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Review article

The management of transitional care of patients affected by phenylketonuria in Italy: Review and expert opinion

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ABSTRACT

Phenylketonuria (PKU) is a metabolic inherited disorder in which transition from infancy to adult care is particularly difficult and not sufficiently regulated. According to the scientific literature, only few medical centers offer healthcare assistance for adult patients with PKU that are therefore still treated in pediatric settings. This generates psychological, emotional, and organizational discomfort among patients, leading them to discontinue the follow-up. European guidelines and national consensus documents underline this unmet need and the lack of practical recommendations for a structured transitional pathway in PKU. The aim of this review and expert opinion is to propose good practices for managing the transition period of PKU patients, based on the literature and the experience of a panel of Italian experts in PKU. The consensus of the experts was obtained through the administration of three rounds of surveys and one structured interview. The result is the first proposal of a pathway for an efficient transition of PKU patients. Key steps of the proposed pathway are the "a priori" planning involving the pediatric and adult teams, the acceptance of the patient and his/her family to the process, the preliminary definition of appropriate spaces in the structure, the organization of meetings with the joint team, and the appointment of a transition coordinator. For the first time, the involvement of decision makers and patient associations is proposed.

Contents

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1. Introduction

Chronic diseases affect patients from childhood to adulthood. Life expectancy of patients affected by chronic pathologies, including inherited metabolic disorders (IMD), increased over the last decades, most of them reaching the adult age. Therefore, care of such patients needs to continue from pediatric to adult setting. This process is called "transition". The transition process is critical and needs special assistance [1]. At this regard, the American Academy of Pediatrics recommends to use special care in performing a well-timed and structured transition from childhood to adulthood for any kind of chronic disease between the ages of 18 and 21 years [2].

The need of a structured transition program in chronic diseases has been underestimated in the past few years [3]. More recently, an effective transition is gaining importance due to the availability of new medical technologies improving the early diagnosis and the life expectancy of children with chronic conditions [4]. A growing number of studies emphasize the importance of a proper transition by providing recommendations and attempting to address the information gap on the issue [2,5]. Nevertheless, there is still a long way to go. According to the *2016 National Survey of Children's Health* most children in the United States do not receive any transition preparation [6].

The transition from childhood to adulthood of patients affected by phenylketonuria (PKU) is particularly difficult and not sufficiently addressed by guidelines globally, including Italy [7–9].

PKU is a rare autosomal recessive disorder. Its incidence rate in Europe is around 1/10,000–1/15,000 births with a higher rate in some countries including Italy, where it reaches 1/4500 [10]. PKU is caused by the deficiency of the phenylalanine hydroxylase enzyme (PAH), which catalyzes the conversion of the essential amino acid phenylalanine (Phe) into tyrosine [11]. This deficiency results in increased blood concentrations of Phe and its accumulation in the brain, leading to a variety of clinical manifestations, including brain damage, autism, seizures, and developmental problems [12]. Deficiency of the hepatic PAH leads to a wide spectrum of hyperphenylalaninemia (HPA), that is now classified according to the treatment options in non-PKU HPA (Phe concentration ranging from 120 to 360 μmol/L) and PKU HPA (blood Phe concentration > 360 μmol/L) [9,13]. The principal treatment of PKU is a low-Phe diet, consisting of low-protein foods, supplemented with Phe-free protein substitutes based on L-amino acids, glycomacropeptides and slow-release large neutral amino acids to cover protein demands [14,15]. The restraints imposed by the strict dietetic regimen have a significant impact on the quality of life of the patients, leading to a progressive withdrawal from the nutritional program during the transition from childhood to adulthood. In fact, in patients over 14 years of age, a cumulative abandonment of dietary treatment of about 30% is observed [8]. The discontinuation of the diet rapidly worsens Phe level, and may result in symptoms such as attention deficit, insomnia, irritability, mood swings, fatigue, and tremors [8]. Until 2018, the only pharmacological therapy approved for PKU was the supplementation of tetrahydrobiopterin (BH_4), the necessary co-factor of PAH, in the orally available form of sapropterin dihydrochloride [16]. BH_4 is not globally available and only about 30% of PKU patients can benefit from it [17]. To address the unmet medical need of an alternative treatment to diet, pegvaliase has been developed. Pegvaliase is a pegylated recombinant *Anabaena variabilis*-derived Phe ammonia lyase, able to reduce blood Phe concentration by substituting for Phe hydroxylase and converting Phe to ammonia and trans-cinnamic acid [18]. With pegvaliase, approved for patients ≥ 16 years old and with Phe levels >600 μmol/L, patients can follow a diet with an amount of protein intake meeting the recommended dietary intake for the general population, even leading to liberalization of diet [9,19,20]. The Italian national consensus describes in detail the use of BH_4 testing and treatment, and how to better approach the use of novel enzyme substitution therapy pegvaliase [9].

