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# The organizational dimension in rare and complex diseases care management: an application of RarERN Path© methodology in ataxias, dystonia and phenylketonuria

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## Abstract

**Background and methods** The organization of care profoundly impacts the variability in the quality of care provided to patients and the equity of access to care. The lack of coordination of care, of communication among healthcare providers, healthcare professionals, and patients, and the duplication of services provided to the patients represent some paradigmatic examples of organizational barriers to deliver high-quality patient-centered care and to promote equitable access to healthcare services.

Patient care pathways (PCPs) are valuable tools for the (re)design and the (re)definition of the provision of healthcare services to patients.

This work represents the first application of the RarERN Path© methodology for the (re)design of Patient Care Pathways (PCPs) to Ataxias, Dystonia, and Phenylketonuria (PKU).

The study was conducted with the support of Academic Partners and in collaboration with experts from two of the 24 European Reference Networks for rare diseases (ERN RND and MetabERN).

**Results** The application of some of the phases of RarERN Path© methodology enabled the translation of the good practices already in place in the centers of expertise into a common optimized PCP, one for each of the three diseases, integrating the expertise of some reference centers of excellence with the patients' perspectives, and principally focusing on the organization of care.

**Conclusions** The PCPs proposed for progressive ataxias, dystonia, and PKU provide insight into the value of specialized centers in diagnosing and managing patients with rare and complex conditions and are the results of a

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co-designed optimized process integrating the good practices of the centers of excellence and expertise with the perspectives of the patients' representatives. This integrated approach allowed for the re-design and optimization of the organizational dimensions of the patient's care pathways.

**Keywords** Neurological diseases, Rare neurometabolic diseases, Progressive ataxia, Dystonia, Phenylketonuria, Organization of care, Patient care pathways, Patient-centered care, Equity of care, European reference networks

## Introduction

Delivering high-quality patient-centered care, promoting equitable access to healthcare services everywhere in Europe, promoting the efficient use of resources, and favoring the economic sustainability of the healthcare systems are some of the main targets of the European Commission's healthcare policy and the national healthcare systems in Europe. The lack of coordination of care, the lack of communication among healthcare providers, healthcare professionals, and patients, and the duplication of many services provided to patients represent some paradigmatic examples of the difficulty of achieving those targets [1].

These issues appear more evident in the care of rare diseases due to the limited knowledge and resources, which often lead to delayed diagnosis and treatment, the burden on patients and families, and disparities in outcomes.

It is well known that a good organization of care has a profound impact on the variability in the quality of care provided to patients and the equity of care access [2]. It is accepted that codifying the organization of the care process provides better care to patients [3, 4].

The European Pathway Association [5] defines patient care pathways as "a methodology for the mutual decision-making and organization of care for a well-defined group of patients during a well-defined period." Patient care pathways (PCPs) are valuable tools for the (re)design and the (re)definition of the provision of healthcare services to patients [6].

PCPs can represent an organizational strategy for implementing and applying the Clinical Practice Guidelines (CPGs) nationally and within healthcare providers' environments.

The aim of the present work was to apply the RarERN Path© methodology [7, 8] to design phase-oriented PCPs for managing the following rare and complex neurological diseases, progressive ataxias, dystonia, and rare neurometabolic disease phenylketonuria (PKU). The work was conducted in the framework of the European Brain Council (EBC) Value of Treatment (VOT) research project on rare and complex brain disorders [9]. The VOT project looked at early intervention and explored the benefits of coordinated care by examining health services, multidisciplinary care patterns (also addressing comorbidity), patient outcomes, and costs.

Progressive ataxias are a group of rare neurological conditions [10] as: hereditary ataxias are a group including Friedreich's ataxia, spinocerebellar ataxia, and episodic ataxia; idiopathic progressive ataxias, a group of forms of cerebellar ataxia associated with neurodegeneration of unknown aetiology; specific neurological disorders, in which progressive ataxia is the dominant symptom [11]. Dystonia disorders are still labeled as rare diseases, although recent studies stressed that the prevalence was increasing. Indeed, the estimated prevalence of isolated dystonia in Europe is 16.4/100.000 [12, 13]. Phenylketonuria (PKU) is a rare autosomal recessive inborn error of phenylalanine (Phe) metabolism. In Europe, PKU prevalence is about 10:100,000 newborns, with a higher rate in Turkey and Ireland and a meager rate in Finland. In most European countries, the national newborn screening (NBS) programs include Phe measurement [14].

