Master thesis

Exploring post-diagnostic patient pathways in rare diseases: leveraging data sources and practice-based insights for personalised care

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Preface

Dear reader,

This document presents my master's thesis on how practice-based insights and available data sources can contribute to understanding and mapping post-diagnostic patient pathways in rare diseases, with the aim of supporting personalised care. This research was conducted as the final project of my master's in health sciences at the University of Twente.

First of all, I would like to express my gratitude to my thesis supervisors, Dr. Anneliene Jonker and Dr.-Ing. Shiva Faeghinezhad from the University of Twente, for their valuable support and feedback during my graduation period. I would also like to thank all the respondents who voluntarily participated in this research. Their time and effort made it possible to carry out this research.

The knowledge and experience I have gained throughout my study, and particularly during the process of conducting and writing this thesis, will be carried forward with pride as I continue to grow both personally and professionally.

I wish you an enjoyable read.

Emma Schrijver,

Nijverdal, 23 June 2025

Abstract

Introduction – Rare diseases, also called orphan diseases, have an impact on millions of people around the world, yet they remain largely overlooked in routine healthcare. Because these conditions are so diverse and often poorly understood, many patients face long waits for a diagnosis and struggle to get the right care. This research focuses on the post-diagnostic patient journey and pathway: how care is organised, where the gaps are, and how experiences and available data can help shape more personalised and supportive care for people living with rare diseases.

Methodology – This research employed a mixed-methods approach, combining qualitative interviews and an exploratory data framework analysis within a cross-sectional approach. Semi-structured interviews were conducted with patients, parents, and professionals. Interviews were transcribed and subsequently analysed using Atlas.ti. Subsequently, an exploratory data framework was carried out to identify necessary data elements and assess their availability within the Dutch data landscape, ultimately aiming to support the mapping and personalisation of rare disease patient pathways.

Results – This research included 11 respondents, 7 of whom are professionals (mean age 48,1 years, SD = 10,0 years), 2 are patients (mean age 59,0 years, SD = 5,7 years) and 2 are parents of patients (patient mean age 9,5 years, SD = 7,8 years). The interviews with these respondents show that post-diagnostic care pathways for patients with rare diseases are often complex and fragmented. Respondents indicate that there are challenges in the coordination of their care, communication between care providers and communication between care providers and patient themselves. Moreover, the respondents indicate that there is an unclear division of roles, which means that a single point of contact is often unclear or absent. The available psychosocial support also lacks ability to meet the complex needs of patients, which negatively affects their well-being. In order to map and understand these care pathways, data elements are essential for among others, symptoms before and after diagnosis, treatment options or subsequent support. The availability of these data elements varies within the Dutch data landscape, with international data also needed to provide a complete picture. However, much information is not consistently recorded across data sources.

Discussion – The findings support earlier research showing that rare disease care is often fragmented, which leads to major problems with communication and coordination. Many patients and families end up managing their own care, which adds considerable emotional and practical burdens. This research therefore indicates the urgent need for better, more integrated care for individuals with rare diseases. Care that considers the patient as a whole, not just their illness. Technologies, such as Artificial Intelligence (AI) and wearables are hereby seen as having the potential to improve care throughout a patient's entire care journey to provide more personalised care. Moreover, the findings indicate that understanding and visualising patient pathways can work as a tool in identifying gaps and challenges in care delivery, which is important for advancing personalised care. However, their success depends on the data availability, quality, and interoperability of diverse data sources.

Conclusion – Understanding and mapping post-diagnostic patient pathways in rare diseases requires the combination of various data sources and practice-based insights. Data sources provide structured information on diagnoses, symptoms, and healthcare usage, while practice-based insights show important patient experiences and needs. Their combination enables a comprehensive, holistic view essential for developing personalised care pathways.

Keywords: rare diseases; post-diagnostic; patient pathway; patient journey; personalised care

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List of Abbreviations

AI	Artificial Intelligence	
AVG	Algemene Verordening Gegevensbescherming	Dutch version of the GDPR
BSN	Burgerservicenummer	Citizen service number
CCMO	Centrale Commissie Mensgebonden Onderzoek	Central committee on research involving human subjects
CDEs	Common Data Elements	
COREQ	Consolidated criteria for Reporting Qualitative research	
CPG	Clinical Practical Guidelines	
CPW	Care Pathway	
CTIS	Clinical Trial Information System	
CTMS	Clinical Trial Management System	
DBC	Diagnose Behandelcombinatie	Diagnosis treatment combination
DigiD	Digital Identification (Dutch)	
DIS	DBC-Informatiesysteem	DBC-Information System
eCRF	Electronic Case Report Form	
EHR	Electronic Health Record	
ERNs	European Reference Networks	
EU	European Union	
EU-CTR	EU Clinical Trials Register	
GDPR	General Data Protection Regulation	
GP	General Practitioner	
HGNC	HUGO Gene Nomenclature Committee	
HPO	Human Phenotype Ontology	
ICD	International Classification of Diseases	
ICPC	International Classification of Primary Care	
LBZ	Landelijke Basisregistratie Ziekenhuiszorg	National hospital care registration
LSP	Landelijke schakelpunt	National switching point
MDT	Multidisciplinary Team	
NZa	Nederlandse Zorgautoriteit	Dutch Healthcare Authority
OMIM	Online Mendelian Inheritance in Man	
PGO	Persoonlijke Gezondheidsomgeving	Personal health environment
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms	
WHO	World Health Organization	
WMO	Wet Maatschappelijke Ondersteuning	Dutch social support act

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1. Introduction

Rare diseases, also referred to as orphan diseases [1], collectively affect an estimated 6-10% of the world's population [1, 2, 3]. This proportion amounts to approximately 300-446 million people worldwide [1, 4, 5, 6]. The estimated number of people affected by a rare disease in the European Union (EU) is expected to be 30 million (around 6%) [7, 8]. Remarkably, 70-75% of those affected are children [7, 9], 50% of rare diseases are life-limiting, and 67% are disabling and severe [9]. In Europe, a disease is classified as rare if it affects fewer than one in every 2,000 individuals, although definitions differ across countries [5, 7, 9, 10, 11, 12]. The prevalence of 85% of rare diseases is extremely low, at less than one in 1,000,000 people [5]. However, epidemiological studies on rare diseases are often insufficient to accurately determine their actual prevalence and disease burden, as most rare diseases remain poorly studied [7, 8].

Rare diseases include a wide variety of diseases, including rare cancers, genetic and neurological conditions, infections, and autoimmune disorders [7]. Although the causes and symptoms of rare diseases vary greatly, many share common characteristics: they are usually chronic, severely debilitating, and potentially life-threatening [5, 7].

Despite the individual rarity of each rare disease, their cumulative burden on healthcare systems is huge, resulting in challenges in diagnosis, treatment, and disease management [3, 6]. To date, around 6,000-8,000 unique rare diseases have been documented [1, 3, 4, 5, 8, 9], with 80% being genetic in origin [1, 8]. Moreover, a notable 5–7% of patients have multiple rare diseases, complicating their clinical diagnosis and management [9]. These statistics underscore the critical need for advances in diagnostics and therapeutics to address frequently life-threatening illnesses [2].

In particular, diagnosing rare diseases is challenging due to their diverse clinical presentations and non-specific symptoms, often resulting in delays of 4–5 years or longer [4]. These diagnostic delays refer to the time between the first medical contact for the onset of symptoms and the final confirmed diagnosis [13, 14]. Limited clinician familiarity and the lack of opportunities for healthcare providers to develop specialised expertise increase the risk of misdiagnosis, underdiagnosis, or delayed diagnosis [3, 4].

Even if a diagnosis is made, individuals with rare diseases generally notice that there are few, if any, medical treatments available [10]. Rare diseases can be treated or managed through various approaches, such as nutrition plans, vitamins, and co-factor supplements, (orphan) drugs, stem cell and organ transplantation, RNA/gene therapy, and orphan devices [15]. In certain circumstances, there is no approved medical treatment, leaving patients with few options to manage their disease [9, 16]. When treatments do exist, they are typically prohibitively expensive [10]. The high cost of orphan medications hinders access to treatment options for rare diseases, particularly in countries where healthcare systems or insurance programs may not completely or partially compensate for medication expenses [7].

Interventions, such as therapy or neonatal screening could prevent, stabilise, improve, or reverse symptoms of the disease [15, 17]. However, many rare diseases have a timeframe for treatment before irreversible damage occurs. Therefore, not only diagnostic delays but also therapeutic delays, the time

between diagnosis and the start of appropriate treatment can have serious consequences. Minimising diagnostic and therapeutic delays are therefore vital [15].

The lack of accessible treatment options is compounded by the limited number of people affected by rare diseases, meaning many patients receive inadequate care or no treatment at all [3]. Currently, only 6% of rare diseases have available therapeutic options [3, 9], and fewer than 1% offer curative outcomes [9]. As a result, the majority of patients remain without access to definitive treatments [9]. This results in dependence on symptomatic therapies or pharmaceuticals that were originally developed for different conditions [3].

Patients and their families encounter similar challenges at different phases of their patient journey [16]. In many cases, patients struggle to find a specialist for their condition, which makes the prospect of receiving appropriate treatment even more challenging [3]. Moreover, navigating a fragmented healthcare system can be difficult, often requiring patients and parents to coordinate care themselves while also facing potential delays or complications in treatment [16, 18]. Therefore, rare diseases negatively influence the quality of life for individuals and their relatives, causing a mental and financial burden [7].

These challenges are particularly pronounced for patients residing farther from specialised healthcare facilities [19]. Many must travel long distances to receive specialised care, leading to significant inequalities in the availability and accessibility of medical treatments between rural and urban settings [16]. Consequently, these greater distances often lead to hospitalisation in regional hospitals with limited diagnostic capabilities [19]. This forces patients into prolonged diagnostic uncertainty, repeated medical evaluations, and potentially inappropriate treatments, all of which can impact their health outcomes and quality of life [4].

Recognising that people with rare diseases have the same right to receive treatment as those with common diseases, global policies have been implemented to promote the study, development, and marketing of orphan drugs [7]. In the European Union, specific legislation has been enacted to encourage the development of orphan drugs [3, 8]. However, despite existing legislations in some countries and efforts to encourage the development of therapies, many rare disease patients continue to struggle with inadequate care. Due to a lack of awareness, restricted access to specialised medical knowledge, challenges in obtaining diagnoses, and limited availability of targeted treatments, they often face significant barriers to the proper management of their condition [4, 6, 8]. The restricted availability of clinical practice guidelines (CPGs) exacerbates these issues by contributing to diagnostic delays, discrepancies in care, and barriers to appropriate treatment [6, 12].

These healthcare gaps highlight the need for a deeper understanding of how patients navigate the healthcare system [20]. The patient journey provides a framework for analysing these complexities, as they map the common needs from first symptoms to disease management [16, 21]. Understanding these patient journeys is therefore essential for identifying gaps in the patient pathways and offering opportunities for improvement [20, 21]. Whereas the patient journey focuses on challenges and needs, the term patient pathway refers to a structured, multidisciplinary, and often standardised framework of healthcare activities and organisational steps that patients navigate as they move through the healthcare system [21, 22]. It aims to promote evidence-based and consistent care for patients to enhance patient outcomes [21, 22]. Integrating the patient journey insights into the patient pathways holds the potential to improve the alignment of healthcare delivery with patients' needs [21].

This study focuses on the phase of the patient journey and pathway that begins with diagnosis and extends through disease management, regardless of whether disease-specific treatment is available. A thorough understanding of how patients navigate and experience this post-diagnostic period, combined with insights from healthcare professionals, enables the identification of challenges in the delivery and experience of care, as well as areas for improvement. These insights can inform the development of more integrated approaches that address existing gaps in healthcare delivery for rare diseases [5].

Given the substantial challenges outlined, this research aims to achieve several key objectives. First, it seeks to collect experiences and knowledge about rare diseases from patients, their parents, and healthcare professionals. Second, it aims to determine the necessary data required for understanding and mapping post-diagnostic patient pathways. Third, it investigates where this essential data can be found within the Dutch data landscape. Finally, it explores how the combination of data sources and practice-based insights could improve and promote personalised care for rare disease patients.

To address these objectives, this study explores the following main and sub-questions:

"How can available data sources and practice-based insights contribute to understanding and mapping post-diagnostic patient pathways in rare diseases to support personalised care?"

- *What practice-based insights are identified regarding patient journeys in rare diseases, highlighting the challenges and opportunities for improvement?*
- *What are the essential data elements required for understanding and mapping patient pathways in rare diseases?*
- *Where can these essential data elements be found within the Dutch data landscape?*

According to the literature, understanding the various stages in the care pathways (CPW) of patients with rare diseases, from pre-symptomatic to post-diagnostic, is critical for addressing the unique challenges and needs of this patient population, as it provides a foundation for optimising personalised care and enhancing the overall patient experience [15].

Understanding patient journeys and creating a clearer picture of the diverse post-diagnostic pathways helps uncover both the challenges patients face along their care trajectories, as well as the challenges in collecting the necessary data for mapping post-diagnostic patient pathways. These insights support the establishment and formulation of future strategies or guidelines that could improve care for rare diseases, ultimately promoting personalised care tailored to patient-specific needs.

2. Methodology

This study employed a mixed-methods approach, incorporating both qualitative (interviews) and an exploratory data framework analysis within a cross-sectional design. The research was conducted from February 2025 to June 2025.

