.

3.5.1.1. Digital and innovative solutions. With the increased use of telemedicine during the COVID-19 pandemic, metabolic control of patients with PKU has been reported to improve, although it is unknown if this was related to the use of telemedicine and/or the obligation to stay at home [95,96]. Now that telemedicine is better integrated into healthcare systems, virtual visits may provide opportunities to complement in-clinic visits, thus ameliorating the impact of geographical barriers and allowing easier access to care. As demonstrated from evidence with individuals with other chronic metabolic disorders, adolescents and young adults with PKU could benefit from the development of mobile applications (secure and/or Health Insurance Portability and Accountability Act [HIPAA-] compliant) designed to assist with tracking and understanding their disease and management [97]. Besides being a point of care, such a mobile application could provide more rapid feedback on blood Phe levels. This could be supported by social media groups to reach out to adolescents and young adults with PKU allowing them to share experiences. Another innovative solution that has the potential to improve metabolic control is the development of devices for self-monitoring of blood Phe levels comparable to the ones used in diabetes [98].

3.5.1.2. Flexibility and engagement of treating HCPs. Due to increasing life demands in young adulthood, HCPs need to be flexible when scheduling appointments and allocate sufficient time to meet with adolescent/

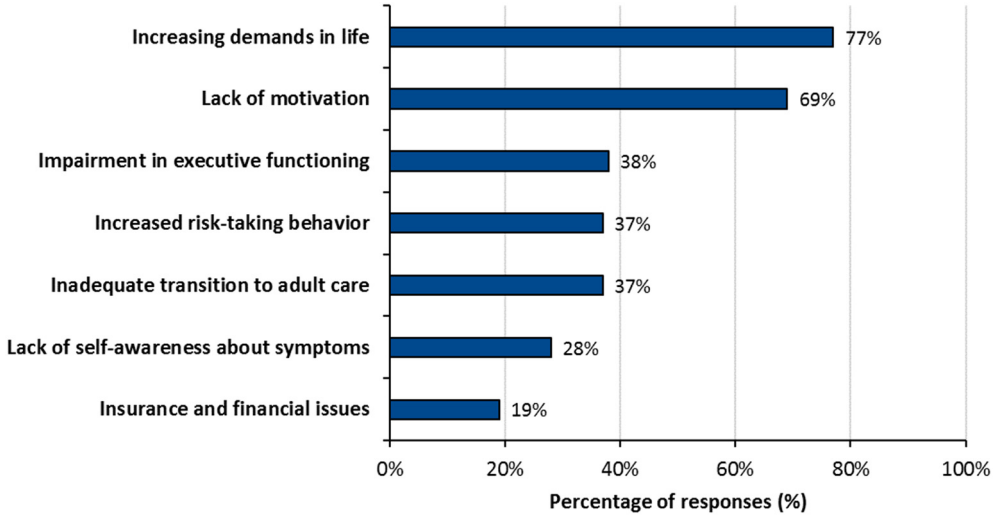

Fig. 3. Key factors contributing to loss to follow-up from adolescence onwards.
Factors were rated on a 7-point Likert scale (1–3: most important; 4: somewhat important; 5–7: least important). The figure shows the most important factors (score: 1–3) ranked in order of importance as reported by the experts.

young adult patients separately from their parent(s)/caregiver(s). Clinics and HCPs should actively and regularly stay in contact with adolescents/young adults with PKU, even if patients are unable to control their blood Phe levels. This includes an ability to incorporate strategies to track patients via their electronic medical health records, patient registries, or other follow-up systems, offering virtual visits, transition and management education, guidance about possible financial assistance, and providing information about new treatment options. If capacity allows, clinics can help to maintain future appointment schedules by sending regular reminders for blood spot tests and clinical appointments through secure and/or HIPAA-compliant emails or text messages. Having open communication to determine if reminders are helpful or bothersome, increases the likelihood of positive responses. Partnering with primary care providers can also be a viable strategy to ensure regular contact with the adolescent/young adult but only if these providers understand the need for continuous follow-up and the challenges faced by individuals with PKU.

3.5.1.3. Positive empowerment. Management should focus on positive empowerment and education should be constructive as loss to follow-up is likely to increase when only negative feedback is given to the adolescent/young adult with PKU. The role of the medical team should include active listening to understand and support the adolescent/young adult patient with PKU rather than use of authoritarian or punitive strategies that may increase feelings of isolation or guilt about failure to adhere to the medical nutritional therapy. An example of a potential strategy used to support positive empowerment is calling adolescents/young adults not only to report elevated and uncontrolled blood Phe levels, but also to provide positive feedback when blood Phe levels are within target range. Additionally, a strong patient-provider alliance will stimulate the patient to remain adherent with the restrictive diet and/or understand the potential consequences of increased blood Phe levels. HCPs can also empower patients by describing PKU and potential outcomes in a manner that promotes collaboration and focuses on the positive effects of achieving metabolic control while avoiding use of words such as 'non-compliant', 'brain damage', 'mental retardation', or 'moody'. Many patients are overwhelmed by the number of providers seen during their clinic visits, the volume and rate of information provided, and the complexity of instructions conveyed. Therefore, greater awareness and effort is needed from HCPs to provide adequate but limited information. Another potential strategy to promote positive self-empowerment is to support the adolescent/young adult with managing the medical nutrition therapy for a brief period of time (e.g., 2 weeks) to be followed by a discussion with the patient to determine if he/she experienced any perceived benefits of lower blood Phe levels.