As mentioned above, adherence to diet progressively decreases from childhood to adolescence [21–24]. Recent studies suggest that adherence to diet during the transition period is variable among patients. A direct correlation between psychosocial difficulties of PKU adult patients and discontinuation of the diet has not been demonstrated yet [25,26]. European guidelines recommend that all adult PKU patients should be followed-up at specialist metabolic centers, where they should undergo Phe level testing at least monthly, as well as receiving annual outpatient visits [12]. A dietary handbook accompanying PKU guidelines provides some considerations to help sustain dietary management [27].

In Italy and abroad the attention of the medical community is focused on the transition phase of different chronic diseases, for example in the fields of immunodeficiency or gastroenterology [28–30], but no recommendations have been made available on PKU yet.

Italian researchers and clinicians are aware that transition from childhood to adulthood is a critical time in the treatment of PKU, as underlined by the European guidelines [12] and national consensus documents [9]. However, a reflection and expert opinions on good organizational and management practices to be implemented in the daily clinical practice are still lacking [8].

The aim of this article is to put forward an expert opinion on good practices for managing the transition period in daily clinical practice in Italy. The experiences are based on the available evidence and the direct approaches of four Italian centers to transition models for PKU patients.

2. Methods

2.1. Literature review

In September 2021, the available scientific literature on "transition from childhood to adulthood in PKU" was identified using PubMed. No date limit was set, and all papers were screened for relevance and duplication. Results were restricted to articles published in peer reviewed journals, in English, with full text available.

2.2. Generation of the expert opinion panel

In May and June 2021, the experts gathered for two virtual meetings. The centers of the experts manage the treatment of more than 50% of the Italian patients affected by PKU. Participating centers were:

Department of Medical and Surgical Sciences, S. Orsola University Hospital, Bologna, Italy; Metabolic and Muscular Unit, Meyer Children's Hospital and Interdisciplinary Internal Medicine, Careggi University Hospital Florence, Italy; Inherited Metabolic Diseases Division, Regional Center for Expanded Neonatal Screening, Women and Children's Health Department of Integrated Diagnostic, University Hospital, Padua, Italy; Unit of Internal Medicine and Rare Diseases, Unit of Internal Medicine and Genetic Dyslipidemia, University Hospital "Paolo Giaccone", Palermo, Italy. The expert opinion was agreed through a step-by-step program consisting of three surveys and one structured interview. The workflow of the program is shown in Fig. 1.

2.2.1. Survey pre-work

Prior to the first expert meeting, a survey (survey pre-work) was administered for the participants to collect their agreement/disagreement on the main topics of PKU transition management. The survey pre-work was consisted of six questions with the possibility to express agreement/disagreement, from 1 (total disagreement) to 9 (total agreement). Marks above 5 were considered in agreement, while marks below 5 in disagreement. Question number 3 required direct answers. Results were then discussed during the first meeting in May 2021 (see Table 1).

2.2.2. Structured interview

Interviews were conducted among participants to investigate organizational aspects and their own experiences with transition in PKU patients during the first meeting.

2.2.3. Survey

During the second meeting, participants answered a survey; later they were asked to discuss strengths and weaknesses of the transition program implemented in their centers. Finally, strategies to emphasize the strengths and to reduce the weaknesses of a transition pathway were proposed by the panel of experts.

2.2.4. Survey post-work

Experts were asked to provide indications for an efficient management of PKU patients transitioning from childhood to adult healthcare services.

3. Results

3.1. Available literature for "transition from childhood to adulthood in PKU"

A small number of publications focused on the issue of "transition from childhood to adulthood in PKU" was identified. Overall, nine articles were found: six research articles (four observational studies [14,24,31,32], two retrospective studies [33,34]), one Italian survey [8], one Italian consensus and one European guideline on PKU management [9,12].