## Methods

### RarERN Path© methodology

Developed in the framework of the European Reference Network ReCONNET [15] for designing an organizational reference model for PCPs in rare connective tissue diseases (rCTDs), RarERN Path© methodology is composed of six consecutive phases, which are briefly summarized below [7].

#### *Phase 1*

Mapping existing patients' care pathways and collecting patients' stories using a survey based on the principles of narrative medicine [16] and created in co-design in English with patients.

#### *Phase 2*

Merging each validated flowchart obtained in phase 1 into a single optimized flowchart that illustrates a common PCP for diagnosis, treatment, and monitoring. Analysis of patients' stories to identify the recurrent topics and specific comments related to patients' care and pathways. The expected result of phase 2 of RarERN Path© is to integrate the list of needs and priorities related to care and care pathway extrapolating from the patients' stories into the optimized common patients' care pathway flowchart.

***Phase 3***
Reaching a consensus among the stakeholders on an optimized common reference organizational model for the PCP.

***Phase 4***
Co-design of specific key performance indicators (KPIs) needed to assess the performance of organizational procedures, their impact on disease outcomes, and healthcare providers'economic and organizational sustainability.

***Phase 5***
Assessment, final refinement, and potential inclusion of additional KPIs and instructions that can be useful to implement the common optimized organizational model.

***Phase 6***
A pilot study is foreseen for applying the organizational model, collecting the KPIs, and identifying obstacles to using the organizational flow in specific contexts.

In the present work, a partial application of the method was carried out covering phase 1, "mapping of existing patients' care pathways," phase 2, "Design of optimized common patients care pathway," and phase 3, "consensus on an optimized patients' care pathway."

### Participants
In phase 1 and phase 2, patients' representatives for progressive ataxias, dystonia, and PKU were involved using an ad-hoc survey as an alternative to the narrative medicine tool.

The mapping exercise aimed at exploring the patient care pathway (PCP) involved Healthcare Providers' (HCP) members of ERN RND and MetabERN and participating in the VOT project.

Data collection has been carried out between April 2021 and December 2021.

### Mapping exercise and data analysis
Ad-hoc questionnaires containing semi-structured questions exploring the organization of care for patients with progressive ataxias, dystonia, and PKU into the HCP specialized units were presented and discussed and refined together via video call and then sent by email for review and comments. These included two main topics: (a) a detailed description of how the care pathway is organized and managed, distinguishing the patient access to the specific unit, the procedures implemented for the diagnosis of the disease, the treatment(s) managed, the monitoring/follow-up; (b) the sharing of good practices in the coordination of the care between the expert center and non-hospital care, and the barriers and challenges in the organization of care for patients affected by rare neurological diseases. The English version of this survey used in the study was reported as a Supplementary file 1.

Respondents to the survey were European experts in the fields of PKU, dystonia, and ataxias from three European metabolic units in Ireland, Spain, and the United Kingdom treating children and adult PKU patients; four European reference clinics for Dystonia in Croatia, Germany, Italy and the United Kingdom (UK), and three European specialist Ataxia centers (SACs), in Germany, Italy, and the UK.

Moreover, patient perspectives were included by involving in the mapping exercise the patients' representatives of the PKU Association of Ireland, the patients' representatives of the German PKU Association (DIG PKU), the patients' representatives of the Ataxia Association of the UK, and the patients' representatives of Dystonia Europe, the European Dystonia Federation.

Based on their experience, the panel of respondents provided their expert opinions about the clinical and organizational challenges to improving the disease-specific patient care pathway.

The preliminary results were transferred in flowcharts describing the different phases of the care pathways followed by the patients. A first draft of the optimized patient care pathway for each of the three diseases, dystonia, progressive ataxias, and PKU, was presented and discussed in a plenary online meeting with the participation of the research groups.

Subsequently, a refinement was made with a second ad-hoc survey, collecting feedback and further suggestions about the good practices and criticalities related to the organization of PCPs. The English version of this survey used in the study was reported as a Supplementary file 2.

## Results
### The ataxias optimized patient care pathway
The request for diagnostic referral represents the patient's entry point to the optimized PCP for ataxias. The patient arrives at the SAC and is usually referred by a general practitioner, a general neurologist, other healthcare professionals, or by self-referral. Moreover, the patients' association can advise the patient on accessing the SAC.