3.5.1.4. Management beyond blood Phe. Management should be individualized focusing on setting life goals and considering potential mental health and neurocognitive challenges that affect day-to-day functional skills, with the aim of achieving the optimal QoL for each patient regardless of their metabolic control. Although lifelong metabolic control is the aim of treatment, care should be personalized, avoiding undertreatment but also overtreatment in patients with good clinical outcomes [25,26,47]. Regular screening for PKU-associated comorbidities, such as allergies, gastrointestinal disorders, mood/anxiety disorders, and attention/executive functioning can help to keep PKU adolescents/young adults engaged by offering treatments for these comorbidities or referring them to HCPs specialized in these comorbidities. Although this will be limited to some clinical centers, engagement of adolescents/young adults with PKU can be improved when HCPs are able to monitor PKU adolescents beyond blood Phe, e.g., dietitians experienced in both PKU and sports nutrition or experts in adolescent medicine. Additionally, PKU peer support groups offering skill-building activities, including cooking workshops and grocery tours, could aid to prevent lapse in care, reduce loss to follow-up, improve adherence to the treatment regimen, and facilitate the transition to more independence in managing PKU. Alternatively, engagement can be improved by caseworkers or social workers who frequently communicate with the adolescents/young adults to check-in. For young adult patients, involving their partner in PKU management is fundamental to ensure adherence to in-clinic appointments and treatment.

3.5.2. The parental or caregiver role during transition to adulthood

In practice, parents often continue to be responsible for their child's PKU management allowing the adolescent or young adult to focus on school, sports, and social activities. However, to be successful, the transition process should lead to the gradual development of independence while decreasing parental or caregiver support [99–101]. Nevertheless, it is important that parents/caregivers are encouraged to stay involved in some capacity throughout the entirety of the adolescent period. Through the process of gaining independence, adolescents/young adults may initially forget medication or become non-adherent to the medical nutritional therapy, exacerbating impairments in neurocognitive functioning, resulting in a vicious cycle of poor metabolic control and comorbidities. Well-balanced and flexible parental and/or caregiver guidance is, therefore, needed to support the adolescent/young adult throughout the entire transition process.

Statement #31	Consensus %
The transition process should initially involve both adolescents and parents with adolescents gradually required to assume more responsibility for managing their PKU, including being taught how to take their own blood tests and prepare their own meals. The parental role and the age during which the focus shifts from parent to adolescent will be dependent on the level of independence, degree of functionality, emotional intelligence, and level of engagement	91%
Statement #32	**Consensus %**
Parenting skills may play a role in future adherence of adolescents to PKU care. Parents/caregivers need to be involved from the beginning to appropriately educate their children on PKU. However, the importance of independence in the long-term should be emphasized	77%

Particularly between the ages of 12–18 years, adolescents should start developing an independent, trusting, and collaborative relationship with their HCP who often will bridge the gap between the adolescent and the parent/caregiver. Sensitive topics, such as birth control and alcohol and/or substance use, are often more freely discussed in the absence of parents/caregivers. Furthermore, adolescent's self-advocacy development will progress when they learn to communicate about their health and well-being.

Statement #33	Consensus %
Between the ages of 12–18 years old, it is important to allocate sufficient time to meet privately with adolescents in clinic to encourage the adolescent to take over the responsibility for PKU management	77%

3.5.3. Ensuring successful transition to adulthood

In the absence of validated assessment tools available to determine the readiness of the patient to transition to adult care, the neurocognitive status, particularly executive functioning skills, can be assessed along with understanding the patient's knowledge about PKU and their ability to independently manage their disease on a daily basis in various settings, such as work, school, home, and relationships. Clinical centers aiming to standardize their transition protocol may use the Boston Children's Hospital Transition Toolkit as a template, adjusting it to comply with their local regulations and center policies [102]. This toolkit (available via the reference link) provides medical information on PKU and a general transition plan to be completed with the treating HCP. Additionally, it includes a health readiness questionnaire, albeit not PKU-specific, used to assess if a patient is ready to handle his/her health care as an independent adult. Alternatively, diabetes transition toolkits and questionnaires,

such as the Transition Readiness Assessment Questionnaires (TRAQ) for youth/young adults and/or their caregivers/parents, can serve as templates for the development of PKU-specific transitional protocols with adaptations reflecting PKU [103,104].

In PKU, only two studies have described a transition-to-adult care protocol keeping most patients in follow-up [99,105]. This limited experience is related to the scarcity of adult-focused PKU clinics due to relatively few adult-specific metabolic physicians and the lack of financial resources, often resulting in non-standardized or even non-existent transition protocols [16,106]. Adult care programs should ideally be staffed by a multidisciplinary team knowledgeable about PKU and consist of metabolic physicians, dietitians, nurses, genetic counselors, social workers, and (neuro)psychologists.

Statement #34	Consensus %
Despite regional differences, the transition to adulthood is best managed by specialized metabolic clinics experienced in managing individuals with PKU. Ideally, the team consists of metabolic physicians, dietitians, nurses, genetic counselors, social workers, and (neuro)psychologists/mental health clinicians who are all appropriately educated on PKU as well as on the prevention and identification of potentially PKU-associated comorbidities. When clinically indicated, adolescents/young adults with PKU should be referred to a psychiatrist and/or neurologist knowledgeable about PKU	86%

As providers involved in the transition process have often not received specific training on managing health issues in adolescents with metabolic disorders, improving education on PKU and its associated comorbidities is a prerequisite in many countries [106]. When patients are having a good relationship with the pediatric care team, the transition to adult care process can be improved by ensuring for a few years continuity of care with the presence of the same HCPs (nutritionists and psychologists) in the pediatric and adult care team [16,99]. Although patients with PKU would benefit from adult-oriented resources, these are often not available and patients need to continue being followed in a pediatric care setting [16]. Regardless, successful transition to adulthood should consider the key factors contributing to loss to follow-up (Fig. 3).