3.1.1. Transitional care in PKU, available evidence

To date, only few medical centers offer medical care for adult patients with PKU. Most adults with PKU are still treated in pediatric centers. A recent American retrospective study analyzed transition from the point of view of 50 PKU patients transitioned from the pediatric to the adult care setting. Patients reported poor access to adult resources and to adult specific PKU educational materials in their pediatric center. On the other hand, they enjoyed the relationship with the pediatric team and familiarity with treatment plans [33].

To the best of the authors' knowledge, there are only two European studies reporting the experiences of specific management of transition of PKU patients from childhood to adulthood.

In 2005, an adult outpatient clinic for inborn metabolic diseases was established in cooperation with the pediatric outpatient clinic at the University Hospital of Leipzig, Germany. During this project, all patients with PKU aged 18 years and older were transferred from pediatric to adult care. Transition was planned six months before the actual transfer in an interdisciplinary meeting together with each patient. Each patient was informed about transition through detailed written and verbal information. With the patient's agreement, the adult outpatient care was informed about the patient's PKU history. Physicians and dieticians from adult and pediatric clinics met on a regular basis to discuss specific issues about individual patients. This observational study showed that a successful transition relies on several factors, with the presence of a multidisciplinary team composed by both the pediatric and adult health care providers as the most important one. The authors suggest that the best age for the transition is 18 years. The majority of patients were satisfied with the transition both from a psychosocial and socioeconomic point of view [31]. A 10-year retrospective evaluation of adult PKU patients involved in the above project revealed a successful transition with satisfactory metabolic control and social outcomes [34]. A similar experience was conducted in Portugal, where a dedicated center was established from the cooperation of the *Centro de Genética Médica* and the pediatric hospital with the *Centro Hospitalar Universitário do Porto*. In this case also, patients with PKU older than 18 years were transferred from pediatric to adult care and followed for two years. According to their transitional program, the medical and nursing staff changed during transition to adult services, while the nutritionists, psychologist and geneticist remain the same throughout the pathway. Results of this observational study showed a significant increase in the median number of annual blood spots, in the number of follow-up visits and very few patients lost to follow-up [32].

Apart from the German and the Portuguese experiences, transition is not well organized worldwide and in Italy. A survey of 77 centers of the

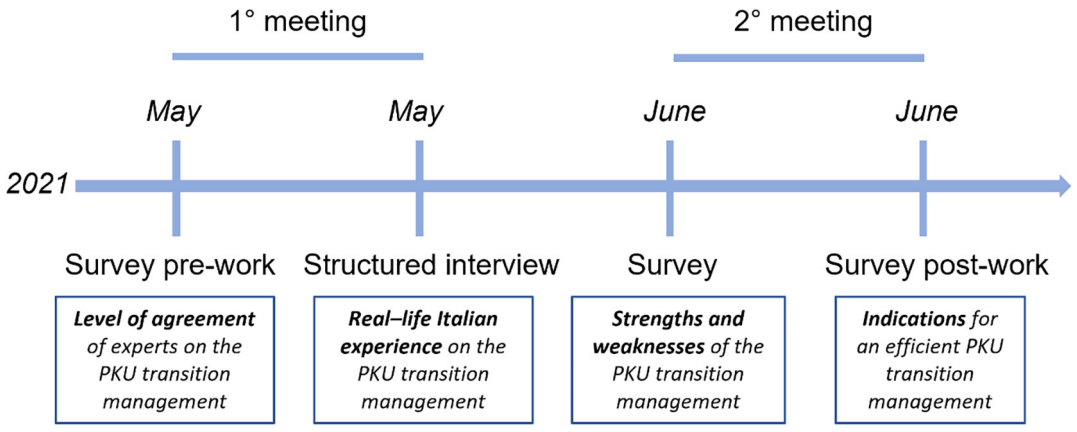

Fig. 1. Workflow for the formation of the expert opinion.

Table 1
Results of the survey pre-work to assess agreement/disagreement of the experts on the principal topics of PKU management during transition.