The diagnostic organizational phase should foresee a care coordinator (e.g., a nurse) guiding the patients through the diagnosis process, providing information about the procedures and the organization of the care, as well as the contact information about the patients' associations involved in the pathway. The optimized multidisciplinary team should involve the following healthcare professionals: ataxia specialist, neuro-ophthalmologist, audiologist, psychologist, gastroenterologist, urologist, cardiologist, neurosurgeon, orthopedist, speech and language therapist, occupational therapist, and physiotherapist.

Diagnostic investigations are numerous and range from simple blood tests to next-generation sequencing (NGS) gene panels, nerve conduction studies, lumbar puncture, and neuroimaging [11, 17].

Some laboratory tests might already be organized and provided by the general practitioner (first-line care) or at the healthcare professional level, such as the general neurologist (second-line care), before patients present to the SAC (third-line care) [18]. The optimized PCP into a specialized Ataxia Center should include the following diagnostic procedures: whole genome sequencing, antibodies test for auto-immune ataxias and biochemical measures (cholestanol, plasma oxysterols, bile acids, coenzyme Q10 (ubiquinone), very-long-chain fatty acids, phytanic acid, white cell enzymes, muscle biopsy, remaining genetic tests - next-generation sequencing), and many instrumental exams (electromyography, electroencephalography, peripheral nerve conduction studies, MRI, total body PET scan, ophthalmology/optical coherence tomography). An additional reference on the adult ataxias diagnostic flowchart has been developed by ERN RND [19].

Treatable forms of ataxias are episodic ataxias, vitamin E deficiency, coenzyme Q10 deficiency, gluten ataxia, Niemann-Pick disease type C, ataxia with vitamin B12 deficiency, cerebrotendinous xanthomatosis.

Medical and non-medical management for ataxia patients should be organized homogeneously. Ataxia symptoms addressed with medication are tremors, spasticity, nystagmus, urge symptoms, sialorrhea, urinary symptoms, bowels symptoms, and sexual dysfunction; the main medications are steroids and intravenous immunoglobulin (IVIg) immunosuppressive drugs. The non-medical treatment should be discussed in a multidisciplinary approach: speech and language, physical, occupational, and neuro-ophthalmology. Moreover, when necessary, the treatment organization should include the involvement of the urologist, psychiatrist, audiologist, psychologist, gastroenterologist, cardiologist, neurosurgeon, orthopedics specialist, and palliative care in the later stages of the disease [20].

The optimized PCP should include codified coordination between the SAC and the primary care and secondary care providers (e.g., general practitioner, home rehabilitation therapist, and general neurologist) to organize better the monitoring of the ataxia patients and the continuity of care, ideally closer to the place where the patients live. Ataxia patients usually need follow-ups on an annual basis. Regular follow-up may allow the specialist neurologist to monitor disease progressions and enable the introduction of timely management of new symptoms. Telemedicine should be implemented to integrate the follow-up of ataxia patients to help them overcome the difficulties of getting to the SAC.

Figure 1 is a graphical representation, with a flowchart, of the optimized Patient Care Pathway for Ataxias. The proposed PCPs result from a co-designed optimized process integrating the good practices of the centers of excellence and expertise in ataxias belonging to ERN RND, one of the 24 European Reference Networks for rare diseases focusing on rare neurological diseases.

### The dystonia optimized patient care pathway

The patient's entry point to the optimized PCP for Dystonia is represented by a request from a general practitioner, another healthcare professional such as a general neurologist, other hospitals, or the patients themselves seeking a movement disorder specialist referral.

At the diagnosis phase, it is mandatory to organize and establish the optimized PCP in a specialized Dystonia center for homogeneous care with a multidisciplinary team. This team should involve a specialist neurologist expert in movement disorder, an internist, a psychiatrist, a physiotherapist, an occupational therapist, an ophthalmology consultation, and a neuropsychologist. A neuropsychiatric consultation could be arranged during the overall diagnostic assessment when necessary. Dystonia diagnosis needs syndrome-specific investigations: neuroimaging to rule out the presence of atrophy, structural lesions, iron deposit, and other signal abnormalities; laboratory workup to rule out metabolic abnormalities; genetic testing (single gene test or next-generation sequencing panel) [21]. The diagnostic organizational phase in a Dystonia specialist center should foresee each component of the diagnostic process, including neuroimaging, laboratory investigation, abdominal ultrasound, and chronic response to Levodopa. Neuroimaging of the dopamine transporter by single photon emission computerized tomography (DAT SPECT) could be employed to support the diagnosis of parkinsonism combined with Dystonia.