2.1. Qualitative analysis

2.1.1. Research population and criteria

The study population included patients diagnosed with one or more rare diseases, their parents, and healthcare professionals. To participate, individuals had to be at least 18 years old. Patients were eligible if they had a rare disease and were capable of independently answering questions, meaning those with severe cognitive impairments were excluded. Additionally, patients were only included if they had received their diagnosis at least one year prior to participation, to ensure participants (patients/ parents) had sufficient time to engage with and reflect on post-diagnostic experiences. Besides, healthcare professionals were required to be actively involved in the diagnosis, treatment, or research of rare diseases.

2.1.2. Measurement instrument

Data were collected through semi-structured interviews with (sub)questions that had been specifically developed for this study. Two interview guides were developed, one for healthcare professionals, and one for patients or their parents. The following topics were discussed in the interviews with professionals: care pathway after diagnosis and challenges; factors influencing care pathways; collaboration between specialists and institutions; support and information provision; improvements and innovations; personalisation of care; and future vision. With regard to the interviews conducted with patients and parents, the focus was on the following topics: diagnosis and initial care experiences; care pathway after diagnosis; challenges and obstacles; collaboration and communication; experiences with support; access to information; improvements; and future vision. See Appendix 6.1 for the topic list of the interviews and Appendix 6.2 and 6.3 for the interview guide.

2.1.3. Research procedure

This study was conducted in accordance with the COREQ (COnsolidated criteria for REporting Qualitative research) guideline, which includes a number of study-related aspects [23]. The information letter and informed consent form were mailed to the respondents, see Appendix 6.4 and 6.5. Respondents received information about the goal, context, and length of the study, as well as how anonymity and data were handled. Specific private details, including name and email address, were obtained but not processed for this study. These data were only used to contact the respondents.

During the processing of the interviews, each participant was assigned a number to ensure anonymity. All interviews were conducted and analysed by the same person. The online interviews were conducted one-on-one, with only the researcher and the participant present in the (virtual) room. In addition, during the interviews with patients and parents, attention was paid to the emotional state of the interviewees. A mitigation plan was developed to notice and respond to any potential stress or distress, see Appendix 6.6. All recordings were deleted after transcribing the interviews and the transcripts were kept until the study was fully completed. Respondents were recruited through the first supervisor's network. In some cases, the first supervisor started the initial contact through email. Individuals who expressed interest in participating received an email from the researcher with the

information letter and the informed consent form, along with a request to provide availability for an interview. In a few cases, the supervisor shared contact information with the researcher, who contacted the potential participants via email and provided the same documents.

2.1.4. Ethical approval

Prior to data analysis, ethical approval was obtained from the Ethics Committee of the Faculty of Behavioural Management and Social Sciences (BMS) of the University of Twente (UT) (application number: 250189).

2.1.5. Analysis

The audio/video recordings of the interviews via Microsoft Teams were transcribed by Microsoft Teams. These were then manually checked and corrected for errors. After that, Atlas.ti (Germany, Berlin, version '25.0.1') was used to code all the transcripts. The coding of the transcripts was carried out in three phases, starting with the exploratory phase. In this phase, the transcript was first segmented into pieces of coherent text. Open coding was then applied, assigning codes to the text segments in line with the research questions. This process was inductive, with codes being developed throughout the analysis based on the data. Next, in the specification phase, codes with similar meanings were grouped into categories, a process known as Axial coding [24]. All categories were then combined into main categories, based on underlying themes. Finally, in the reduction phase, the findings were linked to the research question(s) of this study. This last step involved selective coding, in which connections or relationships between the main categories were established [24].

2.2. Exploratory data framework analysis

The exploratory approach was chosen, given that rare disease care pathways are complex and heterogeneous. As a first step, a general flowchart was created with all possible steps and activities after receiving a rare disease diagnosis. Both the selection of these steps and the creation of the map were based on information from interviews and literature. In addition, it was also presented to various professionals, including researchers in the field of rare diseases, to collect their perspectives and receive suggestions for improvement.

Next, the data elements essential for understanding and mapping patient pathways were defined through a combination of literature review and insights gathered from the interviews. The interviews were used as a starting point for defining relevant data elements, followed with the literature review to complement and refine them. This approach ensured that the data elements were relevant to all stages of patient care and sufficiently comprehensive to capture the complexity of care pathways across different types of rare diseases. The data elements covered key stages of the patient pathway, including the moment of diagnosis, treatment, care coordination, patient outcomes, as well as contextual factors such as timing and location.

Once the necessary data elements were defined, the next step was to identify where such data could be found within the existing healthcare data infrastructure in the Netherlands, and internationally when necessary. Mapping out current data sources that are frequently used for healthcare research and monitoring was a key step in assessing the extent to which the necessary data elements were captured within these sources. This included sources such as Electronic Health Record (EHRs), hospital care registries, patient-held records, patient/rare disease registries, claims data, and several clinical trial data sources [25]. Ultimately, the objective was to assess the availability and relevance of these data sources in relation to the required data elements.

3. Results

3.1. Results from the interviews

The interviews lasted an average of 48 minutes and 48 seconds (SD =11 min 24 sec). The recordings lasted an average of 39 minutes and 12 seconds (SD = 9 min 24 sec). The coding scheme of these interviews can be found in the Appendix 6.7.

3.1.1. Demographic data interview participants

This study included eleven participants. Their demographic data, along with their background are presented in Table 1.

Table 1: Demographic data (N = 11)

	Number of participants (%)	Average age (SD)
Gender		
Male	5 (45,5%)	
Female	6 (54,5%)	
Participant type/ background		
Patients	2 (18,2%)	59,0 (5,7)
Patients (parent interviewed)	2 (18,2%)	9,5 (7,8)
Research/ management (non-clinician)	2 (18,2%)	48,1 (10,0)
Research/ management (clinician)	5 (45,5%)	

3.1.2. Post-diagnostic pathway

The post-diagnostic pathway for individuals with rare diseases is described in the interviews as a complex and often demanding journey involving interactions with multiple healthcare professionals, institutions, and support systems. The challenges faced by patients and parents are categorised into four categories which can be seen in Figure 1. The first category highlights challenges directly after diagnosis and initial adjustments, where the first needs, challenges, and uncertainties occur. The second category encompasses challenges in accessing and navigating the healthcare system, such as the limited availability of treatment options and conflicting advice from healthcare professionals. Care coordination and system challenges, which is the third category, addresses challenges such as ambiguity regarding the role distribution of professionals and a lack of accessible, up-to-date information for healthcare professionals. The fourth category focuses on daily life and practical/social challenges, such as the insufficiency of practical advice for patients/parents and low public awareness.

In addition to these challenges faced by patients and parents, the interviewees highlighted one systemic issue: the weak connection between diagnostics outcomes and treatment planning. Even if no curative or evidence-based treatment or therapies are available, management of symptomatic treatment remains poor. While a diagnosis, mostly a genetic diagnosis, is often viewed as a key step forward, it does not consistently link to targeted care plans.

"Very often there is no systematic link to what treatment options are available. And if, at least for some, but a growing number of diseases, treatment can be given based on the respective diagnosis." P2

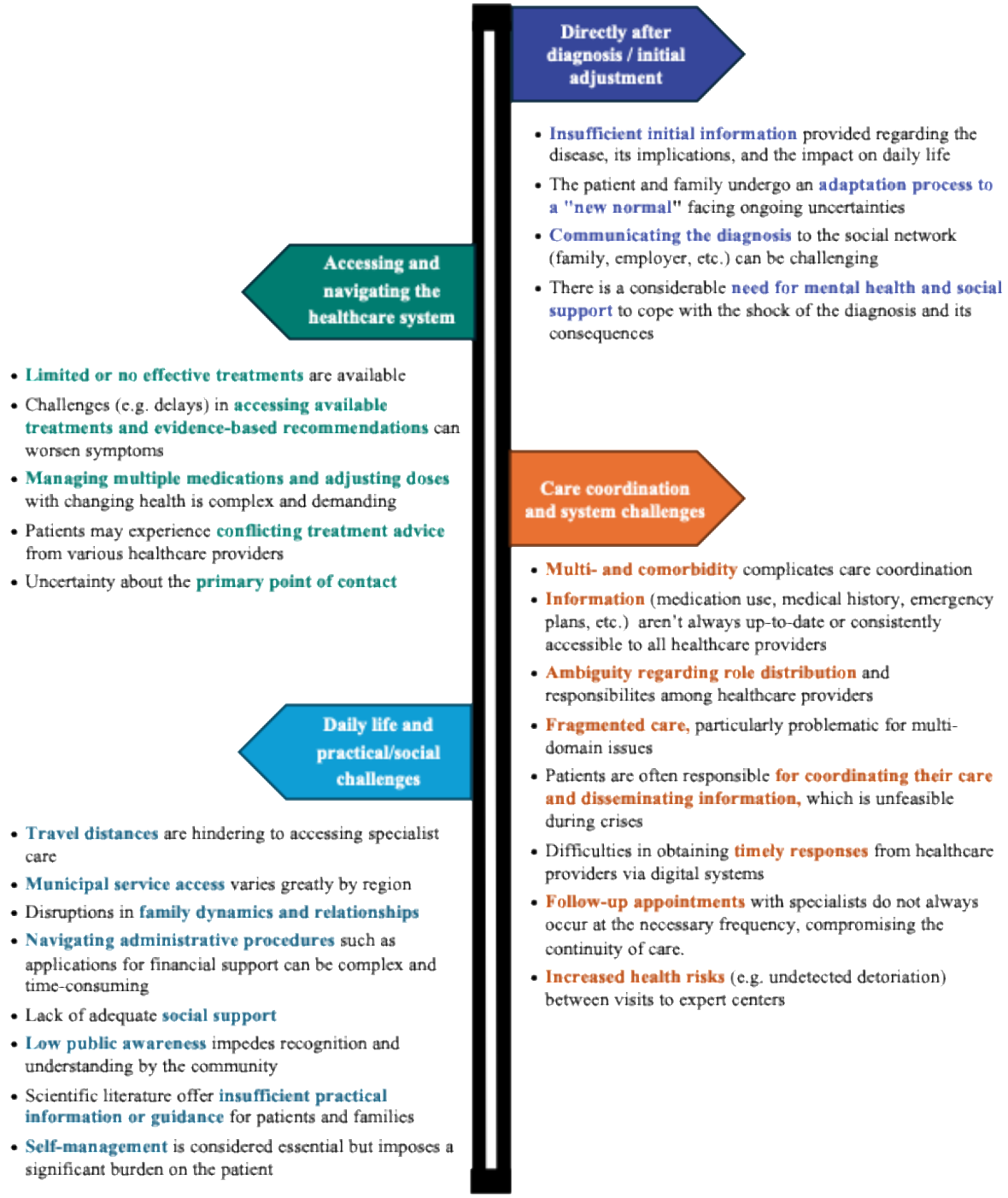

Figure 1: Overview of the most prominent challenges identified by patients/parents

The disconnect between diagnosis to treatment is further shaped by a variety of factors that influence how care pathways evolve and how easily accessible appropriate treatment and psychosocial support becomes. These factors include (psychiatric) multi- and comorbidities, geographical barriers, cultural/ linguistic diversity, stigma, and social/financial/educational factors. These factors are also frequently present in a combination.

" So, the social and financial status [of the patient/parents] is a very important factor. In the area that I have been working for, it's an area which covers many rural parts and the big number of people

and families who are resident in those areas are of very low educational level." P1

Additionally, the healthcare system is focused on common diseases. Specifically with regard to rare disease care, there is a greater focus on research involving children. Care processes are generally more structured and focused on paediatric rare diseases. In addition, adults are frequently excluded from clinical trials and experience challenges related to comorbidities. As a result, access to appropriate rare disease care is therefore easier for paediatric rare diseases and more complex for adult-onset diseases. Some interviewees also report gender (e.g. pregnancies) as an influencing factor. Lastly, lack of knowledge and resources are two crucial factors shaping the patient pathways for rare diseases.

3.1.3. Psychological and social support

The need for adequate psychological and social support is a recurring theme in the interviews, highlighting the significant impact of a rare disease diagnosis. The psychosocial impact of rare diseases is profound and often insufficiently or incorrectly addressed in healthcare systems, undermining the well-being of patients and parents.

"I think mental health and wellbeing is often under-addressed or not addressed routinely. And I use well-being very deliberately because I think sometimes approaching things through a well-being lens is much more palatable to families rather than necessarily coming at from a mental health only perspective." P3

The impact of rare diseases extends beyond the patient to the entire family, with interviewees recognising the need to consider the needs of siblings and the family as a whole. Receiving a diagnosis can be a shocking and overwhelming experience. Many uncertainties and ambiguities are currently faced by patients and families in the period following diagnosis. This causes a serious psychological and social burden. Patients, parents, but also professionals frequently describe these feelings as isolating, anxious, helplessness. The psychosocial burden is often compounded by long diagnostic journeys, the way of communication at the time of diagnosis, initial information provision, uncertainty about prognosis and disruption or changes in personal, educational, or work life.

"And so, it's then embarking on a new set of uncertainties: how do I get access to care; how do I get access to expertise; how do I get mental health support; how do I connect to other people in similar situations and support groups; how do I get access to research; how do I get access to clinical trials; how do I get access to treatments if they exist; and how do I tell everyone else in my network about this in an appropriate way. So, how do I use this with the education system, with the disability system, with the community service and social service system depending on your age, your employment opportunities, and your employer." P3

A key challenge here is the marginal role that mental health services currently play within rare disease care. Medical psychology and other forms of support are provided; however, their availability, duration or number of sessions may be restricted. This is problematic for patients who have numerous crises or hospitalisations due to chronic, variable (rare) diseases. In addition, the psychological support offered may not fully meet the patient's needs, which affects the trust in the healthcare system by the patient. Patients may find difficulties in finding services that are a suitable fit for their specific needs, especially considering the complex nature of rare diseases and potential multi- and comorbidities.