Question	Experts in agreement	Experts in disagreement	Comments for disagreements
The change of medical reference generates anxiety and loss of motivation in the patient and represents a barrier to the new treatment	4	3	Transition turns out to be more problematic for the family than for the patient
An adequate transition process can be associated with an improvement in the health status of adult PKU patients	7	0	
The ideal age to start a gradual transition process to prepare the adolescent, parents and physicians involved is between 16 and 19	5	2	Two experts suggested 12–16 or 14–16 years of age as the ideal age to start a gradual transition process
During the transition, the clinical, psychosocial, and educational needs of the adult patient must be considered	7	0	
It is useful to set up transition clinics, i.e. pediatric outpatient clinics where the patient can meet and be seen by the new team that will be caring for him or her	7	0	
The transition from pediatric care to adult medicine must follow a structured and uniform pathway at national level	7	0	

European Reference Network for Hereditary Metabolic Disorders (MetabERN) showed that only 40% of the metabolic pediatricians participating in the survey received a training about transition and that there was a lack of professionals to coordinate in this process (transition coordinators) [7]. A recent survey, conducted in six key centers for PKU management in Italy, showed that transition of PKU patients from childhood to adulthood has still to be implemented in the country [8]. The study described the main reasons for the decreasing compliance of the patients during transition: the move away from parental control; the refusal to comply with a treatment with a major impact on the social and personal life; diet-related logistical and organizational difficulties; the embarrassment of admitting to health professionals that they have failed to comply with therapeutic instructions; inadequate idea of the risks of the disease and even the denial of the diagnosis [8]. Another study, involving twenty-one PKU adult patients from Italy, highlighted their need for a non-pediatric, adult PKU clinical setting. This unmet need generated psychological, emotional and also practical and organizational discomfort among patients, leading them to be not compliant or even to discontinue the treatment [24].

Cazzorla and her team performed an observational study on 111 PKU adults to identify psychological factors influencing disease perception and adherence to diet; results suggested the need of structured transitional care processes to improve the compliance to low-Phe diet of patients aged between 10 and 14 [14].

The European guidelines on PKU suggest general recommendations for the transition of patients affected by PKU. The guidelines recommend that adult patients should be transferred to a specialized metabolic adult team, that transition should be performed in a structured process that should be started in adolescence, and that all PKU patients should have access to a metabolic physician, dietician, and psychologist. It also recommends starting the transition process at 12 years of age, although the actual transition to adult setting occurs between the ages of 16 and 18 on an individual case basis [12]. The recently published Italian consensus document on the management and pharmacological treatment of PKU also addresses the issue of transition, highlighting the critical points and the importance of the presence of a well-structured care plan. The authors underline the need of an integrated multidisciplinary transversal approach throughout pediatric and adult care, including one pediatrician with expertise in IMD, who should accompany adolescents towards an internist or metabolic expert for specific adult care, collaborating with at least one dietician and one psychologist [9]. Adult specific care is required to manage possible comorbidities emerging in these patients—e.g., bone disease, risk of diabetes and cardiovascular pathologies [9].

3.2. The opinion of the panel of experts

3.2.1. Results from the pre-work survey

Table 1 shows the level of agreement on the main aspects of the management of PKU during transition. All experts agreed on: the association of an adequate transition process with an improvement in the health status of adult PKU patients; the consideration of the clinical, psychosocial and educational needs of the adult patient during transition; the usefulness to set up transition clinics, preferably pediatric outpatient clinics where patients can meet and be visited by the new team that will be caring for them; the definition of a structured and uniform clinical approach at national level from pediatric care to adult medicine during transition. In particular, psychosocial aspects should include the distance from the Center, the patients' or parents' (if minor) economic status, the possible presence of neurodevelopmental delay and/or linguistic barrier, as in case of any patient missed at the neonatal screening test and/or in case of foreign migrants.

The authors identified some hot topics which should be discussed during the transition: pregnancy and different Phe cut off values, contraception, bone health, mental health, concentration, memory, sleep disturbance. Finally, the authors agreed that the number of transition clinics varies according to the patient's need, ranging from one to three, depending on the local transition clinic organization and patient's needs.

A divergence of opinions emerged about the change of medical reference generating anxiety and loss of motivation in the patient and representing a barrier to the new treatment options. According to the experts, transition appeared to be more problematic for the family than for the patient.

Another point of disagreement was the ideal age to start the transition. One author proposed an early transition process (12–16) because it coincides with the patient entering adolescence. Another expert proposed 14–16 years as the best age range to start transition because it coincides with entering upper school. However, most of the authors believed that the best range was between 16 and 19 years, age at which patients may reach the ability to act and take autonomous decisions even from a legal point of view. Subjects of disagreement were discussed and resolved in the discussion among panelists.