Statement #35	Consensus %
Depending on differences among clinical centers, successful transition to adulthood can be achieved by either continuous follow-up by providers in the metabolic specialty care clinic located within the pediatric care setting or, when available, by transitioning from a pediatric metabolic clinic to an adult metabolic care center. Regardless of the setting in which care is provided, the general transition process or program needs to be individualized depending on the functionality of each patient and the level of independence	91%
Statement #36	**Consensus %**
The success of transition to adult care will be highly dependent on the capacity of the treatment center and will be improved if continuity of care is assured by limiting changes in treating physicians. Furthermore, metabolic pediatricians should speak positively of the adult care provider who should be motivated and appropriately educated on PKU	83%
Statement #37	**Consensus %**
Primary care centers can help support the transition, under the direction of the PKU clinic. Telemedicine tools are helpful to overcome geographic barriers	71%

4. Limitations

Due to the limited availability of peer-reviewed literature on the management of adolescents and young adults, these consensus recommendations are in part based on personal experiences within PKU and other metabolic disorders along with opinions of the multidisciplinary international expert panel, though supported with evidence from literature when available. Albeit consensus generation was used to develop the recommendations, they cannot be seen as evidence, encouraging continued efforts to expand the evidence base for the adolescent and young adult PKU population. Implementation of these consensus recommendations will largely depend on clinical capacity, staffing, and availability of resources of each clinical center. Therefore, these consensus recommendations are intended only to provide guidance as they may not be generalizable to clinical centers with limited resources. Additionally, the consensus recommendations are focused on early treated adolescents and young adults with PKU, requiring adaptation to those patients with a severe impact on neurocognition.

5. Conclusions

Consensus among an international multidisciplinary group of PKU and non-PKU experts was achieved on five aspects of the management of adolescents and young adults with PKU: general physical health, mental health and neurocognitive functioning, blood Phe target range, PKU-specific challenges, and transition to adulthood. These consensus recommendations aim to provide guidance and offer tools to clinics supporting adolescents and young adults with PKU with consideration of differences in clinical capacity and country-specific limitations. In addition to providing guidance, the consensus recommendations can inform the updating of current PKU management guidelines. Dissemination of the consensus recommendations will be important for implementation, as well as an evaluation to determine if they improve clinical outcomes of adolescents and young adults with PKU.

Funding

This work was supported by BioMarin Pharmaceutical Inc.

Authors' contributions

All authors participated in the two virtual meetings leading to the development of the consensus recommendations described in this manuscript. All authors have reviewed and approved the submitted manuscript.

Declaration of competing interest

The content of this manuscript was based on preparatory pre-meeting activities and presentations and discussions during two advisory board meetings that were coordinated and funded by BioMarin Pharmaceutical Inc. All authors or their institutions received funding from BioMarin to attend at least one or both meetings. Additional disclosures: BKB received consulting payments from BioMarin, Shire, Genzyme, Alexion, Horizon Therapeutics, Denali Therapeutics, JCR Pharma, Moderna, Aeglea BioTherapeutics, SIO Gene Therapies, Taysha Gene Therapy, Ultragenyx, and Inventiva Pharma, participated as clinical trial investigator for BioMarin, Shire, Denali Therapeutics, Homology Medicines, Ultragenyx, and Moderna as well as received speaker fees from BioMarin, Shire, Genzyme, and Horizon Therapeutics. AH received consulting payments from BioMarin, Chiesi, Shire, Genzyme, Amicus, and Ultragenyx, participated as clinical trial investigator for Ultragenyx as well as received speaker fees from Alexion, Amicus, BioMarin, Genzyme, Nutricia, Sobi, and Takeda. ABQ received consulting payments from BioMarin, speaker fees from BioMarin, Nutricia, Vitaflo, Sanofi, Takeda, Recordati, and travel support from Vitaflo. SEC received consulting payments and speaker fees from BioMarin as well as consulting payments from Synlogic Therapeutics. COH was clinical trial investigator for BioMarin and received consulting and speaker payments from BioMarin. SCJH received consulting payments and travel support from BioMarin and Homology Medicines. NL received consulting payments

from Alnylam, Amicus, Astellas, BioMarin, BridgeBio, Chiesi, Genzyme/Sanofi, HemoShear, Horizon Therapeutics, Jaguar, Moderna, Nestle, PTC Therapeutics, Reneo, Shire, Synlogic, and Ultragenyx, participated as clinical trial investigator for Aeglea, Amicus, Astellas, BioMarin, Genzyme/Sanofi, Homology, Horizon, Moderna, Pfizer, Protalix, PTC Therapeutics, Reneo, Retrophin/Travere therapeutics, Shire, and Ultragenyx, as well as received speaker fees from Cycle Pharmaceuticals, Leadiant and Recordati. MCM II received consulting payments from BioMarin, Horizon Therapeutics, Rhythm Pharmaceuticals, Applied Therapeutics, Cycle Therapeutics, and Ultragenyx. ALSP received speaker fees from BioMarin. JCR received consulting payments from Applied Pharma Research, Merck Serono, BioMarin, Vitaflo, and Nutricia, speaker fees from Applied Pharma Research, Merck Serono, BioMarin Pharmaceutical, Vitaflo, Cambrooke, PIAM, LifeDiet, and Nutricia, as well as travel support from Applied Pharma Research, Merck Serono, BioMarin, Vitaflo, Cambrooke, PIAM, and Nutricia. SS received consulting payments, research grants, speaker fees, and travel support from BioMarin and participated as clinical trials investigator for BioMarin. ASV received consulting payments from BioMarin, Horizon Therapeutics, and Ultragenyx and participated as clinical trial investigator for Acadia, Alexion, BioMarin, Genzyme, Homology Medicines, Kaleido, Mallinckrodt, and Ultragenyx. JV received consulting payments from BioMarin, LogicBio Pharmaceuticals, Sangamo Therapeutics, Orphan Labs, Synlogic Therapeutics, Sanofi, Axcella Health, Agios Pharmaceuticals, and Applied Therapeutics as well as travel grants from BioMarin and LogicBio Pharmaceuticals. MW received consulting payments, speaker fees, and travel support from BioMarin, and participated as clinical trial investigator for Mallinckrodt, Roche, Wave, Cycle Therapeutics, and Intrabio. ACM participated in strategic advisory boards and received honoraria as a consultant and as a speaker for Merck Serono, BioMarin, Nestlé Health Science (SHS), Applied Pharma Research, Actelion, Retrophin, Censa, PTC Therapeutics, and Arla Food.