"They registered me with a psychology practice that had a waiting time of eight months. Beforehand, I had to fill out all sorts of questionnaires, while it's already difficult enough to just share all that personal information. After eight months, I finally had an appointment, and ten minutes into the conversation they told me, in terms of care, I wasn't the right fit for their practice, and then I was outside again" P11

Alongside the mental impact that a rare disease imposes, there are also practical challenges in the care associated with rare diseases. These challenges significantly add to the emotional strain, contributing to the overall burden of the disease. Navigating complex and lengthy support systems, such as the Dutch municipal social support system called WMO ("Wet Maatschappelijke Ondersteuning"), is a significant obstacle mentioned by interviewees, even if a client support person is present in this process. Additionally, managing the financial consequences can be overwhelming, especially due to the often insufficient financial support. This may lead to challenges such as out-of-pocket costs for accessing healthcare services and travel-related costs,

"We have been trying to get the bathroom and bedroom on the ground floor for over a year now. That process [arranging practical matters] with the WMO, although they may be doing the right things, how it goes is not how you would want it to go. Let's leave it at that." P10

"Well coincidentally I had a conversation with the WMO on Monday where our client support worker was also there and he said yes, I also had to count to 10 several times to prevent from going insane about how things are proposed. So, we have a client support worker with that process, but even with that support it is sometimes a struggle." P10

Patient associations and online communities act as crucial sources of both practical information and peer support, allowing for shared experiences and emotional understanding that healthcare providers may not always provide or possess.

3.1.4. Healthcare system interaction

Interacting with the healthcare system presents significant challenges for everyone involved in the care of rare diseases. These challenges are often characterised by communication gaps, lack of coordination across different professionals or institutions, and fragmentation.

One major obstacle is the lack of interoperability between electronic health records (EHR) across different hospitals or institutions. Important information, such as medication lists, allergies, or emergency plans may not be readily available to treating physicians. This necessitates the patient or their parents acting as the central point of information transfer, communication, and coordination. This task poses an obstacle that is particularly hindering in critical or urgent situations. Ultimately, patients and families often become experts in their own condition, relying on their own knowledge and information to fill gaps in understanding and managing their condition day-to-day.

"If I don't keep an eye on it myself, there's no one else who knows what's happening to me and that's really annoying. As long as I'm reasonable and can tell you, I'm fine, but as soon as I get into a crisis or have to go to the hospital, that's no longer possible."
P11

The fragmentation of the healthcare system for rare diseases can lead to conflicting advice from different healthcare professionals. Even within the same institution, professionals sometimes do not have access to the full medical history or profile of the patient's complex health status. For patients with multiple diseases (multi- and comorbidity), this often means navigating care across various specialists and institutions. While specialists at expertise centres may have good internal coordination, communication and coordination between different hospitals or even different departments within the same hospital can be problematic.

Additionally, the role of the general practitioner (GP) in the care of rare diseases is perceived as absent or lacking. While some advocate for GPs to be more involved in early detection and ongoing care, others feel that the rarity of these diseases makes it unrealistic for GPs to have the necessary resources or expertise. Some patients report GPs who are unaware of their diagnosis or feel the patient is too complex to manage, referring even simple issues to specialists, causing delays and health deterioration.

"My GP indicated that she finds my situation too complex and therefore couldn't help me further, which also means that there is no initial support for simple complaints." P11

Finally, the lack of clarity regarding who holds responsibility for certain tasks or aspects of care further emphasises the issue of fragmented health care. This problem can arise, either because there are too many professionals involved or too few specialised professionals. Several patients or parents indicate that they find it unclear who to contact in the event of health complaints or questions. They indicate that there is no clear first point of contact, for example, in cases where these problems extend across multiple domains. They indicate that, ideally, there should be one point of contact for multiple problems or general questions about the disease, treatment plan, or the entire patient can be placed with one person without the need to first visit various counters.

"What I'm missing now is a single point of contact: someone I can consult with, who says 'I'll call them for you' or ' I'll get back to you to discuss the treatment plan', that would be nice." P11

"That it is clear who has which role, who takes on which task. Then we can expect that from each other and then we can more easily know who to go to. So, I always find those kinds of agreements really nice and there are few of them, so I think that is an important one, because then it also becomes clearer for parents of oh for this I have to be here and we are going to ask them, etc." P6

3.1.5. Personalisation of care

Personalisation of care, which involves tailoring medical care management and support to the unique needs of individual patients, is presented as crucial for those with rare diseases. However, due to the rarity and heterogeneity of these diseases, implementing such personalised care in practice remains a challenge.

A fundamental aspect of personalisation begins with establishing a specific and accurate diagnosis for each patient. Interviews suggest that achieving truly personalised care requires a deep understanding of the individual's condition, its progression, potential risks, and the impact it has on their daily life and family. Personalising care of rare disease patients therefore requires considering the patient's broader life context. Such a holistic approach is labelled as crucial for providing the best care

possible. However, professionals often mention constraints in achieving holistic patient information due to fragmented data systems, unclear role definitions, and time limitations.

"It's important to find out what the exact underlying cause is, and which gene is impacted because knowing the gene can open the way for treatment. So, putting a correct and fair diagnosis is very, very essential" P1

"But also personalised medicine has to do with the lifestyle of a patient and their family. So, I think it's very important to see the patients very holistically. So, where they live, what other comorbidities they have, to find out what their preferences and priorities are and treat them like partners in this relationship. So not just saying you will do this. We will try this medication, we will do this option, etc. But also find out what really makes their life better. So, I would say that knowing the particular conditions of their life makes us able to treat them more in a more personalised way." P1

In addition, at a systematic level, personalisation involves tailoring care and interventions based on the individuals' patient profile and predicted outcomes and risks. Technology, such as Artificial Intelligence (AI), is seen by professionals as having the potential to contribute to more personalised care.

Additionally, treatment and therapy goals should be based on patient-related outcome measures and contribute to their quality of life. Multiple patients or parents indicate that the goal of care management should be enabling them to live with the disease rather than achieving a cure.

Ultimately, personalised care thrives when there is clear coordination and communication among all involved in the healthcare process, ideally supported by integrated information systems that provide a complete profile of the patient.

"And I think what we would need is kind of having patient individual care networks, which can actually provide then the respective management, well, disease management for the patient, but also take care of the knowledge transfer, so I think you need both you need kind of disease knowledge, which is very often only available at the centre of expertise but also need to transfer the knowledge into the network. So that the care team provided by the other healthcare professionals, is according to the latest state of knowledge." P2

The vision extends to creating individual care networks that are not only based on concentrated expertise but can also adapt to the specific needs of individual patients. Developing care pathways for rare diseases and guidelines internationally must account for cultural and social aspects to ensure personalisation at a local level.

3.1.6. Information gathering

Gathering comprehensive and reliable information about rare diseases is a critical challenge impacting the healthcare professionals, patients, and parents. Due to the rarity of the diseases, medical literature, practical insights, and professionals' knowledge may be limited. Healthcare professionals often have to actively research different sources of information when encountering a patient with a rare disease.

Figure 2 shows the information sources used by the interviewed professionals. Scientific databases, such as PubMed, were most often mentioned for disease-specific information. However, for practical matters and problems, professionals often refer patients and parents to patient websites and organisations. AI has also been mentioned as a search strategy to find relevant articles, but also AI-based information sources have been mentioned.

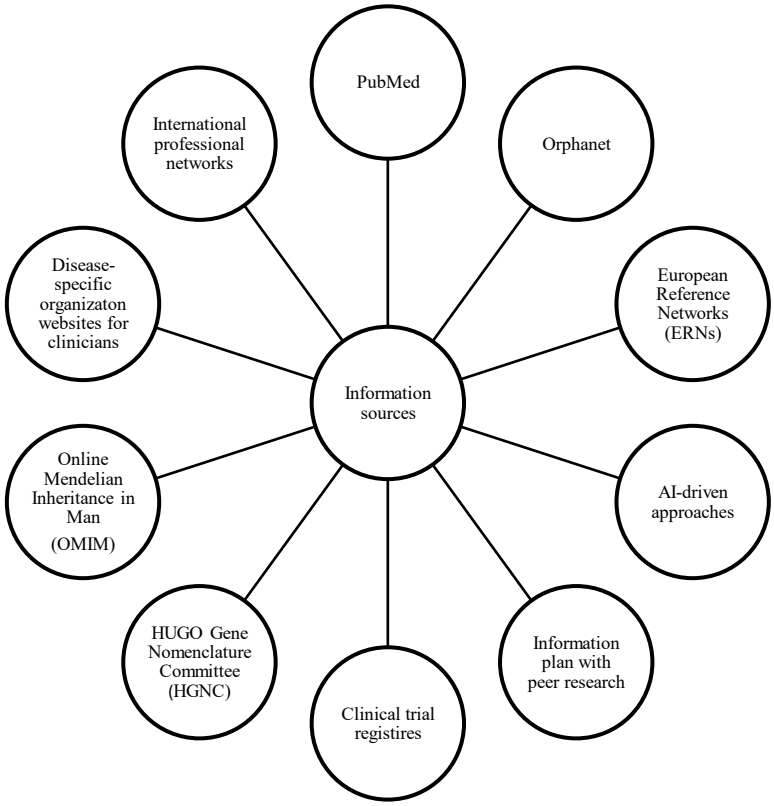

Figure 2: Information sources used by professionals

A frequently raised issue by patients and parents is the shortcomings in information provision from healthcare providers, with an emphasis on the first phase after diagnosis. This gap necessitates proactive information seeking by the patient or parents. Missed information includes, for example, medication information and intake information. This missed information results in a negative impact on the quality of life for patients with rare diseases.

"It's hard to receive a rare disease diagnosis in any way but what I received was an e-mail telling me that my son has a mutation associated with the syndrome and a Wikipedia link describing the syndrome. That was traumatizing. I couldn't even speak for days." P7

"When I had to find out for myself, after my first visit to the doctor, what the disease entails and what the treatment involves, that really shocked me." P11

Online sources, such as patient organisations and peer support information are seen as valuable information sources by patients and parents. These sources offer patients information regarding emergency plans, practical questions, and guidance that may not (or not fully) have been provided during medical consultations.

While the internet provides broad access to medical and practical information, identifying reliable and relevant sources remains a challenge, particularly in the context of rare diseases. Patients and parents indicate that a medical background helps them to find the right information but also to discuss and validate it in medical consultations. Patients and parents who do not have this background state that information gathering can be a long process to make information useful in their specific situations. Furthermore, several patients and parents have stated that articles and literature have potential, but that is not always clear what impact it has on a patient's everyday life and what they can do with the information.

"What does the finding mean in the in the context of living with the disease. It's important that we know the shape of the protein for example, but how does that impact me as a parent? How can I use that information? Does it help me at all at this point in time?" P7

3.1.7. Technology and artificial intelligence

Technology, including AI, wearables, and orphan devices, holds significant potential in improving the care journeys of patients with rare diseases. However, patients, parents, and professionals do mention several aspects that can hinder its implementation and use. Technology has been addressed in the interviews primarily for its potential to support and improve various aspects of rare disease care, such as early detection, personalised treatment, and information management. Specifically for the post-diagnostic phase, technology is seen by professionals as an opportunity to monitor disease progression over time. Examples of such technology mentioned are wearables to monitor specific parameters and signal when medical attention is needed. Insights into these methods of monitoring can contribute to healthcare decision-making, risk assessment, and tailored support. Home-based technology can also facilitate remote care for rare diseases to integrate healthcare management into daily life, reducing the need for on-site consultations. AI is seen by professionals as a supportive and assistant tool in rare disease care processes and decision-making. Various examples are highlighted by professionals, such as patient selections for clinical trials, understanding treatment effectiveness, and extracting relevant insights from knowledge-driven networks and data.

"So, mainly, at least for now, I think it's a supportive role which can provide the respective information knowledge with the conditions and then can use for decision-making, but the decision will have to be by the clinician."
P2

However, some professionals expressed uncertainty about AI's potential to aid in the treatment process, whilst others see AI as a present reality shaping healthcare and daily life. Privacy concerns and cloud distrust are mentioned as potential barriers to AI implementation in practice. Additionally, professionals found it important to make AI thought and reasoning transparent in order to optimise trust and use. AI must fit in well with current clinical decision-making processes in order to be able to provide a supporting role for healthcare providers.

"*And I think critical to AI is at whatever level of abstraction you can do it, that you are providing the reasoning as to why the AI has made that decision. Because that engenders trust, if people have some sort of idea of I kind of see why that conclusion has kind of come to me, it's much more trusted." P3*

Therefore, to bridge the gap between innovation and implementation, multi-stakeholder collaboration and consultation are crucial. Effective integration of technology into clinical practice requires seamless implementation that enhances rather than complicates and confuses existing care approaches and strategies. Building trust among all is essential, with a particular emphasis on the accuracy and reliability of proposed solutions. In addition, professionals have indicated that new physicians must quickly and properly master technologies.