3.2.2. Experience with transition in daily clinical practice: Results of the structured interview

The structured interview described the clinical practice followed by the experts for transition management in their centers:

1. *Department of Medical and Surgical Sciences, S. Orsola University Hospital, Bologna, Italy:* this is the only center where transition has been formalized since 2017 [35]. The process starts from the department of pediatrics. The multidisciplinary team (pediatricians, dieticians, psychologists, a biologist-coordinator, and a trained medical doctor specialized in Clinical Nutrition) in charge of the patient discuss, in weekly meetings, a personalized transition project. The pediatrician obtains the approval of the patient's family and delivers an informative document that reports the broad outlines of what the transition and care will be. The changeover is formalized in a joint visit, which takes place in the pediatrician's outpatient clinic (transitional visit).

From then, the visits will take place in the adult outpatient clinic, in the presence of the adult staff (medical doctor, dietitians, biologist, psychologist). Both the dieticians and the psychologist as well as the analysis laboratory are the same for pediatric and adult settings, to secure support continuity. The overall assessment of the adult patient is conducted once a year.

2. *Metabolic and Muscular Unit, Meyer Children's Hospital and Interdisciplinary Internal Medicine, Careggi University Hospital, Florence, Italy:* the management of pediatric PKU patients was traditionally conducted at the Metabolic and Muscular Unit of Meyer Children's Hospital. Until 2019, an Outpatient Clinic was dedicated to adult PKU patients to better meet the requirements of adult patients. Given the need to start a transition process for the management of PKU adult patients, the Internal Medicine Unit of the Careggi University Hospital was identified as the most appropriate, since it already has a long-standing experience in the management of systemic complex autoimmune diseases. The process of transition started in 2020 and was composed of three phases. The first phase was focused on training for Adult Clinicians and preparation of young patients and families to start the transition process towards the adult setting. This phase ran in March 2020, at Metabolic and Muscular Unit (Meyer Children's Hospital), and it is still ongoing. The second phase started in September 2021 and consisted of the activation of a specific Outpatient Clinic and an Infusional Ward and to the transition of young adult patients to adult care. The education and support of adult clinicians at the Metabolic Unit of the Meyer Children's Hospital are still ongoing and include other IMDs. The third phase, characterized by the full transition of the young patients from the Metabolic Unit of the Meyer Children's Hospital to the Internal Medicine Unit of the Careggi University Hospital, will start in the next 12 months. During this phase other healthcare professionals (such as the dietician and the psychologist) will be involved for the care of these patients.
3. *Inherited Metabolic Diseases Division, Regional Center for Expanded Neonatal Screening Department of Integrated Diagnostic, University Hospital, Padua, Italy*: the center has a transition coordinator who operates according to the principles described in the survey of centers of the *European Reference Network for Hereditary Metabolic Disorders* (MetabERN). This professional figure plays a major role as he/she represents the interface between the pediatric and the adult treatment teams. Indeed, a transition coordinator is central to any transition program. The transition coordinator ensures that the adult treatment teams are informed about the patient's medical condition and organizes meetings between the adult and pediatric teams; he/she also ensures that the specialists involved are present at the patient's scheduled transition visits. The fact that the center is classified as a Complex Operational Unit (*Unità Operativa Complessa*) with a high level of autonomy, allowed a more flexible management of patients. Since 2005 a transition project of PKU patients from childhood to adulthood is ongoing [36]. Patients are visited in the Department of Pediatrics; the adult PKU team is coordinated by a psychologist and includes a dietician and a metabolic pediatrician, the latter working as a PKU expert. All adult patients undergo at least one visit with a metabolic adult neurologist. Brain magnetic resonance examination is performed at the discretion of the neurologist. Annual neurocognitive assessments are performed by a neuropsychologist. Almost all adult patients send their dried blood spot to the center once or twice a week and receive the answer online.
4. *Unit of Internal Medicine and Rare Diseases, University Hospital "Paolo Giaccone", Palermo, Italy:* in 2011 the Center was appointed Regional Referral Center for PKU, although transition activity has not been formalized in a structured process yet. Nevertheless, the pediatric and adult teams are constantly in touch to define the mode of the transition for each individual patient. This center has a genetics and mass spectrometry laboratory which allows the centralization of clinical analysis. Thanks to an application installed on the patient's phone, the latter is constantly in communication with the nutrition specialist to answer food questionnaires and enter Phe and tyrosine values. The outpatient visit for metabolic control is performed every three months, the brain MRI every two years, and the overall assessment of the patient every year.