Treatment options involve counseling and education, oral medications, intramuscular injection of botulinum neurotoxins (BoNT), physical and occupational therapy, and, in selected cases, neurosurgical interventions [22, 23].

The optimized PCP should include codified coordination between the specialist Dystonia center and other healthcare professionals involved in managing the patient and providing care, including the General Practitioners (GPs), general neurologists, psychologists, occupational therapists, and physiotherapists. A codified plan should be organized for the psychiatric and psychological support of the patients and families during the diagnostic assessment and the organization of care in the follow-up. Moreover, the plans for physiotherapy and rehabilitation should be organized to coordinate the care better.

Figure 2 is a graphical representation, with a flowchart, of the optimized Patient Care Pathway for Dystonia. The

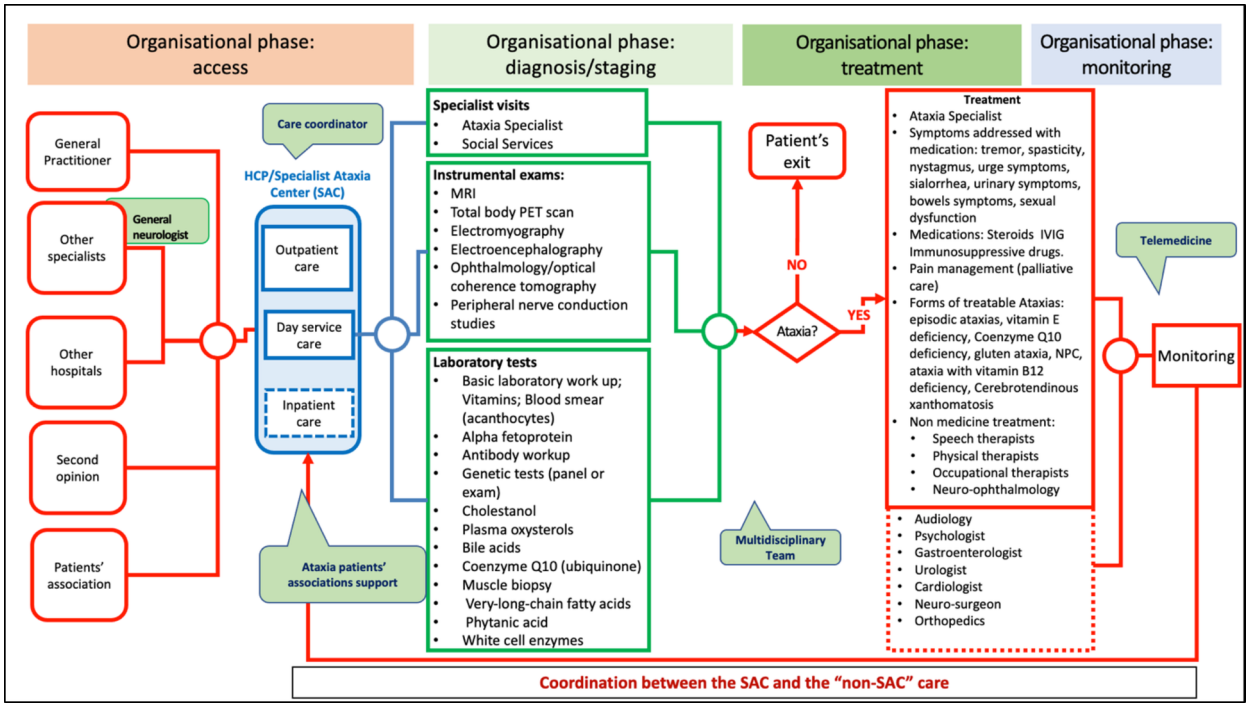


**Fig. 1** The optimized patient care pathway for ataxias. *Abbreviations*. HCP: healthcare provider; SAC: specialist ataxia center; MRI: magnetic resonance imaging; NPC: Nieman Pick Disease type c. *Legend.* A dashed line is used for the graphical representation of the healthcare services that are suggested (not mandatory) to be organized in an optimized PCP; a continuous line is used for the graphical representation of the healthcare services that are mandatory to be organized in an optimized PCP