Acknowledgments

We would like to thank Deborah A. Bilder, François Maillot, and Friedrich K. Trefz for sharing their expertise with managing adolescents and young adults with PKU during the first virtual expert panel meeting. Additionally, we would like to acknowledge Christine S. Brown for her valuable contributions to the first virtual expert panel meeting and the virtual consolidation meeting. The authors are grateful to Ismar Healthcare NV who provided medical writing assistance on behalf of BioMarin Pharmaceutical Inc.

References

[1] N. Blau, F.J. van Spronsen, H.L. Levy, Phenylketonuria, Lancet 376 (2010) 1417–1427.
[2] K. Ashe, W. Kelso, S. Farrand, J. Panetta, T. Fazio, G. De Jong, et al., Psychiatric and **c**ognitive **a**spects of **p**henylketonuria: **t**he **l**imitations of **d**iet and **p**romise of **n**ew **t**reatments, Front. Psychiatry 10 (2019) 561.
[3] A.M.J. van Wegberg, A. MacDonald, K. Ahring, A. Belanger-Quintana, N. Blau, A.M. Bosch, et al., The complete European guidelines on phenylketonuria: diagnosis and treatment, Orphanet J. Rare Dis. 12 (2017) 162.
[4] J. Vockley, H.C. Andersson, K.M. Antshel, N.E. Braverman, B.K. Burton, D.M. Frazier, et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genet Med. 16 (2014) 188–200.
[5] PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use, Highlights of Prescribing Information, Accessed 11 Oct 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761079s000lbl.pdf 2018.
[6] PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use, Summary of Product Characteristics, Accessed 11 Oct 2021 https://www.ema.europa.eu/en/documents/product-information/palynziq-epar-product-information_en.pdf 2019.
[7] N. Longo, D. Dimmock, H. Levy, K. Viau, H. Bausell, D.A. Bilder, et al., Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria, Genet Med. 21 (2019) 1851–1867.
[8] R. Zori, K. Ahring, B. Burton, G.M. Pastores, F. Rutsch, A. Jha, et al., Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria, Mol. Genet. Metab. 128 (2019) 92–101.
[9] B.K. Burton, K.B. Jones, S. Cederbaum, F. Rohr, S. Waisbren, D.E. Irwin, et al., Prevalence of comorbid conditions among adult patients diagnosed with phenylketonuria, Mol. Genet. Metab. (2018) https://doi.org/10.1016/j.ymgme.2018.09.006.
[10] D.A. Bilder, J.A. Kobori, J.L. Cohen-Pfeffer, E.M. Johnson, E.R. Jurecki, M.L. Grant, Neuropsychiatric comorbidities in adults with phenylketonuria: **a** retrospective cohort study, Mol. Genet. Metab. 121 (2017) 1–8.
[11] K.F. Trefz, A.C. Muntau, K.M. Kohlscheen, J. Altevers, C. Jacob, S. Braun, et al., Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities – a retrospective study of German health insurance claims data, Orphanet J. Rare Dis. 14 (2019) 181.
[12] E.R. Jurecki, S. Cederbaum, J. Kopesky, K. Perry, F. Rohr, A. Sanchez-Valle, et al., Adherence to clinic recommendations among patients with phenylketonuria in the United States, Mol. Genet. Metab. 120 (2017) 190–197.
[13] G.M. Enns, R. Koch, V. Brumm, E. Blakely, R. Suter, E. Jurecki, Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence, Mol. Genet. Metab. 101 (2010) 99–109.
[14] V. Kanufre, M.F. Almeida, C.S. Barbosa, C. Carmona, A. Bandeira, E. Martins, et al., Metabolic **c**ontrol of **p**atients with **p**henylketonuria in a Portuguese **m**etabolic centre **c**omparing **t**hree **d**ifferent **r**ecommendations, Nutrients 13 (9) (2021) 3118.
[15] S.A. Berry, C. Brown, M. Grant, C.L. Greene, E. Jurecki, J. Koch, et al., Newborn screening 50 years later: access issues faced by adults with PKU, Genet Med. 15 (2013) 591–599.
[16] J.S. Suddaby, D. Sohaei, H. Bell, S. Tavares, G.J. Lee, M. Szybowska, et al., Adult patient perspectives on phenylketonuria care: **h**ighlighting the need for dedicated adult management and services, Eur. J. Med. Genet. 63 (2020) 103818.
[17] A. Burlina, G. Biasucci, M.T. Carbone, C. Cazzorla, S. Paci, F. Pochiero, et al., Italian national consensus statement on management and pharmacological treatment of phenylketonuria, Orphanet J. Rare Dis. 16 (2021) 476.
[18] Adolescent and Young Adult Health, Accessed 22 Mar 2022 https://www.who.int/news-room/fact-sheets/detail/adolescents-health-risks-and-solutions.