3.1.8. Advocacy and awareness

Advocacy and awareness are seen as critical to improving care and recognition for rare diseases. Rare disease patients commonly encounter a double invisibility. First, their disease and (healthcare) needs are poorly understood by the public and healthcare providers. Second, rare diseases are not always recognised in healthcare systems complicating the coordination of care. Several patients and parents

indicate that they did not feel ethically treated by healthcare providers, causing experiences of emotional harm and a lack of professional empathy.

"Some memories stay with you, like the healthcare professional that told me he has never encountered a case like this in his entire career, and he hopes he never does again. You learn to digest these experiences over time, but they stay with you because they are shocking and traumatic and you lived them during a very vulnerable period of your life. There are two things a patient expects from a healthcare professional: empathy and or solutions. When, as a healthcare provider you provide neither, you're making things worse." P7

Initiatives from individual empowerment to broader societal and professional understanding are therefore necessary to enhance the healthcare (experience) for rare disease patients. Advocacy efforts seek to address this by raising awareness and advocating structural changes in the healthcare system. National campaign initiatives (e.g. 3FM Serious Request in the Netherlands) are viewed as effective in raising awareness and societal comprehension.

"For instance, you probably heard about Serious Request last year, something like that really helped raise awareness. Even our doctor said that people started approaching him, saying: 'Now I finally understand a bit more about what you do', that was really valuable, and perhaps even a bit shocking for some, as they began to realise what's actually going on. But at least there was more understanding, and that really meant a lot to us." P10

However, a third of the rare disease patients still report stigma as a critical issue. Stigma related to rare diseases has received considerably less attention than stigma in other diseases, such as HIV or mental illnesses.

"Stigma is massive, and I think stigma is an area that has received, some, but very little attention in the rare disease space. There's been some good work out there and you know one-third of people who live with a rare disease at least report stigma as being a critical issue for them and so we look at the number of people living with a rare disease and we take that 1/3 that then equals actually more people on our planet than have HIV for instance and look at the amount of work that has gone into stigma associated with HIV or stigma that's going associated with mental illnesses but there is very little work around stigma and rare disease and particularly you know tools and a bit interventions to address that."
P3

Patient organisations and peer support also play a crucial role in this process of advocating and raising awareness. Their efforts range from developing disease-specific resources and support networks to engaging with researchers and policymakers. However, not all rare diseases are represented equally, resulting in disparities in awareness and access to care.

Increasing awareness and knowledge among healthcare professionals is also essential. Rare diseases are frequently overlooked in education programs, resulting in delays in diagnosis and inadequate management of diseases. Education modules on rare diseases and improved clinical guidelines are therefore essential to improve recognition and timely responses.

"Because rare diseases are not taught in university. So, you learn how to treat the patient affected by rare diseases by working, nobody is teaching you." P4

3.1.9. Data elements and sources

The interviews highlight a variety of data elements and sources critical for understanding, diagnosing, and managing rare diseases, while also highlighting important difficulties in their collection, sharing, and utilisation. Linking and sharing data across various healthcare institutions is critical for creating a complete picture of the patient. However, significant obstacles exist, the most notable of which are privacy concerns and regulations such as General Data Protection Regulation/ Algemene Verordening Gegevensbescherming (GDPR/AVG). The lack of interoperability between electronic patient files from various hospitals is a significant practical systems barrier.

"You really need to have the complete picture of the patient to make sure there's no overmedication or medications that interfere with each other. That kind of information really needs to be brought together in one place, both for the patient themselves and for professionals, so they can better understand what works and what doesn't." P5

"The electronic patient records between hospitals cannot communicate with each other, which means that information from hospital A doesn't reach hospital B. As a result, my medication usage isn't up to date and I have to check it myself, and allergies or intolerances aren't always properly recorded everywhere, even when I mention them during consultations." P11

Additionally, participants indicate that rare diseases are often not recognised within existing healthcare registration and coding systems. Some diseases do not have a diagnosis code. For example, the diagnosis or disease coding is filled in as a general delay in growth. This lack of traceability in the healthcare system prevents accurate tracking and monitoring.

"But what happens because the processes and systems in particular hospital coding of data in many places in the world haven't been set up for rare diseases. What happens is you surface the opportunity to make you know really sort of life-transforming and life-changing and sometimes life-saving interventions. But at a systems level that information gets buried again because it's not tracked in the system. It just gets buried under some sort of code called other essentially and it's completely lost again."
P3

Lastly, getting consent from multiple sources for data sharing is difficult. There is also the issue that patients, particularly those who require the most assistance, may not be digitally inclined or interested in managing their data sharing.

3.1.10. Future perspectives

Looking ahead, patients, their parents and healthcare professionals shared clear perspectives on what needs to be improved in the rare disease landscape. Their visions highlight the need for better integrated, efficient, and empathic care, as well as larger systemic changes. These perspectives and desired changes are presented in Figure 3.

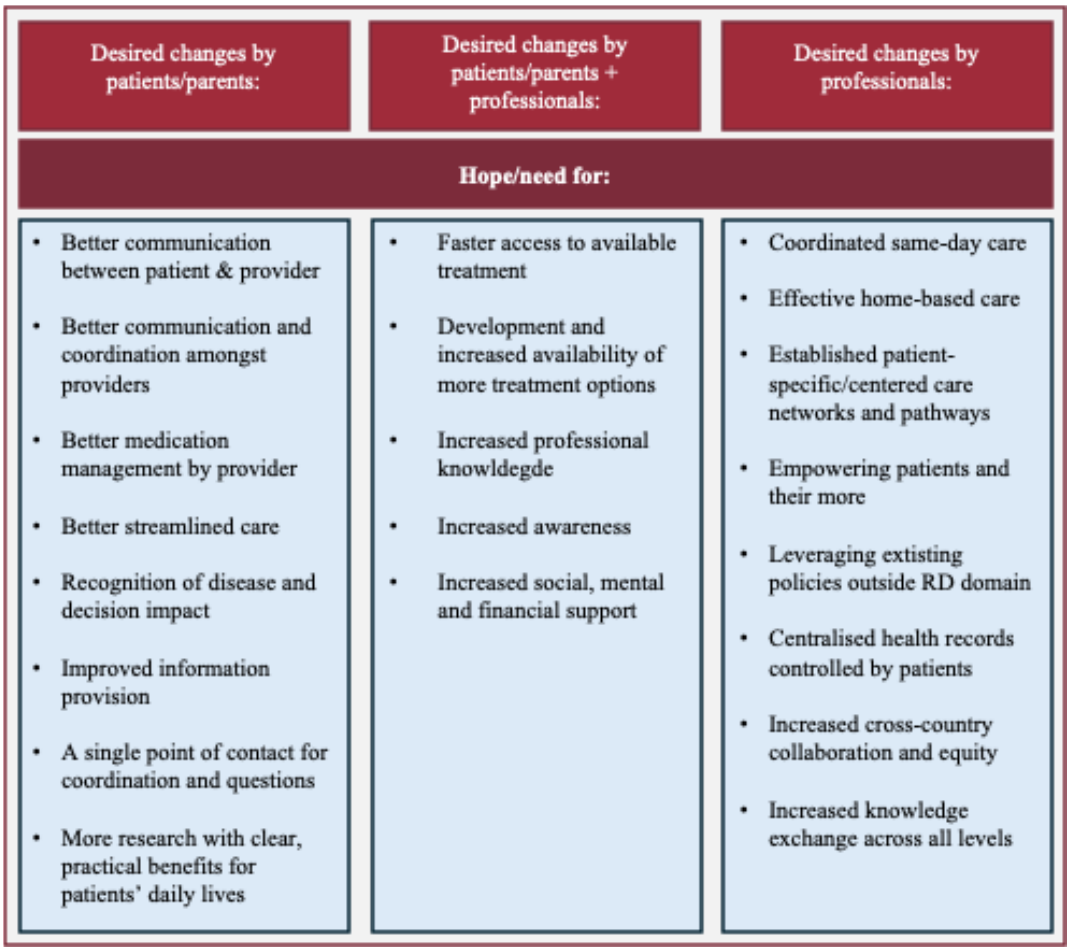

Figure 3: Desired changes by patients/parents and healthcare professionals

3.2. Results from the exploratory data framework analysis

Following the diagnosis of a rare disease, patients often face complex and fragmented care trajectories. To improve these care trajectories and evaluate them, it is essential to better understand and structure the post-diagnostic phase. This section therefore presents findings from post-diagnostic care paths for rare diseases, as well as necessary date-elements and sources to map them.

3.2.1. A general visualised patient pathway

The flowchart presented in Figure 4 provides an overview of the possible care steps for patients with rare diseases, specifically in the post-diagnostic phase. In this context, case management serves as the key coordinating point, ensuring that all relevant steps after diagnosis, including therapies and supportive care, are customised to the particular patient's circumstances. Case management input is based on clinical decision support inputs, which include the natural history (including symptoms before and after diagnosis) as well as available clinical practice guidelines [25]. These inputs guide the decision-making throughout the entire patient care pathway. Additionally, a loop has been incorporated during the diagnosis phase to allow ongoing reassessment and updates.

Due to the wide variety of rare diseases and available therapies, not all patients can follow the same path or complete all the activities presented in the flowchart. The availability of decisive tests, therapy options, and clinical trials varies based on the specific disease, healthcare setting, and patient-specific circumstances.

In general, the flowchart is broadly structured around two main pathways that reflect the possible care strategies in the post-diagnostic phase. The upper pathway focuses on situations where approved or evidence-based therapies and treatments are available. In this case, decisive tests are available to provide information that is essential for making critical decisions about treatment choices and the care management of a patient [25, 26]. Examples of therapies and treatments include curative treatments, disease-modifying therapies, or dietary treatments. Alongside these medical options, parallel care components such as psychological support, social support, symptomatic treatment, and periodic check appointments can be integrated into the patient care plan to address the wider needs of the patient and the family. In contrast, the lower pathway applies to scenarios where no specific or approved therapies are currently available. In such cases, case management emphasises symptomatic treatment alongside other possible support options and period check appointments.

The orange arrows indicate a moment in the pathway where the care plan is reevaluated. For example, if the outcomes or the experiences of patients/families show that the current approach isn't meeting needs, adjustments to the plan may be necessary. Also, for milder rare diseases, there may be no current medical needs. Therefore, a care path has been established starting with case management for such situations. Should the patient require care at a later stage, an orange arrow indicates the return to the process, triggering the reactivation of the care plan.

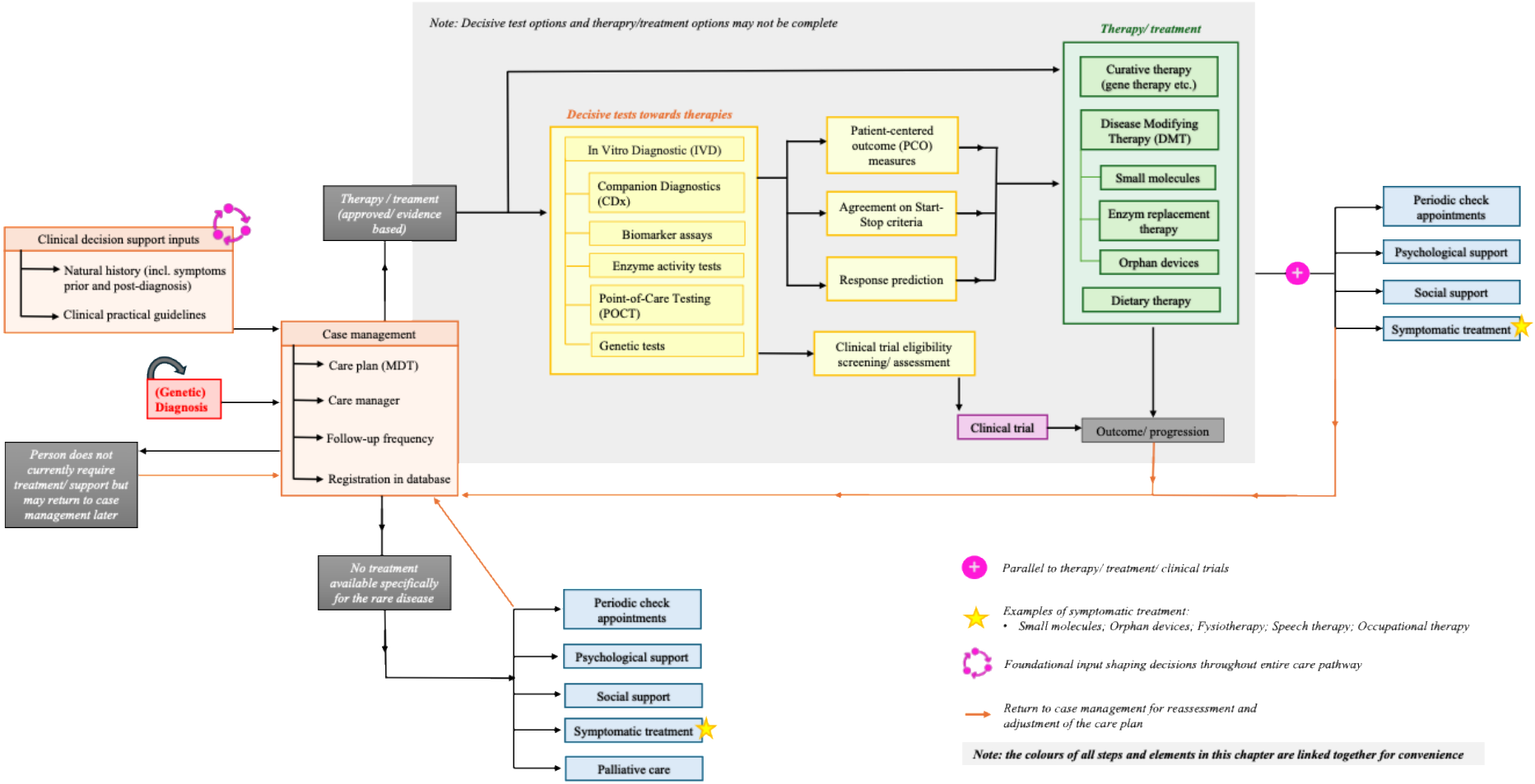

Figure 4: A general flowchart of the post-diagnostic pathway for rare diseases

3.2.2. Data elements needed for post-diagnostic patient pathway analysis

To effectively map and analyse patient pathways, it is essential to collect a diverse set of data elements that encompass both clinical and non-clinical aspects of patient care. These data elements form the cornerstone for assessing healthcare utilisation patterns and identifying inefficiencies or deviations in patient pathways [27, 28]. Table 2 presents these key data elements for analysing patient pathways in the context of rare diseases.