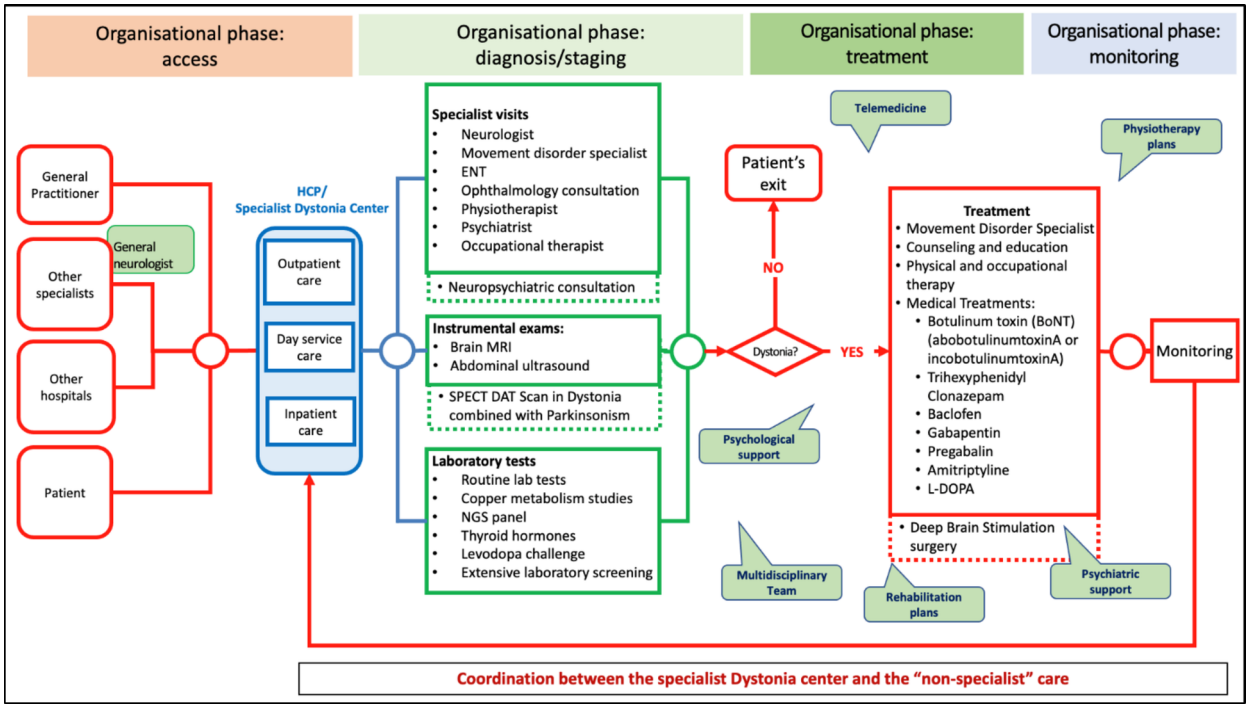


**Fig. 2** The optimized patient care pathway for dystonia. Abbreviations. HCP: healthcare provider; ENT: otolaryngology; MRI: magnetic resonance imaging; SPEC DAT Scan: specific type of single-photon emission computed tomography (SPECT) imaging technique; NGS: next-generation sequencing; L-DOPA: levodopa. *Legend.* A dashed line is used for the graphical representation of the healthcare services that are suggested (not mandatory) to be organized in an optimized PCP; a continuous line is used for the graphical representation of the healthcare services that are mandatory to be organized in an optimized PCP

proposed PCP results from a co-designed optimized process integrating the good practices of the centers of excellence and expertise in Dystonia, which also belong to ERN RND, one of the 24 European Reference Networks for rare diseases focusing on rare neurological diseases.

### The PKU optimized patient care pathway

Early detection of HPA and its treatment can prevent neurological damage [24–30]. Patients are referred to specialized metabolic centers in different ways. Children with a positive Newborn Screening (NBS) test are to be referred to the specialized metabolic center/center of expertise (CE) to confirm the diagnosis and commence treatment, ideally within ten days of age [31].