[19] Delphi Method – RAND Corporation, Accessed 11 October 2021 https://www.rand.org/topics/delphi-method.html.
[20] R. Sharman, K. Sullivan, R.M. Young, J. McGill, Depressive symptoms in adolescents with early and continuously treated phenylketonuria: associations with phenylalanine and tyrosine levels, Gene 504 (2012) 288–291.
[21] R. Sharman, K. Sullivan, R. Young, J. McGill, A preliminary investigation of the role of the phenylalanine: tyrosine ratio in children with early and continuously treated phenylketonuria: toward identification of "safe" levels, Dev. Neuropsychol. 35 (2010) 57–65.
[22] J.B. Hennermann, S. Roloff, J. Gellermann, I. Vollmer, E. Windt, B. Vetter, et al., Chronic kidney disease in adolescent and adult patients with phenylketonuria, J. Inherit. Metab. Dis. 36 (2013) 747–756.
[23] F. Porta, A. Mussa, A. Zanin, N.A. Greggio, A. Burlina, M. Spada, Impact of metabolic control on bone quality in phenylketonuria and mild hyperphenylalaninemia, J. Pediatr. Gastroenterol. Nutr. 52 (2011) 345–350.
[24] L. Aitkenhead, G. Krishna, C. Ellerton, M. Moinuddin, J. Matcham, L. Shiel, et al., Long-term cognitive and psychosocial outcomes in adults with phenylketonuria, J. Inherit. Metab. Dis. 44 (6) (2021) 1353–1368.
[25] F. Nardecchia, F. Manti, F. Chiarotti, C. Carducci, C. Carducci, V. Leuzzi, Neurocognitive and neuroimaging outcome of early treated young adult PKU patients: **a** longitudinal study, Mol. Genet. Metab. 115 (2015) 84–90.
[26] C. Romani, L. Palermo, A. MacDonald, E. Limback, S.K. Hall, T. Geberhiwot, The impact of phenylalanine levels on cognitive outcomes in adults with phenylketonuria: **e**ffects across tasks and developmental stages, Neuropsychology 31 (2017) 242–254.
[27] K.M. Antshel, ADHD, learning, and academic performance in phenylketonuria, Mol. Genet. Metab. 99 (Suppl. 1) (2010) S52–S58.
[28] J. Weglage, B. Funders, K. Ullrich, A. Rupp, E. Schmidt, Psychosocial aspects in phenylketonuria, Eur. J. Pediatr. 155 (Suppl. 1) (1996) S101–S104.
[29] J. Weglage, M. Grenzebach, M. Pietsch, R. Feldmann, R. Linnenbank, J. Denecke, et al., Behavioural and emotional problems in early-treated adolescents with phenylketonuria in comparison with diabetic patients and healthy controls, J. Inherit. Metab. Dis. 23 (2000) 487–496.
[30] A.S.F. Kwong, D. Manley, N.J. Timpson, R.M. Pearson, J. Heron, H. Sallis, et al., Identifying critical points of trajectories of depressive symptoms from childhood to young adulthood, J. Youth Adolesc. 48 (2019) 815–827.
[31] J.M. Lijster, B. Dierckx, E.M. Utens, F.C. Verhulst, C. Zieldorff, G.C. Dieleman, et al., The age of onset of anxiety disorders, Can. J. Psychiatr. 62 (2017) 237–246.
[32] K. Rechenberg, R. Whittemore, M. Grey, Anxiety in **y**outh **w**ith **t**ype 1 **d**iabetes, J. Pediatr. Nurs. 32 (2017) 64–71.
[33] A. Hood, J. Rutlin, J.S. Shimony, D.K. Grange, D.A. White, Brain white matter integrity mediates the relationship between phenylalanine control and executive abilities in children with phenylketonuria, JIMD Rep. 33 (2017) 41–47.
[34] D.A. Bilder, J.K. Noel, E.R. Baker, W. Irish, Y. Chen, M.J. Merilainen, et al., Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria, Dev. Neuropsychol. 41 (2016) 245–260.
[35] Z. Hawks, A.M. Hood, D.B. Lerman-Sinkoff, J.S. Shimony, J. Rutlin, D. Lagoni, et al., White and gray matter brain development in children and young adults with phenylketonuria, Neuroimage Clin. 23 (2019) 101916.
[36] R. Jahja, F.J. van Spronsen, L.M.J. de Sonneville, J.J. van der Meere, A.M. Bosch, C.E.M. Hollak, et al., Social-cognitive functioning and social skills in patients with early treated phenylketonuria: a PKU-COBESO study, J. Inherit. Metab. Dis. 39 (2016) 355–362.
[37] M.G. Gejao, A.T. Ferreira, G.K. Silva, L. Anastacio-Pessan Fda, D.A. Lamonica, Communicative and psycholinguistic abilities in children with phenylketonuria and congenital hypothyroidism, J. Appl. Oral Sci. 17 (Suppl) (2009) 69–75.
[38] D. Janzen, M. Nguyen, Beyond executive function: non-executive cognitive abilities in individuals with PKU, Mol. Genet. Metab. 99 (Suppl. 1) (2010) S47–S51.