Table 2: Necessary data elements for analysing patient pathways

	Data element	Description
	Patient ID/ Case ID	Pseudonymised patient ID
	Sex at birth	Male/Female/unknown
	Date of birth	At least (mm)/YYYY
	Country of residence	Current country patient is living in
	Pre-diagnostic symptoms	Clinical complaints that a patient experiences before the diagnosis is made
	Post-diagnostic symptoms	Clinical complaints that a patient experiences after the diagnosis is made
	Date of diagnosis	Date of initial confirmed diagnosis of the rare disease
	Diagnosis code	A unique numerical code of the disease
	Diagnosis code version	Describes which version of the coding system is used, to ensure traceability and interpretability of diagnosis codes over time.
	Comorbidities	No or specified other disease code(s)
	Decisive test code	Code linked to a decisive test name (e.g. companion diagnostics/ biomarker assays)
	Care code	A unique code or set of codes that refer to a specific care activity
	Clinical trial patient ID	Unique identification code assigned to a patient participating in a clinical trial
	Clinical trial eligibility code	Screening status: eligible/not eligible/withdrawn/etc.
	Clinical trial code	The unique registration code of a clinical trial in which the patient is participating or has been screened for
	Clinical trial outcome test code	The coding for a test that has been done to determine whether the clinical trial is actually successful
	Outcome	Survival status/ follow-up (e.g. stable, deceased, transferred, loss to follow-up)
	Timestamp	Date/ time of event, corresponding to the specific: - Care activity; Decisive test; Clinical trial (+screening)
	Location	Care setting/ institution (*department*), corresponding to the specific: - Care activity; Decisive test; Clinical trial (+screening)
	Healthcare professional (specialism)	Healthcare professional/ specialism, corresponding to the specific: - Care activity; Decisive test; Clinical trial (+screening)

** The colours of all steps and elements in this chapter are linked together for convenience*

3.2.3. Availability of data elements in the (Dutch) data landscape

The effective analysis of patient pathways relies on the availability and accessibility of relevant data-elements. Within the Dutch data landscape, a range of data sources and infrastructures enable the collection and integration of these elements. However, certain data elements may only be accessible through international registries. This section mainly focuses on the current state of data availability within the Dutch data landscape, focusing on key national sources and addressing the need for international data where applicable. For a detailed overview of these data sources and the corresponding data elements availability, see Table 3 and Table 4.

Table 3: Data sources connected to the necessary data elements

	Electronic Health Records (e.g. hospital EHRs)	Landelijke Basis-registratie Ziekenhuis- zorg (LBZ)	Persoonlijke Gezondheids-omgeving (PGO)	Patient/ Rare disease registries	Nederlandse Zorgautoriteit (NZa)	Note:
Reference(s):	[29, 30, 31, 32, 33, 34]	[35]	[36, 37]	[38, 39, 40, 41]	[42]	
Patient ID/ Case ID	✓[1]	✓[2]	~ [3]	✓[1]	✗	[1] Unique internal (pseudonymised) patient ID [2] Pseudonymised BSN number + PatientID_inst (the unencrypted patient number of the institution where care was provided) + PatientID (the encrypted, consistent patient identifier generated by the institution) [3] Limited: identification via DigiD
Sex at birth	✓	✓	✓	✓	✗	
Date of birth	✓	✓	✓	✓ (Approximate)	✗	
Country of residence	✓	✓	✓	✓	✗	
Pre- and post-diagnostic symptoms	✓[4]	✗	✗	✓[5]	✗	[4] Mainly SNOMED CT for hospitals and ICPC for general practitioner care [5] HPO; OMIM; SNOMED CT code
Date of diagnosis	✓	✓	✓	✓	✗	

Diagnosis (code)	✓[6] (Multiple ontological coding languages)	✓ (DBC diagnosis code [7] & ICD 10)	✓ (In words without code)	✓[6] (Multiple ontological coding languages)	✓[7] (DBC diagnosis code)	[6] E.g.: ICD-10/11 code; SNOMED CT code; ORPHAcode; OMIM [7] Dutch diagnosis code in combination with specialty
Diagnosis code version	✓	✓	✗	✓	✗	
Comorbidities	✓	✓ (DBC diagnosis code[7] & ICD-10)	✓ (In words without code)	✓	✗	
Decisive test code	?[8]	?[8]	✗	?[8]	?[8]	[8] Decisive tests are generally registered in existing systems as regular laboratory tests or diagnostic procedures; it is not clear whether there are dedicated codes for decisive tests regarding rare diseases.
Care code	✓	✓	✓ (In words without code)	✓	✓ (DBC codes)	
Outcome	✓	?	?	✓	✗	
Timestamp	✓	✓ Only date	✓	✓	✓ Only date	Start date/time is a traceable data element however, finding an end data/ time is harder and rarer in data sources
Location	✓	✓	✓	✓	?	
Healthcare professional (specialism)	✓	✓ Treating specialty	✓	✓ (Specialised centre)	✓ ((treating)specialty)	

? = Unclear whether it is available

Table 4: Data sources connected to the necessary data elements (Clinical trials)

	Electronic Case Report Form (eCRF) in Clinical Trial Management System (CTMS)[1] / Company registries (e.g. pharmaceutical companies)	Clinical Trial Information System (CTIS)	Centrale Commissie Mens-gebonden Onderzoek (CCMO)[2]	EU Clinical Trials Register (EU-CTR)	WHO Trial Registration Data Set:	ClinicalTrials.gov (National Library of Medicine)	Note:
Reference(s)	[43, 44]	[45]	[46]	[47]	[48]	[49]	
Decisive test code	?[3]	✗	✗	✗	✗	✗	[3] Decisive tests are generally registered in existing systems as regular laboratory tests or diagnostic procedures; it is not clear whether there are dedicated codes for decisive tests regarding rare diseases.
Clinical trial patient ID	✓	✗	✗	✗	✗	✗	Can be led back to the patient ID (only by the clinician)
Clinical trial eligibility code	✓	✗	✗	✗	✗	✗	
Clinical trial code	✓	✓ Trial number	✓ CCMIO ID	✓ EudraCT Number	✓ Primary Registry and Trial Identifying Number	✓ NCT code	
Clinical trial outcome test code	✓	✗	✗	✗	✗	✗	

[1] In the management of sponsor or CRO (Clinical Research Organisation) [43].

[2] CCMO is the manager of OMON, which is an official data supplier to the International Clinical Trial Registry Platform (ICTRP) of the World Health Organization (WHO) [50].

? = Unclear whether it is available

EHRs are records that contain the medical data of patients from a single organisation, such as a hospital. These records contain the personal data of patients such as name, address, date of birth, age, and gender. In addition, the system also keeps track of all medical information. Think of medical history, results of physical examinations, the course of the disease, interventions, medication use, allergies, and more [29, 30, 31].

There are different levels regarding the exchange of data from EHRs [51]. Firstly, data can be exchanged within one healthcare institution (locally). Healthcare providers within one organisation such as a hospital can then view the relevant data. Secondly, the data can be exchanged between organizations, e.g. healthcare institutions (regional). Agreements on which data and the method of exchange are necessary. However, these agreements differ per region. Finally, data can be exchanged at a national level. At a national level, data can then be requested and granted via a data infrastructure. However, there is a misconception that this concerns a central data location, which is not the case. In reality, the so-called national switching point ('landelijke schakelpunt', LSP) facilitates the exchange of data without storing medical information centrally. This last level is however limited in the exchange of medical data [51].

The Dutch national hospital care registration (LBZ) provides a variety of data. It includes information such as the diagnosis, procedures, complications, expensive medicine provided, involved specialties, and DBC care-products of all patients who visited a Dutch hospital or had a digital contact moment with care providers [52].

Additionally, in recent years, there has been an increase in the development of personal health data management systems known as personal health environments (PGOs). Patients can use these platforms to build data linkages with a variety of healthcare organizations and providers. To help this procedure, the Netherlands has created a national agreement system known as MedMij. MedMij defines a set of standards and protocols for the safe sharing of medical information. PGOs with MedMij-certified labels adhere to these rules and protocols [36, 37].

A PGO contains a variety of data from different healthcare providers, see Table 5 for an overview [53]. The data that is actually visible in a PGO depends on the extent to which healthcare providers enable data exchange and on the initiative of the patient to retrieve and manage this data [53]. However, at the moment, a PGO can only be utilised by individuals aged 16 and older. Despite ongoing efforts to change this, children under the age of 16 are currently unable to create their own PGO [37].

Table 5: Medical data availability in Dutch PGOs [53]

Healthcare sector	Care activities
General practitioner	Documents; Lab results; Diagnosis; Medication; Self-measurements (in test phase); View appointments (limited possibility); Measurements and vital functions; Contact note; Allergy and intolerance; Questionnaires (in test phase)
Hospitals & clinics	Lab results; Lifestyle; Documents; View appointments (limited possibility); Self-measurements (in test phase); Measurement values; Treatment; Treatment information (in test phase, limited possibility) Radiological images (in research phase)
Public care (examples)	Prenatal screening (in development)
Long-term care	Lab results (limited possibility); Medical device (*mobility aid*) (limited possibility); Allergy and intolerance (limited possibility); Diagnosis and treatment (limited possibility); Advance directive/ living will (limited possibility); Daily reports (in research phase)
Emergency care	Documents (17 of the 19 Dutch ambulance services exchange information with several PGOs)

Given the complexity and rarity of rare diseases, patient registries are also essential for data collection, advancing disease understanding, and optimising clinical care [54]. They are increasingly seen as important tools for understanding treatment variations and outcomes [54]. Orphanet provides an overview of available patient registries for rare diseases (from countries in the Orphanet network). These registries collect information about a specific rare disease or group of rare diseases with the goal of encouraging monitoring and research [25, 47].

The data elements collected vary between patient registries. Although the collection of specific data elements is suggested or encouraged, it is unclear to what extent this is actually implemented in practice. Common Data Elements (CDEs) have been established for rare diseases by the European Commission, with the aim to define data elements that could be used in any rare disease registry [39].

Besides patient or rare disease registries, claims data may be useful to gain insight into the number of patients per diagnosis with the associated care products, care activities, and prices. However, the Dutch NZa claims data does not contain information about individual patients or institutions. The NZa data infrastructure contains Dutch medical specialist care with data coming from the DBC-Information System (DIS). This data infrastructure, however, does not include diagnostic codes such as ICD-10, but contains specific NZa (DBC-specific) codes [55].

4. Discussion

4.1. Interpretation and comparison of findings

This research investigated how available data sources and practice-based insights can contribute to understanding and mapping post-diagnostic patient pathways in rare diseases to support personalised care. The findings presented in the results section offer valuable insights into the complexities of rare disease patient journeys and the availability of data in the Dutch healthcare landscape.

The findings of this research highlight the fragmentation of the healthcare system for rare diseases, which leads to challenges in communication and coordination among different professionals, institutions, patients, and parents. This requires patients and parents to often become experts and coordinators of their own care. This self-expertise is seen as necessary, but results in a significant burden on patients and families. This aligns with existing literature indicating that patients and parents experience both financial and psychosocial impacts as a consequence of taking the responsibility of coordinating care themselves [56].

Hence, there is a need for more tailored mental and social support specifically addressing the unique and complex needs of people living with rare diseases. Improvements can be made by embedding psychosocial support as a standard part of patient (care) pathways, not as an extra option. This is essential for improving disease management and healthcare engagement eventually leading to improved long-term outcomes and patient empowerment. This finding confirms previous research advising a better integration of psychosocial support in the healthcare system [57].

Furthermore, the respondents (patients and parents) highlight that the main challenges lie in the organisation and guidance throughout the entire care process, rather than receiving curative treatment. Patients and parents report gaps in information provision, both on a medical and practical level. With regard to medical information provision, they report a lack in the specific communication of the disease meaning and implications, as well as medication management and drug combinations. Patients also indicate the absence of a single point of contact due to a complex care need across multiple domains. This finding supports previous research highlighting the challenges of navigating multidisciplinary care across different departments and institutions [58].

Additionally, while scientific literature often focuses on the medical background and challenges of all involved, it frequently lacks clear practical advices for patients' daily lives. Respondents indicate that current publications lack information on short-term benefits or actionable advice that can support their care management. Addressing this gap by providing more practical self-management strategies may strengthen patients' ability to manage their condition and thereby support more personalised care pathways. In line with these findings, patients indicate the need for more streamlined care delivery, specifically aimed at alleviating the day-to-day burden of the disease and enhancing overall quality of life.