Despite the high diffusion of NBS, there are still late-diagnosed patients or undiagnosed patients, such as immigrant children from countries where NBS is lacking or adults born before the introduction of the NBS. Late-diagnosed or undiagnosed patients may be identified by other hospitals (e.g., the general metabolic treatment centers), their GP, other expert clinicians, themself, by a patients' association, and they are referred to the specialized metabolic center/(CE) for the diagnostic confirmation. When the patients gain access to the specialized metabolic center, a fast-track procedure should be organized for undiagnosed cases to prevent any further diagnostic and treatment delay [32]; as there is already a diagnostic delay in all patients who NBS has not identified, the fast-track procedure aims to avoid further delay.

Organizing a multi-disciplinary team consisting of a metabolic expert physician, metabolic dietician, clinical psychologist, medical social worker, clinical biochemist, and specialty nurse should be mandatory. The multidisciplinary team could potentially include an internist-endocrinology consultant, a neuropsychologist assessment, and a psychiatric assessment when necessary. Finally, the organization of biochemical laboratory tests (blood Phe measurements) should be mandatory.

The primary goal of treatment is normal neurocognitive and psychosocial functioning [24–30]. PKU treatment consists of dietary management: natural protein restriction, Phe-free/low phenylalanine protein in substitutes, and low protein (LP) special food. Potential two therapeutic options for some patients are the oral administration of a pharmacologic chaperone co-factor (sapropterin dihydrochloride) and subcutaneous delivery of a biological formulation (Penylalanine-Ammonialyase or Pegvaliase) enzyme substitution therapy.

During follow-up, blood Phe concentrations should be regularly monitored, aiming for blood Phe levels to be maintained within a given target treatment range defined for a given age [31]. Regular follow-up by a multidisciplinary team should include a medical and dietary history, an assessment of anthropometry including body mass index estimation, a physical and neurological examination, and a psychological review. A telemedicine service should include phone coaching, video counseling, monitoring of Phe levels, medical advice, dietary advice, facilitating the provision of supplies required for blood measurements at home, and social workers/support workers' advice.

Finally, early-diagnosed PKU is not life-limiting, and the oldest patients are already in their fifties. Thus, developing a transition care management to geriatrics should be considered [33].

#### *Children and the transition to adult care*

As anticipated, children with a positive NBS test are to be referred to the specialized metabolic center/center of expertise (CE) to confirm the diagnosis and commence treatment, ideally by ten days of age.

The diagnosis organizational phase of the optimized PCP into a specialized metabolic center should foresee a counseling support plan for parents of early-diagnosed children with NBS, including the arrangement of peer and psychological support services and nutritional education programs like breastfeeding and weaning.

The treatment phase of the optimized PCP should consider the organization of a codified educational plan discerning empowering strategies accordingly with the different PKU patients' needs: the close cooperation with midwives to achieve normality and close interaction with patients' associations for young parents of early diagnosed NBS children; parental screening for diagnosis induced post-traumatic stress disorder; teenagers support for increasing autonomy and for encouraging healthy eating, and their parents support. Despite teenager's need for independence, they still require much support to enable them to adhere to their therapy. It is a significant burden for them to carry all the burden of cooking for themselves, remembering to take all their treatments when their executive function may not be optimal. The diagnosis itself has a vast traumatic potential on parents and caregivers, which will affect the patients' disease acceptance and coping style prospectively, as reported by a considerable part of the PKU community [34].

A transition management plan is necessary for early-diagnosed patients to coordinate the transition from pediatric to adult care (when children are over 16 years old) and prevent the risk of falling out of or exiting care. This transition program should include a case manager for both healthcare professionals and caregivers, patients and their families, and a communication strategy to inform patients, families, and caregivers about the transition and the modalities and procedures to access the specialized metabolic center/CE (e.g., the European clinical guidelines recommend a follow-up visit per year).