[39] R. Gassió, R. Artuch, M.A. Vilaseca, E. Fusté, C. Boix, A. Sans, et al., Cognitive functions in classic phenylketonuria and mild hyperphenylalaninaemia: experience in a paediatric population, Dev. Med. Child Neurol. 47 (2005) 443–448.
[40] S.E. Christ, E.E. Abbene, H.E. Clocksin, A.K. Wegrzyn, Motor control and learning in individuals with early-treated phenylketonuria, Neuropsychology 35 (7) (2021) 731–741.
[41] A.L. Janos, D.K. Grange, R.D. Steiner, D.A. White, Processing speed and executive abilities in children with phenylketonuria, Neuropsychology 26 (2012) 735–743.
[42] J. Weglage, M. Pietsch, J. Denecke, A. Sprinz, R. Feldmann, M. Grenzebach, et al., Regression of neuropsychological deficits in early-treated phenylketonurics during adolescence, J. Inherit. Metab. Dis. 22 (1999) 693–705.
[43] D.L. Hofman, C.L. Champ, C.L. Lawton, M. Henderson, L. Dye, A systematic review of cognitive functioning in early treated adults with phenylketonuria, Orphanet J Rare Dis. 13 (2018) 150.
[44] C.J. Fonnesbeck, M.L. McPheeters, S. Krishnaswami, M.L. Lindegren, T. Reimschisel, Estimating the probability of IQ impairment from blood phenylalanine for phenylketonuria patients: a hierarchical meta-analysis, J. Inherit. Metab. Dis. 36 (2013) 757–766.
[45] K.S. Viau, H.J. Wengreen, S.L. Ernst, N.L. Cantor, L.V. Furtado, N. Longo, Correlation of age-specific phenylalanine levels with intellectual outcome in patients with phenylketonuria, J. Inherit. Metab. Dis. 34 (2011) 963–971.
[46] L. Palermo, T. Geberhiwot, A. MacDonald, E. Limback, S.K. Hall, C. Romani, Cognitive outcomes in early-treated adults with phenylketonuria (PKU): a comprehensive picture across domains, Neuropsychology 31 (2017) 255–267.
[47] V. Leuzzi, F. Chiarotti, F. Nardecchia, D. van Vliet, F.J. van Spronsen, Predictability and inconsistencies of cognitive outcome in patients with phenylketonuria and personalised therapy: the challenge for the future guidelines, J. Med. Genet. 57 (2020) 145–150.
[48] R.E. Gur, T.M. Moore, A.F.G. Rosen, R. Barzilay, D.R. Roalf, M.E. Calkins, et al., Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths, JAMA Psychiatry. 76 (2019) 966–975.
[49] L. Lo Iacono, V. Carola, The impact of adolescent stress experiences on neurobiological development, Semin. Cell Dev. Biol. 77 (2018) 93–103.
[50] S. Doering, P. Lichtenstein, C. Gillberg, Middeldorp C.M. NTR, M. Bartels, R. Kuja-Halkola, S. Lundström, Anxiety at age 15 predicts psychiatric diagnoses and suicidal ideation in late adolescence and young adulthood: results from two longitudinal studies, BMC Psychiatry 19 (1) (2019) 363.
[51] A. Chronis-Tuscano, B.S. Molina, W.E. Pelham, B. Applegate, A. Dahlke, M. Overmyer, B.B. Lahey, Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder, Arch. Gen. Psychiatry 67 (10) (2010) 1044–1051.
[52] C. Barbosa, J.G. Simmons, N. Vijayakumar, P. Dudgeon, G.C. Patton, L.K. Mundy, et al., Interaction **b**etween **p**arenting **s**tyles and adrenarcheal **t**iming **a**ssociated **w**ith **a**ffective **b**rain **f**unction in **l**ate **c**hildhood, J. Am. Acad. Child Adolesc. Psychiatry 57 (9) (2018) 678–686.
[53] S. Whittle, J.G. Simmons, M. Dennison, N. Vijayakumar, O. Schwartz, M.B. Yap, et al., Positive parenting predicts the development of adolescent brain structure: a longitudinal study, Dev. Cogn. Neurosci. 8 (2014) 7–17.
[54] S. Whittle, N. Vijayakumar, J.G. Simmons, M. Dennison, O. Schwartz, C. Pantelis, et al., Role of positive parenting in the association between neighborhood social disadvantage and brain development across adolescence, JAMA Psychiatry 74 (2017) 824–832.
[55] C.E. Ievers-Landis, A. Hoff, C. Brez, M.K. Cancilliere, J. McConnell, D. Kerr, Situational **a**nalysis of **d**ietary **c**hallenges of the **t**reatment **r**egimen for **c**hildren and **a**dolescents with **p**henylketonuria and **t**heir **p**rimary **c**aregivers, J. Dev. Behav. Pediatr. 26 (3) (2005) 186–193.
[56] J. Pietz, B. Fätkenheuer, P. Burgard, M. Armbruster, G. Esser, H. Schmidt, Psychiatric disorders in adult patients with early-treated phenylketonuria, Pediatrics 99 (1997) 345–350.
[57] F. Irannejad, M. Dehghan, Rabori R. Mehdipour, Stress and quality of life in parents of children with phenylketonuria, J. Child Adolesc. Psychiatr. Nurs. 31 (2018) 48–52.
[58] L. Borghi, E. Salvatici, G. Banderali, E. Riva, M. Giovannini, E. Vegni, Psychological wellbeing in parents of children with phenylketonuria and association with treatment adherence, Minerva Pediatr. (Torino). 73 (4) (2021) 330–339.
[59] American Psychological Association, Self-Care Resource Center, Accessed 21 Apr 2022 https://www.apa.org/topics/working-psychologist/self-care.
[60] T. Hendriks, J. de Jong, H. Cramer, The **e**ffects of **y**oga on **p**ositive **m**ental **h**ealth **a**mong **h**ealthy **a**dults: **a** **s**ystematic **r**eview and meta-**a**nalysis, J. Altern. Complement. Med. 23 (7) (2017 Jul) 505–517.
[61] Patient Health Questionnaire (PHQ) Screeners, Accessed 21 Apr 2022 https://www.phqscreeners.com.
[62] Pediatric Symptom Checklist; PSC-17 Description, Accessed 11 Oct 2021 https://www.seattlechildrens.org/globalassets/documents/healthcare-professionals/pal/ratings/psc-17-rating-scale.pdf.
[63] Pediatric Symptom Checklist 17 Youth Form, Accessed 11 Oct 2021 https://ahpnetwork.com/wp-content/uploads/2020/04/PSC.17-Youth.pdf.
[64] Patient Health Questionnaire (PHQ-SADS), Accessed 11 Oct 2021 https://www.corecarefht.ca/PHQ-SADS%20with%20scoring.pdf.
[65] The Four-Item Patient Health Questionnaire for Anxiety and Depression, Accessed 11 Oct 2021 https://www.oregonpainguidance.org/app/content/uploads/2016/05/PHQ-4.pdf.
[66] Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions, Accessed 11 Oct 2021 https://add.org/wp-content/uploads/2015/03/adhd-questionnaire-ASRS111.pdf.