3.2.3. Strengths and weaknesses of the transition process of PKU patients in Italy: Results from the survey

During the survey discussed in the meeting in June, experts indicated the strengths and weaknesses of the transition process in their realities. Results are shown in Table 2.

3.2.4. Suggested activities to capitalize on the strengths and reduce the weaknesses of the transition process of PKU in Italy: Results from the survey

During the meeting in June, the seven experts were asked to suggest activities to emphasize the strengths and reduce the weaknesses of the transition process in PKU. Results are shown in Table 3.

3.2.5. Indications for an efficient transitional phase of PKU patients from childhood to adulthood in Italy: Results from the survey post-work

The above discussions among the experts led to the definition of a pathway for an efficient transition of PKU patients.

- The program starts with planning/designing the pathway. To this regard, one of the centers confirmed a great benefit from organizing in advance the program.
- As a second step, the experts suggested involving decision-makers, that are key players from a financial and operational point of view. The approval of the decision makers is crucial to start a transitional period.
- Subsequently, the approach may be shared between the adult and the pediatric teams, and then is presented to the patient.
- The patient should be prepared for the transition well in advance. The patient should be visited by both teams since the age of 13. At the same time, the patient may be informed about the possibility of new therapeutic options, including enzyme substitution therapy.
- As the last step, expert suggest the involvement of patient associations, that play a key role in facilitating the long-term compliance of the patient.

A schematic representation of the proposed sequence is shown in Fig. 2.

4. Discussion

To the best of our knowledge, this is the first review and expert opinion addressing the practical aspects of transitioning PKU patients from

Table 2
Strengths and weaknesses of the transition process of PKU patients.

Strengths of the transition process of PKU patients	Weaknesses of the transition process of PKU patients
Experience on PKU of the metabolic physician	Difficulties in finding an adult metabolic physician
Presence of guidelines	Chronicity/evolution of the disease
Continuity in dietary, psychological and care settings	Moving away from care centers
Close-knit team of specialists (physicians, dieticians, psychologists)	Different referrals that may disorient the patient
Joint medical visit (transition clinics)	Loss of acquired medical expertise
Shared medical records	Need for personalized therapy
Hospital logistics	Hospital logistics
Dedicated laboratory	Patient compliance/autonomization
Interaction with specialists on comorbidity	Need for the availability of a specialized team
Preparation of the family to the transition	Lack of preparation of the patient/family to the transition

Table 3
Suggested activities to capitalize on the strengths and reduce the weaknesses of the transition process of PKU.

Suggested activities to exploit the strengths of the transition process of PKU patients	Suggested activities to improve the weaknesses of the transition process of PKU patients
Define a structured top-down pathway at hospital level	Raising decision-makers' awareness of IMD
Defining a point of reference for the patient/family	Establishment of PKU transition coordinators
Preparing the patient/family in time during adolescence (13–14 years old)	Preparing the patient/family in time during adolescence (13–14 years old)
Provide recommendations	Working with the patient on risk perception, especially neurological ones
Co-management of the patient/family by the team	Willingness/activity to build a network
Organizing multidisciplinary meetings within the team	Specific knowledge on adult outcomes and PKU-related organ damage
Involving patient associations on the transition pathway	Willingness/activity towards adult medicine
Creating a network for comorbidity management	PKU training of adult clinicians on long-term PKU patients' follow up

childhood to adulthood. The experts involved used the scientific evidence available and the experience of each individual center as a starting point to define practical recommendations. This expert opinion is to be considered as an advice to be adapted to the individual situation.

Eight suggestions have been reported, highlighting key concepts such as the "a priori" planning of the process involving the pediatric and adult teams, the acclimatization of the patient and his family to the process, the preliminary definition of appropriate spaces in the structure and the organization of meetings with the joint (adult and pediatric) team. The setup of such a pathway must necessarily have the previous agreement of the decision-makers involved in the structures, followed also by the participation of patient associations.

Successful transition and adult care often fail due to structural barriers. There is often a lack of experts in IMD in adult medicine. Training of specialized metabolic physicians, especially in the context of internal training, is necessary. Official recognition of "metabolic medicine" as a subspecialty with a defined training program would also be helpful and is being sought in other European countries. In Italy there is a specialization in Endocrinology and Metabolic Diseases which does not fully cover the educational needs outlined above.