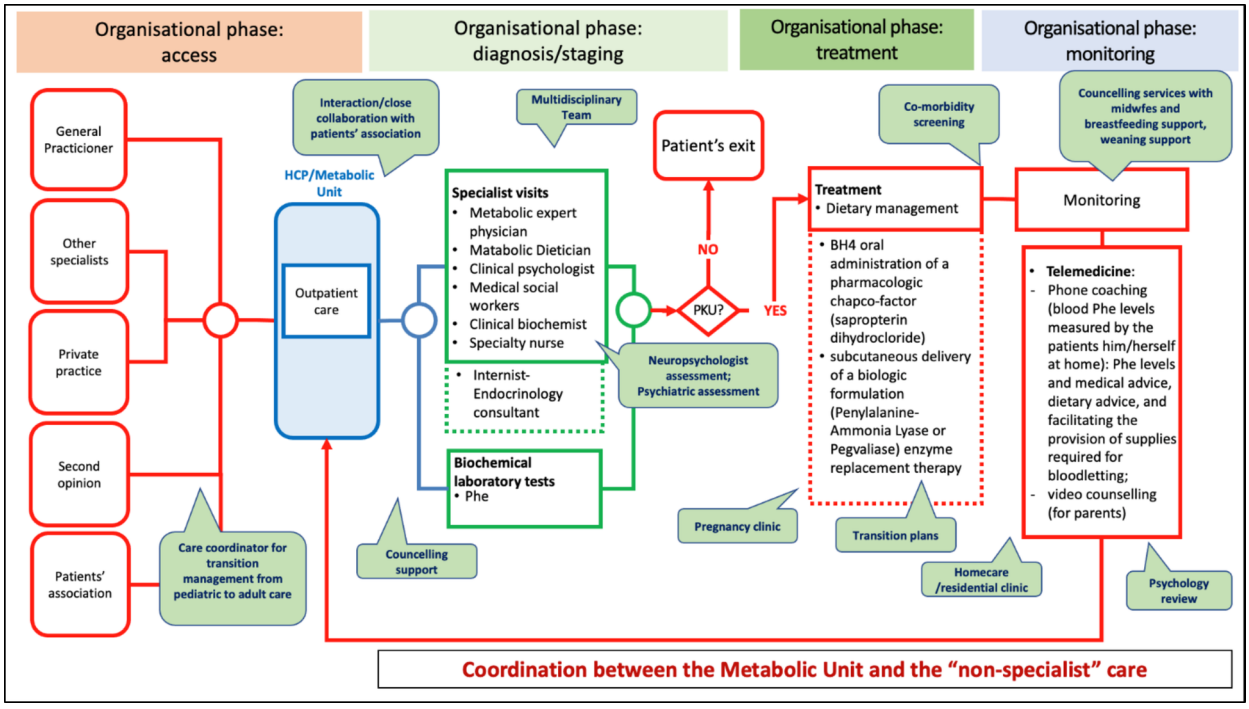


**Fig. 3** The optimized Patient Care Pathway for PKU. *Abbreviations.* HCP: healthcare provider; PKU: phenylketonuria; Phe: phenylalanine. *Legend.* A dashed line is used for the graphical representation of the healthcare services that are suggested (not mandatory) to be organized in an optimized PCP; a continuous line is used for the graphical representation of the healthcare services that are mandatory to be organized in an optimized PCP

Monitoring for early-diagnosed adolescents should include a program managing the coordination of care between the specialized metabolic center/CE and secondary care (e.g., the general metabolic treatment center), primary care, and GPs.

The optimized PCP should include codified coordination with a pregnancy clinic and multidisciplinary advice for PKU women of child-bearing age for counseling regarding pre-conception education, family planning, and nutritional recommendations during pregnancy in line with the gestation age.

Figure 3 is a graphical representation, with a flowchart, of the optimized Patient Care Pathway for PKU. The proposed PCPs result from a co-designed optimized process integrating the good practices of the centers of excellence and expertise in PKU, which also belong to MetabERN, one of the 24 European Reference Networks for rare diseases focusing on inherited metabolic rare diseases.

## Discussion

In this work the RarERN Path© methodology was applied to re-design and optimize the organizational dimensions of the patient's care pathways for the rare neurological diseases diseases, progressive ataxias, dystonia, and rare neurometabolic disease PKU. The proposed PCPs represent the result of a co-designed, optimized process integrating the perspectives of the patients' representatives with the good practices of the centers of excellence and expertise in progressive ataxia, dystonia, and PKU, which also belong to two of the 24 European Reference Networks for rare diseases (ERN RND and MetabERN).