[67] S.E. Christ, H.E. Clocksin, B.K. Burton, M.L. Grant, S. Waisbren, M.C. Paulin, et al., Executive function in phenylketonuria (PKU): insights from the Behavior Rating Inventory of Executive Function (BRIEF) and a large sample of individuals with PKU, Neuropsychology 34 (4) (2020) 456–466.
[68] G.B. Liemburg, R. Jahja, F.J. van Spronsen, L.M. de Sonneville, J.J. van der Meere, A.M. Bosch, et al., Is BRIEF a useful instrument in day to day care of patients with phenylketonuria? Mol. Genet. Metab. 114 (2015) 425–430.
[69] K.W. Wyrwich, K.S. Gries, G. Al-Jassar, D.E. Bacci, Y. Chen, R. Jain, et al., Assessing the content validity of the investigator-rated ADHD rating scale version IV instrument inattention subscale for use in adults with phenylketonuria, J. Inborn Errors Metab. Screen. 4 (2016), e160027.
[70] B.K. Burton, A. Skalicky, C. Baerwald, D.A. Bilder, C.O. Harding, A.B. Ilan, et al., A non-interventional observational study to identify and validate clinical outcome assessments for adults with phenylketonuria for use in clinical trials, Mol. Genet. Metab. Rep. 29 (2021) 100810.
[71] J.J. Moyle, A.M. Fox, M. Arthur, M. Bynevelt, J.R. Burnett, Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU, Neuropsychol. Rev. 17 (2007) 91–101.
[72] P.J. Anderson, S.J. Wood, D.E. Francis, L. Coleman, V. Anderson, A. Boneh, Are neuropsychological impairments in children with early-treated phenylketonuria (PKU) related to white matter abnormalities or elevated phenylalanine levels? Dev. Neuropsychol. 32 (2007) 645–668.
[73] A.G. Carlson, E. Rowe, T.W. Curby, Disentangling fine motor skills' relations to academic achievement: the relative contributions of visual-spatial integration and visual-motor coordination, J. Genet. Psychol. 174 (5–6) (2013) 514–533.
[74] M.A. Cleary, J.H. Walter, J.E. Wraith, F. White, K. Tyler, J.P. Jenkins, Magnetic resonance imaging in phenylketonuria: reversal of cerebral white matter change, J. Pediatr. 127 (1995) 251–255.
[75] J.A.V. Antenor-Dorsey, T. Hershey, J. Rutlin, J.S. Shimony, R.C. McKinstry, D.K. Grange, et al., White matter integrity and executive abilities in individuals with phenylketonuria, Mol. Genet. Metab. 109 (2013) 125–131.
[76] D.A. White, J.A.V. Antenor-Dorsey, D.K. Grange, T. Hershey, J. Rutlin, J.S. Shimony, et al., White matter integrity and executive abilities following treatment with tetrahydrobiopterin (BH_4) in individuals with phenylketonuria, Mol. Genet. Metab. 110 (2013) 213–217.
[77] B. Burton, M. Grant, A. Feigenbaum, R. Singh, R. Hendren, K. Siriwardena, et al., A randomized, placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria, Mol. Genet. Metab. 114 (2015) 415–424.
[78] J. Thomas, H. Levy, S. Amato, J. Vockley, R. Zori, D. Dimmock, et al., Pegvaliase for the treatment of phenylketonuria: **r**esults of a long-term phase 3 clinical trial program (PRISM), Mol. Genet. Metab. 124 (2018) 27–38.
[79] N.M. Burgess, W. Kelso, C.B. Malpas, T. Winton-Brown, T. Fazio, J. Panetta, et al., The effect of improved dietary control on cognitive and psychiatric functioning in adults with phenylketonuria: the ReDAPT study, Orphanet J. Rare Dis. 16 (2021) 35.
[80] S. Whittle, The role of sport involvement in reducing depressive symptoms via changes to hippocampal structure: next steps for research in developing samples, Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4 (2019) 421–422.
[81] P.C. Casarotto, M. Girych, S.M. Fred, V. Kovaleva, R. Moliner, G. Enkavi, et al., Antidepressant drugs act by directly binding to TRKB neurotrophin receptors, Cell 184 (5) (2021) 1299–1313.
[82] A. Pilotto, C.M. Zipser, E. Leks, D. Haas, G. Gramer, P. Freisinger, et al., Phenylalanine effects on brain function in adult phenylketonuria, Neurology. 96 (2021) e399–e411.
[83] S.G. Evinç, E. Pektaş, D. Foto-Özdemir, Y. Yildiz, Y. Karaboncuk, B. Bilginer-Gürbüz, et al., Cognitive and behavioral impairment in mild hyperphenylalaninemia, Turk. J. Pediatr. 60 (2018) 617–624.
[84] R. Jahja, S.C. Huijbregts, L.M.J. de Sonneville, J.J. van der Meere, F.J. van Spronsen, Neurocognitive evidence for revision of treatment targets and guidelines for phenylketonuria, J. Pediatr. 164 (2014) 895–899 (e2).
[85] C. Romani, F. Manti, F. Nardecchia, F. Valentini, N. Fallarino, C. Carducci, et al., Adult cognitive outcomes in phenylketonuria: explaining causes of variability beyond average Phe levels, Orphanet J Rare Dis. 14 (2019) 273.
[86] L. Palermo, A. MacDonald, E. Limback, L. Robertson, S. Howe, T. Geberhiwot, et al., Emotional health in early-treated adults with phenylketonuria (PKU): relationship with cognitive abilities and blood phenylalanine, J. Clin. Exp. Neuropsychol. 42 (2020) 142–159.
[87] J.C. Rocha, H. Bausell, A. Bélanger-Quintana, L. Bernstein, H. Gökmen-Özel, A. Jung, et al., Development of a practical dietitian road map for the nutritional management of phenylketonuria (PKU) patients on pegvaliase, Mol. Genet. Metab. Rep. 28 (2021) 100771.
[88] C.O. Harding, R.S. Amato, M. Stuy, N. Longo, B.K. Burton, J. Posner, et al., Pegvaliase for the treatment of phenylketonuria: **a** pivotal, double-blind randomized discontinuation Phase 3 clinical trial, Mol. Genet. Metab. 124 (2018) 20–26.
[89] S. Luu, T. Breunig, N. Drilias, A. Kuhl, J. Scott Schwoerer, P. Cody, A survey of eating attitudes and behaviors in adolescents and adults with phenylalanine hydroxylase deficiency, WMJ. 119 (2020) 37–43.
[90] K.L. Klump, Puberty as a critical risk period for eating disorders: a review of human and animal studies, Horm. Behav. 64 (2) (2013 Jul) 399–410.
[91] R.H. Singh, J.A. Kable, N.V. Guerrero, K.M. Sullivan, L.J. Elsas 2nd., Impact of a camp experience on phenylalanine levels, knowledge, attitudes, and health beliefs relevant to nutrition management of phenylketonuria in adolescent girls, J. Am. Diet. Assoc. 100 (2000) 797–803.
[92] National PKU alliance (NPKUA), Accessed 14 Dec 2021 https://www.npkua.org/.