The need for a multidisciplinary transversal approach with transition throughout pediatric and adult care appears as the common point between this expert opinion and the Italian national consensus statement on management and pharmacological treatment of PKU [9]. Moreover, several of the suggestions from the expert panel are in line with the European experience on transition in PKU. Planning the path, sharing it with the pediatric, the adult team and the patient, and visiting the patient with the whole team are points in common with the German experience [16]. The Italian, German, and Portuguese experiences outline the importance of professional figures (like, the psychologist) as a continuum in the interface with the patient or the family from childhood to adulthood [16,18]. The experts, in agreement with the international literature, emphasize the importance of a transition coordinator who facilitates and organizes the transition process working in agreement with the adult and pediatric medical teams [7]. As recommended by the European guidelines, the panel of experts suggests that patients should be prepared for transition around 12–13 years of age, according to each specific case [7].

In this review and expert opinion, factors of relevant practical importance for the transition of PKU patients are addressed for the first time. This is the first attempt to discuss the involvement of decision-makers and patient associations; to this regard, experts outlined the insufficient role of public authorities in the management of PKU. Actually, a more active involvement of the public and health authorities as for allocating funding for the transition process implementation, would be desirable at a national and/or regional level. Patient associations could be strategic players to increase the awareness on the topic, empower the patients and prompt regulatory authorities on the issue of transition in PKU. This is also the first expert opinion to consider the involvement of adolescents in a transitional process from pediatric to adult centers, allowing a putative switch from the dietary therapy to new therapeutic approaches, including enzyme substitution therapy. To motivate the adolescent patient in adopting an alternative therapy is an easier challenge than for adults. Adolescent patients may be advised towards a therapy that does not require following a restricted diet, which is extremely influential for social relationships at this age.

This expert opinion has some major strengths. It is the result of the agreement of a multidisciplinary expert panel on the major aspects of PKU transition management, providing the reader with straightforward recommendations. Second, the recommendations consider the actual situation in clinical practice, therefore complementing the recommendations from international guidelines.

Although this review only highlights the situation in Italy, many of the problems described are also known in other European countries. For a successful transition process, overarching (international) standards are necessary, while at the same time national circumstances (health insurance, reimbursement, availability of therapies, etc.) must be taken into account.

Despite being multidisciplinary, the panel of expert does not include a neurologist or neurocognitive expert, which are key specialists in the assessment of a neurocognitive disorder such as PKU. Another limitation is the non-involvement of patient associations in the expert opinion, which the authors consider consulting in tfuture working tables.

In conclusion, the present review and expert opinion provides the first practical recommendations for the management of transition in PKU from the daily Italian clinical practice, answering to the numerous unmet needs raised by researchers, clinicians, European guidelines [12], and national consensus documents [9]. The hope is that this could mark the starting point of change for Italian PKU care, leading to a greater focus on the crucial phase of transition.

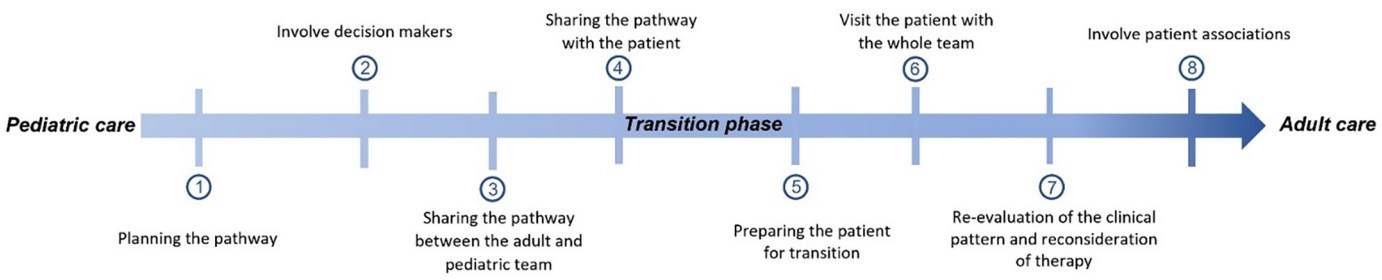

Fig. 2. Proposed sequence for an efficient transition of PKU patients from pediatric to adult care.

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Declaration of Competing Interest

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