Organization matters in the provision of care. The bottom-up approach can actively involve the relevant expert professionals and could significantly impact the implementation of concrete strategies and actions to improve the complexity of the healthcare services provided to patients and their families. Patient representatives' participation in the PCP re-design could ensure the inclusion of patients' needs and expectations in the system.

The organizational challenges faced by healthcare providers during the COVID- 19 pandemic suggested the creation of disease-specific structured care pathways and well-designed patient flow that are integrated with eHealth and telemedicine tools and facilitate optimization in the provision of care [35].

The application of RarERN Path© as a methodology for the re(organization)/re(design) of the organizational aspects of the PCP, may facilitate early diagnosis, promote multidisciplinary care, improve coordination of care between rare disease expert centers and secondary and primary care; improve patient's empowerment and involvement of patients, families, patients' associations in the care process.

We believe that the presented results can offer a valuable reference to stimulate all stakeholders involved in managing rare brain diseases to focus on the

organizational dimension. Further studies are needed to refine the results and assess their impact in patients care.

**Abbreviations**

| | |
|---|---|
| BoNT | Botulinum neurotoxins |
| CE | Center of expertise |
| COE | Centers of excellence |
| COVID- 19 | Coronavirus Disease of 2019 |
| CPGs | Clinical Practice Guidelines |
| DAT SPECT | Single photon emission computerized tomography |
| DIG PKU | German PKU Association |
| EBC | European Brain Council |
| ENT | Otolaryngology |
| ERN ReCONNET | European Reference Network on rare and complex connective tissue and musculoskeletal diseases |
| ERNs | European Reference Networks |
| ERN RND | European Reference Network on Rare Neurological Diseases |
| GPs | General Practitioners |
| HCPs | Healthcare providers |
| HPA | Hyperphenylalaninemia |
| IVIg | Intravenous immunoglobulin |
| KPIs | Key performance indicators |
| L-DOPA | Levodopa |
| LP | Low protein |
| MetabERN | European Reference Network for Hereditary Metabolic Disorders |
| MRI | Magnetic resonance imaging |
| NBS | National newborn screening |
| NGS | Next-generation sequencing |
| NPC | Nieman Pick Disease type c |
| PAH | Phenylalanine hydroxylase |
| PCPs | Patient Care Pathways |
| PET | Positron emission tomograph |
| Phe | Phenylalanine |
| PKU | Phenylketonuria |
| RCDs | Rare and complex diseases |
| rCTDs | Rare and complex connective tissue and musculoskeletal diseases |
| SACs | Specialist ataxia centers |
| SPEC DAT Scan | Specific type of single-photon emission computed tomography (SPECT) imaging technique |
| UK | United Kingdom |
| VOT | Value Of Treatment |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-025-12784-9.

Supplementary Material 1.

Supplementary Material 2.

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**Human ethics and consent to participate declarations**

Not applicable.

**Authors' contributions**

G.T., S.C., and V.Q. conceived the paper; S.C. performed analyses of data from the surveys; S.C. wrote the first draft of the manuscript; G.T., S.C. and L.T. wrote the final draft. S.C., V.Q., M.B., A.F., A.I.F., B.S.G., P.G., H.G., J.G., T.H., A.H., B.H., A.Mc.D., F.M., W.O., G.P., M.G.P., C.R., M.R., E.T., F.V.S., J.V., G.T. were involved in the discussion and interpretation of the results. S.C., V.Q., L.T., M.B., A.F., A.I.F,. B.S.G., P.G., H.G., J.G., T.H., A.H., B.H., A.Mc.D., F.M., W.O., G.P., M.G.P., C.R., M.R., E.T., F.V.S., J.V., G.T. repeatedly edited the manuscript. ALL the authors approved the final version.

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**Data availability**

The authors declare that the data supporting this study's findings are available within the paper. Extra data, questionnaires included, are available from the corresponding author upon request.

## Declarations

**Ethics approval and consent to participate**

The questionnaire respondents were both the expert clinicians and the top management of the national patients' associations. Based on their experience, they provided their expert opinion about the clinical and organizational challenges in improving disease-specific patient care pathways. The respondents involved were invited to complete the questionnaire by email. Except for the research team members and authors of this work, no personally identifiable data was collected during the project. The results discussed in this manuscript are based on voluntary research and do not involve experimental research on human subjects or the use of human tissue samples. Hence, ethical approval and informed consent procedures were not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

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