[93] European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (E.S.PKU), Accessed 14 Dec 2021 https://www.espku.org/.
[94] B.J. Casey, R.M. Jones, T.A. Hare, The adolescent brain, Ann. N. Y. Acad. Sci. 1124 (2008) 111–126.
[95] V. Rovelli, J. Zuvadelli, V. Ercoli, C. Montanari, S. Paci, A.R. Dionigi, et al., PKU and COVID19: **h**ow the pandemic changed metabolic control, Mol. Genet. Metab. Rep. 27 (2021) 100759.
[96] T. Zubarioglu, D. Hopurcuoglu, E. Uygur, S. Ahmadzada, E. Oge-Enver, E. Isat, et al., The impact of telemedicine for monitoring and treatment of phenylketonuria patients on metabolic outcome during coronavirus disease-19 outbreak, Telemed. J. E Health 28 (2) (2021) 258–265.
[97] L. Whitehead, P. Seaton, The **e**ffectiveness of **s**elf-**m**anagement mobile **p**hone and **t**ablet **a**pps in **l**ong-term **c**ondition **m**anagement: **a** **s**ystematic **r**eview, J. Med. Internet Res. 18 (5) (2016), e97.
[98] E. Russell-Minda, J. Jutai, M. Speechley, K. Bradley, A. Chudyk, R. Petrella, Health technologies for monitoring and managing diabetes: a systematic review, J. Diabetes Sci. Technol. 3 (2009) 1460–1471.
[99] M. Peres, M.F. Almeida, E.J. Pinto, C. Carmona, S. Rocha, A. Guimas, et al., Implementing a transition program from paediatric to adult services in phenylketonuria: results after two years of follow-up with an adult team, Nutrients 13 (2021).
[100] P.H. White, W.C. Cooley, Transitions Clinical Report Authoring G, American Academy Of P, American Academy Of Family P, American College Of P, Supporting the health care transition from adolescence to adulthood in the medical home, Pediatrics 142 (2018).
[101] A. MacDonald, M. van Rijn, F. Feillet, A.M. Lund, L. Bernstein, A.M. Bosch, et al., Adherence issues in inherited metabolic disorders treated by low natural protein diets, Ann. Nutr. Metab. 61 (2012) 289–295.
[102] Boston Children's Hospital Transition Toolkit, Accessed 11 Oct 2021 https://static1.squarespace.com/static/5ea9c07209fe541ac782bd9b/t/5f91f5d775196c55b8f72fd2/1603401176462/Transition-Toolkit-Phenylketonuria-PKU.pdf.
[103] Transitions of Care, Accessed 11 Oct 2021 https://www.endocrine.org/improving-practice/patient-resources/transitions.
[104] D.L. Wood, G.S. Sawicki, M.D. Miller, C. Smotherman, K. Lukens-Bull, W.C. Livingood, M. Ferris, D.F. Kraemer, The **t**ransition **r**eadiness **a**ssessment **q**uestionnaire (TRAQ): its factor structure, reliability, and validity, Acad. Pediatr. 14 (4) (2014) 415–422.
[105] U. Mütze, A.G. Thiele, C. Baerwald, U. Ceglarek, W. Kiess, S. Beblo, Ten years of specialized adult care for phenylketonuria – a single-centre experience, Orphanet J. Rare Dis. 11 (2016) 27.
[106] K.M. Stepien, B. Kieć-Wilk, C. Lampe, T. Tangeraas, G. Cefalo, N. Belmatoug, et al., Challenges in transition from childhood to adulthood care in rare metabolic diseases: results from the First Multi-Center European Survey, Front. Med. (Lausanne) 8 (2021) 652358.