This research also highlights the critical role of advocacy and awareness in improving care for rare diseases. The concept of 'double invisibility' refers to two forms of invisibility experienced by patients and parents. First, their disease and needs are poorly understood by the public and the healthcare professionals. Second, (ultra) rare diseases are often not recognised within healthcare

systems, ultimately complicating the coordination of care services. This finding is in line with previous research showing the present gaps in awareness and education [59].

Therefore, increasing awareness and knowledge among healthcare professionals and the public is essential, as rare diseases are frequently overlooked in educational programs and awareness campaigns, contributing to diagnostic delays and inadequate management. While more common diseases benefit from targeted campaigns promoting, for example, research or healthcare optimisation, rare diseases often lack even the initial recognition, let alone subsequent stages of the patient journey. In addition, education for healthcare professionals on the psychosocial burdens of rare diseases could enhance empathy and overall quality of life for patients.

Taken together, these findings suggest that, in addition to the medical care provided, patients perceive a lack of a holistic care approach, despite its recognised importance in the literature and its identification as essential by professionals in this research [22]. This underscores the need for greater emphasis on holistic care in practice to better support patients' well-being and offer more personalised care. [22].

Another key finding from the interviews is the lack of a clear and consistent linkage between diagnostic information and subsequent treatment and/or support options. To improve patient outcomes and facilitate personalised care, diagnostic insights must be linked to up-to-date treatment knowledge and embedded within patient-specific care networks. This linkage is important for coordinated disease management and the effective transfer of information across institutions. While this finding is focused on the technical linkage between diagnostic insights and subsequent care, it aligns with the broader international call for people-centred care models that prioritise coordination, continuity, and responsiveness to individual patient needs throughout the care journey [16]. Hereby, a possible solution could be the integration of clinical guidance layers that work alongside existing care systems, such as EHRs. Patient data, such as symptoms or test results, should constantly be analysed to suggest context-dependent advice, even if there is no confirmed diagnosis. Such an approach may support healthcare professionals by providing personalised services that adapt to the patient's state, as well as encouraging early actions.

Technology, specifically AI, is viewed by respondents as indispensable and having significant potential in supporting these personalised and patient-specific care networks. They consider AI as instrumental for enabling more timely and informed decision-making. They see it as a supportive tool for various aspects, such as early detection, personalised treatment, and information management and provision. However, concerns about privacy, trust, and the need for transparency in AI reasoning were raised. These insights are in line with previous research on the implementation and potential of AI in rare disease care [60].

Complementing the qualitative insights, the exploratory data framework analysis demonstrates that establishing and implementing patient care pathways for rare diseases has great potential for bridging current care shortcomings and providing personalised, patient-centred approaches, aligning well with previous research [22]. The visualised flowchart developed in this research serves as a crucial tool for understanding the various activities and stages that patients navigate post-diagnosis. It illustrates the need for a coordinated care approach that integrates clinical decision support with patient-specific data. The framework emphasises the importance of case management as a central coordinating mechanism, ensuring that all relevant steps, including therapies and supportive care, are tailored to the

individual patient's circumstances. This is particularly relevant in the context of rare diseases, where treatment options may be limited and symptom management often requires a holistic approach that considers the patient's broader life context.

Although patient pathways can function as a foundation for personalised and coordinated care, their development and implementation strongly depend on the availability, quality, and interoperability of necessary data sources. The exploration of data sources reveals a multifaceted landscape, where EHRs, LBZ data, PGOs, patient registries, NZa data, and clinical trial databases serve as essential repositories of information. While these sources each provide valuable insights, establishing patient pathways based on them raises several challenges and barriers related to fragmentation, inconsistent data capture, and limited interoperability. For example, this research revealed significant challenges due to the highly fragmented and dispersed nature of the data. There is a notable difference in data elements captured in data sources and registries, both the type of data elements, as well as the consistency and standardization in which they are captured. Although many essential data elements are for example already captured in Dutch EHRs, these are dispersed across different institutions and systems.

In addition, data related to rare disease care can be difficult to recognise in data systems, because systems do not always make a clear distinction between care specifically for rare diseases and more common diseases. In data systems, it is often difficult to identify people with ultra-rare diseases due to the lack of appropriate coding for these diseases. These obstacles impede efficient follow-up monitoring and prevent complete mapping of their care pathways. This finding corresponds with previous international studies that have pointed out the inadequacies in current healthcare registration systems, which often fail to accommodate the unique needs of rare disease patients [61]. Furthermore, this research demonstrates there is a notable difference in the interoperability amongst data sources. Previous research also shows that only a minority of registries promote interoperability through the use of coding languages and minimum common data sets [40].

Additionally, not all activities visualised in the flowchart can be traced through existing data sources. For instance, social support, which is a crucial aspect of care, is largely absent from registry data. Although some formal services (e.g. municipal support), may be documented, much of the practical and informal assistance (e.g. patient associations or community networks), is not (routinely) registered in data sources and thus remains difficult to track and analyse. An additional challenge has to do with decisive tests, which remain difficult to identify due to the absence of specifically defined data elements.

Furthermore, PGOs are still under development, testing phases, or research phases. Therefore, it may take some time until certain information is captured in these data sources and can be used for analysing. Additionally, PGOs face access limitations, notably excluding minors under 16 years old, thereby preventing them from creating a patient-held data record. This leads to the exclusion of information gathering via this data source for a large group of patients with a rare disease. This exclusion hinders the ability to record and analyse the progression of disease from early life stages via this source, which is something that is important in enabling timely interventions and a better understanding of the natural history of rare diseases.

Lastly, this research supports previous research showing that patient registries are valuable data sources for understanding the natural history of rare diseases, comparing treatment outcomes and

ultimately are key to serving personalised evidence-based medicine [25, 62]. However, the findings further emphasise, consistent with existing literature, that establishing registries is only the first step. For registries to be truly beneficial for future research, data must be collected consistently and maintained to a high standard [40]. As evidenced, early phenotypic progression is important for future interventions, guidance, and decision-making but is not always consistently captured [25].

4.2. Limitations

This research faced several limitations that could influence its findings. While the initial aim was to map detailed post-diagnostic patient pathways for several rare diseases, data accessibility challenges required a shift toward mapping a general patient pathway (flowchart) and identifying necessary and available data sources instead. This approach provided valuable information on the Dutch data infrastructure and (international) stakeholder experiences but limited disease-specific patients pathway mapping. Moreover, the study's scope was broadened from a focus on a specific group of rare diseases to a wider range due to practical constraints. This reduced the depth of disease-specific insights. Additionally, the respondents included Dutch and international individuals. Whereas, the exploratory data analysis mainly focused on the Dutch healthcare context, due to time constraints, which may limit the outcome's generalizability. Furthermore, only one patient/parent interviewee was non-Dutch, which restricts the applicability of patient perspectives to other healthcare systems. Another limitation concerns the availability and accessibility of data structures. Many registry data structures are not publicly accessible, complicating the analysis and making it difficult to fully capture essential information. Lastly, while the general pathway presents a useful framework, it might be too broad to adequately reflect each patient's unique and specific needs. Given the explanatory nature of the data research, certain details or steps of the general pathway may not have been completely captured.

4.3. Further research

Future research should investigate the practical feasibility of integrating the currently fragmented data sources relevant to rare diseases. An even more in-depth analysis of existing data sources is needed to assess how they can be effectively brought together. A key priority is to explore the secure linkage of registries and datasets, given that connecting patient identifiers from different sources is only possible under strict regulatory frameworks. Therefore, further research should examine under what conditions such linkages are feasible using privacy-preserving methods. In addition, to strengthen the research findings, the respondent group should be broadened. While a variety of medical and international backgrounds were already represented among the professionals interviewed for this research, including more perspectives could enhance the generalisability and validity of the findings. Moreover, to strengthen the generalisability and validity of the findings, it is important to include more patients with different diseases. Alternatively, focusing on one group of rare diseases or one specific healthcare system in a country could provide more in-depth insights and assist in the development of specific recommendations. Lastly, while the general post-diagnostic patient pathway is useful as a starting point, it may be too general to address the specific patient's needs. Therefore, the development of post-diagnostic patient pathways could be tailored to groups of similar rare diseases or based on similar symptoms, focusing on commonalities across conditions to enable more personalised care strategies.

4.4. Conclusion

Understanding and mapping the post-diagnostic patient pathways in rare diseases to support personalised care requires the integration of available data sources and practice-based insights. Post-diagnostic patient pathways are revealed as complex, fragmented, and heterogeneous, varying highly between patients and often lacking clear structures. Available data sources, such as EHRs and rare disease patient registries, are crucial for systematically gathering essential information about patient pathways, demographic information, diagnoses, and healthcare usage. These data sources hold potential, particularly when incorporating AI, for identifying patterns, predicting risks, and identifying and mapping post-diagnostic patient pathways. However, challenges related to data fragmentation, interoperability, standardisation, and sharing limit their current effectiveness. Additionally, insights, gathered from the experiences of patients, parents, and healthcare professionals, offer an indispensable qualitative perspective. The insights highlight the often-unseen realities of navigating care, highlighting critical challenges like information gaps, insufficient care coordination, burdens on families, and psychosocial needs that quantitative data alone may not capture.

Combining data sources and experiences from patients, parents, and professionals is therefore essential for developing an overall understanding of post-diagnostic patient pathways. Data offers a solid and structured basis, while the experiences add essential context, explaining the impact of the disease and care process on daily life and revealing the underlying reasons behind observed data patterns. This integrated knowledge enables the identification of specific medical, practical, and psychosocial needs. Therefore, this detailed understanding is the basis for tailoring care pathways and interventions to the unique circumstances of each individual with a rare disease, thereby supporting and enhancing personalised care.

5. References

AI statement: AI assistance was used to support grammar, spelling, and language refinement. I revised all the content myself and take full responsibility for the final version.

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6. Appendix

6.1. Appendix 1 – Topic list

6.1.1. Topic list for interviews with patients/ parents

- Introduction
- Asking the interviewee to introduce themselves/asking general information
- Diagnosis and initial care experiences
- Care pathway after diagnosis
- Challenges and obstacles
- Collaboration and communication
- Experiences with support
- Access to information
- Improvements
- Future vision
- Debriefing/ Ending

6.1.2. Topic list for interviews with healthcare professionals

- Introduction
- Asking the interviewee to introduce themselves/asking general information
- Care pathway after diagnosis and challenges
- Factors influencing care pathways
- Collaboration between specialists and institutions
- Support and information provision
- Improvements and innovations
- Personalisation of care
- Future vision
- Debriefing/ Ending

6.2. Appendix 2 – Interview guide – Patients/Parents

Good morning/ afternoon,

I'll shortly introduce myself first. My name is Emma and as part of my graduation research at the university of Twente, I am conducting a study on rare diseases, specifically focusing on the post-diagnosis phase. Through this interview, I would like to gain insight into your experiences and knowledge regarding rare diseases.

The interview is expected to take approximately 30 to 60 minutes. With your permission, I would like to record this conversation so that I can listen back and analyse it for my research. Please be assured that your name will not be documented anywhere within this study, and all data will be handled in strict confidence.

You may stop the interview at any time without providing a reason, and you are not required to answer any questions that you do not wish to. Additionally, I have quite a general list of questions and some may fall outside your area of expertise, if so, please free to let me know. And feel free to answer and elaborate from your own angle of expertise.

Before I start the recording, I will ask you 1 general questions:

- Gender: (self-determined)
- What is the age of your child? (it's not mandatory to say)

Do you have any questions before we begin with the interview?

Then I will start the recording and first ask for your permissions to record the interview and to proceed with the interview itself.

Starting the Recording

Now that the recording has started, I would like to confirm:

- ➔ Do you consent to this interview being recorded?
- ➔ Do you consent to the interview based on the points stated in the informed consent form you received via email?

Diagnosis and initial care experiences:

- Can you tell me about your/ the child's rare disease?
- How long did it take before your/ the child received the right diagnosis?
- How did you and the child experience the time before the diagnosis?

Care pathway after diagnosis:

- Can you describe what happened after your/ the child received the diagnosis?
- Which healthcare professionals were involved in the care process after the diagnosis?
- How has the care developed in the months and years after the diagnosis?
    - Were there moments when the care had to be adjusted?

- Did your/ the child receive(d) care from an expertise centre (specialised centre) during the healthcare process?
    - How did that process go and how was the accessibility?
    - What difficulties did you experience?
- What were the most important moments for *you (and* the child) after the diagnosis?

Challenges and obstacles:

- What problems did you face in your/ the child's care after the diagnosis?
    - Were there any organisations or people that helped you with this?
- What was or is the most difficult aspect of navigating the healthcare system?
- Did you face any unexpected changes in your/ the child's care? (*experience*)
- Did your place of residence have or had an influence on the access of care after diagnosis?
- Did you experience waiting times during the care after diagnosis, and how was this for you?

Collaboration and communication:

- How was or is the collaboration between different healthcare providers or institutions?
    - What went well in this regard and what could have been better?
- How was the communication between healthcare providers and you as the parent and the patient?
- Has the child ever received conflicting information or advice? If so, how did you handle this?

Experiences with support:

- Did you receive psychosocial support, and if so, when in the process?
- Where their times when you needed more support and felt insufficiently supported?
    - In which situations did this happen?
    - What would have helped you in those moments?
- Did you use patient organisations or peer support? How did this help you?
    - How has connecting with other parents of children helped you navigate the journey of care?

Access to information and support:

- Did you have to search for information about your disease and treatment options yourself?
    - If so, how did you experience this?
    - Where did you find this information?
    - How was it for you to find reliable information?

Improvements:

- As a final question, what would you like to see changed in the care for people with rare diseases, maybe specifically in the post-diagnosis phase or in general?

Debriefing/ Ending of the Interview

Before we finish the interview, is there anything else you would like to add or any questions?

End of recording

Then now we have come to the end of this interview. Your answers and insights are a valuable contribution to my research, and I would really like to thank you for your participation and your time. If you have any questions or additional thoughts at any other time, you can always contact me by email. But for now, thank you again for your participation, wishing you a great rest of your day

6.3. Appendix 3 – Interview guide – Healthcare Professionals

Good morning/ afternoon,

I'll shortly introduce myself first. My name is Emma and as part of my graduation research at the university of Twente, I am conducting a study on rare diseases, specifically focusing on the post-diagnosis phase. Through this interview, I would like to gain insight into your experiences and knowledge regarding rare diseases.

The interview is expected to take approximately 30 to 60 minutes. With your permission, I would like to record this conversation so that I can listen back and analyse it for my research. Please be assured that your name will not be documented anywhere within this study, and all data will be handled in strict confidence.

You may stop the interview at any time without providing a reason, and you are not required to answer any questions that you do not wish to. Additionally, I have quite a general list of questions and some may fall outside your area of expertise, if so, please free to let me know. And feel free to answer and elaborate from your own angle of expertise.

Before I start the recording, I will ask you a few general questions:

- Gender: (self-determined)
- What is your profession, and how are you involved with rare diseases?
- May I ask your age? (it's not mandatory to say)

Do you have any questions before we begin with the interview?

Then I will start the recording and first ask for your permissions to record the interview and to proceed with the interview itself.

Starting the Recording

Now that the recording has started, I would like to confirm:

- ➔ Do you consent to this interview being recorded?
- ➔ Do you consent to the interview based on the points stated in the informed consent form you received though email?

Then I will begin with a general question:

- Do you have experience with specific rare diseases, or is your expertise more related to multiple rare diseases?

Care pathway after diagnosis & challenges:
Then, I would like to continue with some questions about the care pathways/ journeys for these rare diseases. So, every patient follows a certain trajectory after being diagnosed, but of course this can vary significantly.

- Could you describe how the care pathway/ journey typically progresses after the diagnosis of a rare disease? (so as in the activities and steps taken)
    - Who is generally involved, and how? *(case manager?)*
    - What is your role in this process?
    - Do you perhaps have a concrete example of a typical journey you encountered or know of?

- What are the most common challenges or bottlenecks patients face after diagnosis in accessing appropriate therapies? (how does it influence timeliness of treatment/ delays of treatment/ treatment options?)

- How do patients and their families experience these challenges in daily life?

- When looking at <u>different</u> rare diseases, do you see common patterns in care approaches, or do they tend to take different paths throughout the patient pathway?

- How well do you think the current healthcare system meets the needs of patients with rare diseases?

- What challenges do you experience or know of in coordinating care for these patients?

Factors influencing care pathways:

- Are there factors such as age, gender, co-morbidities, or place of residence that influence care pathways, and if so, how?
    - Where do you see the biggest variations in care pathways between patients?
    - (How does care pathways differ between children and adults?)
    - How does care for common metabolic diseases differ from that for rare metabolic diseases

Collaboration between specialists and institutions:

- How is the collaboration between different specialists and institutions in the care of rare diseases?
    - What challenges do you experience in working with other specialists or healthcare institutions?
    - How do specialists communicate and share patient information? (experiences?)

- What role do ERNs play in streamlining care pathways for patients?

- What obstacles or successes do you experience in the international or European collaboration for rare diseases? *(how could these be addressed?)*

Support and information provision:

- What strategies or sources do you use to gather information about rare diseases?

- How are patients supported in finding information about their rare disease and treatment options? (What are the most commonly used sources of information?)

Improvements and innovations:

- Based on the experiences of patients and families, where do you see the greatest need for improvement of the care process after diagnosis?

- What would you like to see changed (first) in care pathways/ journeys for rare diseases?

- What technological innovations or orphan devices are you familiar with or currently using for the post-diagnoses phase, and how do you see the role of them in improving care pathways/ journeys after diagnosis?
    - Treatment technology/ information technology?

- How do you see the role of AI in the future for care for rare diseases?

Personalisation of care:

Tailoring care to individual patient needs is off course important, but for rare diseases this can be challenging. From your perspective:

- Do you see ways in which care could be more personalised to meet the needs for patients with without it becoming too impractical?

(I realise it is quite a broad question, so feel free to approach it from any angle whether that's medical treatments, care coordination or something else).

    - And what do you think are the main barriers or challenges to making that practical and implementing it?

- Which new (or existing) policies or initiatives do you see as most promising for improving rare disease care in the upcoming years?

Future vision:

To wrap up the interview, I would like to ask a final general question. Looking ahead:

- What is your vision for the future of care for patients with rare diseases

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Debriefing/ Ending of the interview

Before we finish the interview, is there anything else you would like to add or any questions?

End of recording

Then now we have come to the end of this interview. Your answers and insights are a valuable contribution to my research, and I would really like to thank you for your participation and your time. If you have any questions or additional thoughts at any other time, you can always contact me by email. But for now, thank you again for your participation, wishing you a great rest of your day!

6.4. Appendix 4 – Information letter

Exploring Experiences and Perspectives on the Care Pathway, Treatment, and Management for Rare Diseases

Dear Mr./Ms.,

With this information letter, we would like to invite you to participate in an interview about your experiences and perspectives on the care pathway for rare diseases, with a focus on treatment and management after diagnosis. This letter explains the purpose of the study and how you can participate. This study is conducted by Emma Schrijver. If you have any questions, you can contact me via email at: j.g.schrijver@student.utwente.nl or my supervisor: a.h.jonker@utwente.nl

1. Purpose of the Research
The goal of this study is to gain insight into the care pathway of people diagnosed with a rare disease. By understanding the experiences and perspectives of patients, parents and healthcare professionals, this research aims to identify potential barriers, challenges, and opportunities for improvement in rare disease care.

2. What is Expected from You?
The study consists of a 30- to 60-minute interview about your experiences with the care pathway, treatment, and management of rare diseases after diagnosis. The interview will take place via Microsoft Teams, and you will receive a link via email. The interview will be recorded to review the conversation and analyse it for the study. Your identity will remain anonymous. After processing the recording, the file will be permanently deleted.

3. Your Rights & Anonymity
Participation in this study is entirely voluntary. You may withdraw at any time, even during the interview, without providing a reason. Your personal data, such as your name or contact details, will not be stored or processed in this study. The results of the interview will therefore not be linked to any identifiable personal information and will only be used for intended research purposes.
This study has been approved by the Ethics Committee of the Faculty of Behavioural, Management, and Social Sciences (BMS) at the University of Twente (within the Domain of Humanities & Social Sciences).

4. Consent Form
If you decide to participate in this study, please carefully review the informed consent form. At the beginning of the interview, you will be asked for verbal consent, which will be recorded as part of the recording.

Your insights and experiences will be highly valuable to this research.

Thank you very much!

Best regards,
Emma Schrijver
(Student Health Sciences, University of Twente)
Mail: j.g.schrijver@student.utwente.nl

6.5. Appendix 5 – Informed consent form

Linking diagnostics to therapies: identification of diverse patient pathways for rare disease patients.

- I have read and understood the information letter.
- I understand that I will be asked about the process from diagnosis to post-diagnosis, with a focus on the treatment and management of rare diseases.
- I understand that only the researchers involved in this study will have access to the research data.
- I understand that my personal data will not be stored or processed in this research.
- I have had sufficient time to decide whether I want to participate in this study.
- I am aware that participation is voluntary and that I can withdraw at any time without providing a reason.
- I consent to the recording of the interview.

At the start of the interview, you will be asked to provide verbal consent.

6.6. Appendix 6 - Mitigation plan for interviews

Mitigation plan for research on patients with rare diseases and parents:

1) **Recognising Stress and Distress** (To identify stress in participants, I will look for the following signs):
    - Emotional reactions such as crying, increased anxiety, anger, or withdrawal.
    - Physical reactions such as rapid breathing or trembling.
    - Verbal indications of discomfort or the need for a break.
2) **Response to Stress and Distress** (If a participant shows signs of stress):
    - A break will be offered to allow the participant to regain composure.
    - The participant may choose to leave the session without any further obligations.
3) **Beginning of the interview**
    - Participants will be informed that they are not required to answer all questions. They are free to skip any questions they feel uncomfortable with, and they can stop the interview at any time without any further obligation.
4) **Criteria for Discontinuation of Participation** (A participant may discontinue participation if):
    - They indicate that they no longer wish to participate.
    - The researcher assesses that further participation may be harmful to the participant.
5) **Debriefing and Follow-up** (*After the interviews):*
    - A debriefing will be offered, allowing participants to share their experiences and ask questions.
    - Participants can receive a summary of the discussed topics or PDF of the thesis if desired, ensuring transparency.
    - Participants may contact the researcher if they have any further questions or concerns after the session.

By implementing these measures, we minimise risks and ensure a safe and supportive research environment for all participants.

6.7. Appendix 7 - Coding scheme

Table 6: Coding scheme of interviews

Main category	Category	Code
● **Advocacy and awareness**	● Awareness and knowledge amongst all those involved	● Awareness can lead to motivation to learn about rare diseases among healthcare professionals
		● Early patient education and engagement in paediatric care
		● Early self-education and active disease management
		● Gap in adult healthcare expertise for rare diseases
		● Improved diagnostic guidelines & clinician awareness across care levels (2)
		● Lack of attention to rare diseases in the education system, impacting children and families
		● Lack of awareness among physicians hinders appropriate diagnostic referrals
		● Need for high-quality disease information to reduce uncertainty among patients, families, and non-expert professionals
		● Need for professional education on rare diseases to increase awareness
		● Professionals mainly learning about rare diseases through experience
		● Recurrent need to educate colleagues due to lack of awareness
		● Treatment availability reduces disease awareness, risking missed diagnosis
	● Role of national or international initiatives	● Advancements in diagnosis to treatment through initiatives like MAxO and Treatabolome (2)
		● Economic limitations hinder full potential of ERNs
		● Enabling cross-domain collaboration through new funding models
		● Ensuring that models and solutions are relevant and applicable both domestically and internationally to ensure equitable healthcare access and quality.
		● International collaboration enhances research, harmonises guidelines and ensures equitable access to care for rare diseases.
		● Leveraging existing policies outside the rare disease domain for better outcomes
		● Personalised care pathways through AI-driven approaches like Utopia
		● Promising initiative: supporting small-scale therapy development based on platforms
		● Role of ERNs in advocating for treatment access and supporting drug availability
		● Role of ERNs in directing patients to expert care and accurate information (2)
		● Role of ERNs in knowledge production, accumulation, and provision
		● Role of ERNs in providing common structures for rare disease care across countries
		● Role of ERNs in providing cross-border healthcare and expertise exchange (2)
		● Role of ERNs in providing guidelines, visualised patient journeys and solutions for rare diseases
		● WHO and United Nation resolutions as key policies for rare disease advancement
	● Stigma and ignorance around rare diseases	● Ignorance of the situation makes it hard to explain, affecting social life
		● Stigma around rare diseases are decreasing but still present
		● Stigma complicates care management and treatment adherence
		● Under addressed stigma in rare diseases compared to other conditions
● **Artificial intelligence**	● AI in diagnosis	● AI as an assistance tool in diagnosis
		● AI in diagnosing rare diseases through big data analysis.
		● Research to AI in youth health care for early detection of childhood disorders
	● AI in post-diagnosis proces	● AI as an assistance tool in treatment
		● AI for patient selection in clinical trials
		● AI for targeted care for high-risk children
		● AI for understanding therapy effectiveness
		● AI helps extract relevant insights from knowledge driven networks for personalised care in rare diseases
		● AI helps extract relevant insights from large, heterogeneous data for individual patient situations

		● AI in a supportive role for knowledge and information provision in rare disease care
		● AI to speed up preclinical work for therapies
		● Personalised care pathways through AI-driven approaches like Utopia (2)
		● Trusted and curated information for families through AI and human verification
		● Uncertainty about AI's potential to aid in treatment from a professional's perspective.
		● Use of AI for integrated patient information and timely specialist re-engagement
		● Use of AI for managing information overload in patient data sharing.
		● Use of AI for personalised support (2)
		● Use of AI for support to patients and families
		● Use of AI to monitor disease progression
		● Using AI to automate information processing and reduce clinician workload
		● Using AI-driven approaches for information gathering and synthesis (2)
	● Implementation of AI in practice	● AI needed focus on ethical and purposeful use
		● Ensuring high-quality input data to build trust and accuracy in AI tools for care
		● GDPR and regulations around medical AI for trust and transparency
		● Implementation challenge: ensuring AI tools are usable and trusted by health systems
		● Importance of tailoring AI outputs to relevant, timely information for specific situations
		● Importance of transparency and reasoning in AI decision-making for trust
		● Necessary implementation strategy for seamless AI integration into existing workflow
		● Need for responsible AI data use and user awareness of data transparency
		● Non-technical barriers: privacy concerns and cloud distrust in health systems
	● Perspectives on AI from professionals	● AI as indispensable in rare disease care
		● AI as supportive tool, not replacement
		● Complementing technology-driven solutions with AI to enhance care
		● Maintaining human interaction in AI-supported care
		● Need for on-premises AI solutions tailored for low-resource health systems
		● Recognition that AI is a present reality shaping healthcare and daily life
● Data elements/ sources	● Challenges in data systems	● Inadequate systems for tracking rare disease knowledge due to hospital coding limitations
		● Lack of interoperable systems and structural integration hinders coordinated care (2)
		● Lack of official diagnostic coding for ultra-rare diseases in health systems
		● Need for centralised, patient-owned health record to enable information sharing across different institutions
		● Need for more Orpha codes to improve knowledge, diagnostic pathways, and enable connection to reference networks
		● Need for operational definitions and criteria for undiagnosed rare diseases
		● Patient has insight into medical data but cannot make use of it
		● Possible challenge of sharing patient information across multiple institutions without causing information overload
	● Data sharing perspectives, barriers and challenges	● Challenges in obtaining consent from all relevant sources but crucial for seamless data sharing in healthcare.
		● Expertise centres reduce need for data exchange between providers
		● Importance of role of engaged lawyers in enabling data sharing partnerships
		● Lack of interest in digital tools prevents full participation in data sharing for some patient groups
		● Patient values and actively facilitates data sharing
		● Privacy and consent barriers hinder the integration of healthcare data from multiple sources.
		● Sharing individual data at institutional level in rare diseases is essential but remains a challenge
		● Underestimating the need for data sharing in diseases with lower rarity
	● Digital health data management and access	● Therapy adherence data is sent automatically to the pharmaceutical company's server and accessed via dashboards for patients and healthcare professionals
		● Use of international patient registry from enzyme manufacturer for data collection and insights

		• Used BDS elements from DD JGZ (digital youth health care record)
		• Using Clinical trials registries for information gathering (2)
		• Using electronic health record (EHR) data to identify post-diagnostic care pathways
• Diagnostic process	• Diagnostic challenges	• Addressing diagnostic difficulties is important
		• Delayed or missed diagnoses in adulthood due to past diagnostic limitations in childhood
		• Diagnosis communicated impersonally via email with Wikipedia link (2)
		• Evolution and ambiguity of diagnosis: from histology to genetics, ongoing uncertainties in defining the condition
		• Healthcare professional's discouragement of diagnostic pursuit due to perceived lack of treatment options
		• Insurance obstacles delay or prevent genetic testing and result delivery
		• Lack of access to newborn screening in certain regions, seen as a missed opportunity for early detection
		• Lack of awareness among physicians hinders appropriate diagnostic referrals (2)
		• Limited access to diagnosis and diagnostic technologies like whole genome sequencing
		• Long diagnostic journeys (due to lack of education)
		• Need for operational definitions and criteria for undiagnosed rare diseases (2)
		• Non-uniform newborn screening due to contextual factors
		• Parental concerns invalidated by healthcare professionals
	• Perspectives on diagnosis from professionals	• Diagnosis as Iceberg
		• Diagnosis is a process not an event
		• Improved diagnostic guidelines & clinician awareness across care levels
		• Improvement but gaps remain in rare disease diagnosis
		• Need to improve affordability and accessibility of diagnostic tools to reduce diagnostic delay
• Future perspectives	• Desired changes by patients and parents	• Hope for better communication with healthcare professionals
		• Hope for better coordination and communication between healthcare providers
		• Hope for better medication management by professionals to reduce disease burden
		• Hope for better streamlined care to reduce the number of healthcare contacts, hospital admissions and burden of disease
		• Hope for healthcare providers to fully recognise the impact of all care decisions and agreements on patients' lives, emphasising quality of life
		• Hope for improved access to affordable orphan drugs and treatment
		• Hope for Improved information provision by professionals
		• Hope for increased knowledge amongst healthcare professionals
		• Hope for increased public awareness and understanding of rare diseases to improve recognition and support
		• Need for a single point of contact who is actively involved in the care process (2)
		• Need for more research with direct impact potential for patients and families (2)
	• Desired changes by professionals	• Empowering parents to focus on parenting, not caregiving or expert roles
		• Empowering patients with control over their data and tools for meaningful use in healthcare and daily life
		• Hope for increased availability of drugs and therapies for rare diseases
		• Hope for increased social support for patients with rare diseases.
		• Leveraging existing policies outside the rare disease domain for better outcomes (2)
		• Need for centralised, patient-owned health record to enable information sharing across different institutions (2)
		• Need for comprehensive support: financial, psychological, and societal inclusion
		• Need for coordinated same-day care
		• Need for effective home-based care and therapies to improve quality of life
		• Need for establishing patient-specific care networks to support individualised disease management (2)
		• Need for general medical workforce awareness to recognise and suspect rare diseases
		• Need for increased cross-country collaboration and equity in rare disease care

		• Need for patient-centred, seamless care pathways where healthcare professionals coordinate around the patient, not vice versa
		• Patient control over data can drive significant change
		• Providing tools to enable practical and meaningful use of health data to patients
		• The need for knowledge exchange on local, national, and international levels to ensure quality care for rare diseases. (2)
		• Hope for better communication with healthcare professionals
• **Healthcare system interaction**	• Barriers to cross-border collaboration in rare disease care	• Infrastructure obstacle: lack of structural integration of the ERNs role within national health systems
		• lack of resources and time for local clinicians to engage in international collaboration
	• Communication amongst healthcare professionals, specialties and institutions	• Difficulties in collaboration and communication with healthcare professionals outside the core care team
		• Focus on commonalities and equity to reduce tensions and improve collaboration across specialties.
		• Inclusive, broad, and traversal approach fosters engagement and reduces competition among specialties
		• Insufficient collaboration between youth health physicians and paediatricians could limit early family support
		• Internal miscommunication within specialist departments leading to scheduling of unnecessary repeat procedures.
		• Intra-hospital discrepancies between emergency and clinical departments causing inconsistent patient information
		• Lack of awareness of expertise centre involvement among emergency care providers
		• Lack of interoperability between electronic patient records of different hospitals causing inconsistent medication and allergy information
		• Lack of interoperable systems and structural integration hinders coordinated care
		• Referral letters not sent despite patient reminders
		• The need for knowledge exchange on local, national, and international levels to ensure quality care for rare diseases.
	• Communication between professional and patient/ parent	• Challenge with out-of-hours communication with specialists
		• Challenges in communication between patient and multiple healthcare providers due to multi-morbidity
		• Clear contact instructions after enzyme therapy became available
		• Collaboration among specialists is challenging due to limited time for discussions
		• Conflicting specialist advice and diagnostic doubt despite established patient history
		• Difficulties in collaboration and communication with healthcare professionals outside the core care team (2)
		• Digital communication via hospital portals lacks timely responses
		• Disruption in care chain due to ER physician's refusal to consult specialists (2)
		• Experience of healthcare professionals using rare disease context to justify blunt or unethical communication.
		• Frustration when healthcare professionals don't proactively provide necessary information
		• Healthcare professionals sometimes react with frustration or defensiveness when parents demonstrate extensive knowledge.
		• Incomplete or delayed communication from specialists leading to gaps in information flow to families
		• Lack of communication during critical care undermines patient trust
		• Lack of essential patient education by professionals leading to preventable health crises and patient frustration
		• lack of structured coordination system for collaboration between specialists
		• Patient carries identification to facilitate emergency care and ensure proper communication
		• Unnecessary medication discussions in emergency care between patient and professional
		• Waiting times leads to reliance on impersonal communication (e.g., email)
	• Coordination of care	• A whole-of-life approach to care coordination, integrating health, education, community, and employment to improve overall well-being

		• Bridging the expertise of paediatricians and youth healthcare professionals to improve family support
		• Care coordination requires clear guidelines and role definitions to ensure efficiency and clarity for everyone
		• Care coordination requires rigorous implementation, evaluation, and outcome measurement to add value without duplication
		• Care coordination unclear due to too many or too few specialised professionals involved
		• Collaborative care management with local healthcare providers
		• Comorbidities complicate care coordination in adult rare disease patients
		• Coordinated one-stop post-diagnosis care to save time, effort, and money
		• Dedicated, centralised care coordination requires highly skilled professionals
		• Dedicated, centralised care coordination services essential to avoid fragmentation
		• Disruption of patient-specialist relationships due to care restructuring
		• Distributed care coordination risks being overtaken by acute clinical demands
		• Evolution from dispersed expertise to centralised care in one expert centre
		• Expert centre reduces patient choice in care due to care centralisation
		• Fragmented care and poor coordination
		• Ideal coordinated care from diagnosis to management, involving experts, non-experts, and patient/family as equal contributors
		• Ideal model: care coordination between expertise centre and local care
		• Lack of structural agreements for collaboration between youth health services and paediatric care across regions
		• Need for a single point of contact who is actively involved in the care process
		• Need for coordinated same-day care (2)
		• Patient-driven care coordination and challenges of self-management in crisis situations
		• Regional coordinating centres manage hospital networks
		• Strict divide between healthcare and social support complicates access and understanding for everyone involved
		• Taking ownership of care coordination as a person with a rare disease
		• Youth health physician coordinating local first-line care based on community knowledge and family needs
	• General approaches to rare diseases	• Individual rare disease-agnostic approach for sustainable and equitable care
	• International communication between professionals	• Few barriers to international knowledge sharing partnerships, mostly time zones and language
		• Knowledge sharing and partnership in international collaborations exceed expectations
		• Role of ERNs in providing cross-border healthcare and expertise exchange
		• Utilising international professional networks for complex case discussions
	• Multidisciplinary team involvement	• Complex multi-morbidity managed by multidisciplinary team
		• Cornerstone of patient care: multidisciplinary team discussions and support
		• Lack of established multidisciplinary team approach in some countries
		• Multidisciplinary care needed from the start to manage diagnosis and treatment, including psychiatric and somatic aspects
		• Need for access to multidisciplinary teams locally and at expert centres
		• Need for multidisciplinary care including evidence-based symptomatic treatment
		• Need to shift from single clinician to team-based care approach
• Information gathering	• Challenges with information gathering or provision	• Challenges in comprehending medical information due to unfamiliar terminology by parent
		• Challenges in finding reliable and relevant information on the WWW (web and social media)
		• Challenges in providing translated information to patients with low educational status
		• Difficulty translating scientific research into clear, practical insights for daily care
		• Limited knowledge and experience with ultra rare diseases leading to lack of clear care pathways and reliance on personal experience
		• Need for high-quality disease information to reduce uncertainty among patients, families, and non-expert professionals (2)
		• Need for more research with direct impact potential for patients and families

		● The impact of language on understanding and connection with medical information
	● Gathering of information by patients and parents	● Access to expert healthcare professionals as a key source of information
		● Active information seeking by patient or parent through literature and resources
		● Patient organisations and networks as valuable sources of information
		● Self-directed use of scientific databases and author networking for rare disease knowledge acquisition
		● WWW (web and social media) as a source of information
	● Gathering of information by professionals	● Using AI-driven approaches for information gathering and synthesis
		● Using an information plan for rare diseases with peer research
		● Using Clinical trials registries for information gathering
		● Using clinical knowledge platforms (e.g. UpToDate) for information gathering
		● Using ERNs for information gathering
		● Using HGNC for information gathering
		● Using OMIM for information gathering
		● Using patient association websites for information gathering
		● Using professional networks for information gathering
		● Using PubMed for detailed information and case reports on rare diseases (complications)
		● Utilising international professional networks for complex case discussions (2)
		● Visiting disease-specific organisation websites for recent treatment updates
		● Visiting websites of international and European organisations for clinician-specific rare disease information
	● Professional communication of information to patients and families	● Diagnosis communicated impersonally via email with Wikipedia link
		● Encouraging patients to join patient associations and search for peer support for reliable information.
		● ERNs as a source for patient information
		● Inadequate information provision following diagnosis
		● Parental knowledge surpasses healthcare professionals' expertise of the rare disease
		● Providing patient and family-specific material from organisations for discussion
		● Role of ERNs in directing patients to expert care and accurate information
		● Trusted and curated information for families through AI and human verification (2
● **Personalisation of care**	● Barriers to personalisation	● Need for improving educational and social levels for better care participation
		● Need for more knowledge to enable true personalisation of therapy in rare diseases
	● Holistic care perspectives	● A whole-of-life approach to care coordination, integrating health, education, community, and employment to improve overall well-being (2)
		● Holistic care approach is more crucial for rare disease patients due to limited awareness and patient networks
		● Need for holistic approaches in rare disease care
		● Personalised care through a holistic view of patients' needs, including quality of life and social services.
		● Personalised medicine through holistic care, considering lifestyle, comorbidities, and patient preferences
		● The importance of linking data from different systems to provide a complete patient view
	● Perspectives of personalisation from professionals	● A well-being approach is preferred over a mental health-only focus, as it's more palatable to families
		● Automated data from treatment devices supports therapy adherence monitoring and personalised care decisions
		● Diagnosis as an integrated intervention, directly linked to personalised treatment and post-diagnosis care (2)
		● Empowering patients with control over their data and tools for meaningful use in healthcare and daily life (2)
		● Knowledge-driven networks are essential to deliver personalised care
		● Need for correct and precise diagnosis to enable targeted treatment
		● Need for establishing patient-specific care networks to support individualised disease management
		● Personalised care pathways through AI-driven approaches like Utopia (3)

		• Tailored care approaches for remote, culturally diverse populations with rare diseases
		• The importance of spirituality in understanding rare disease experiences, especially in indigenous populations
		• The need to transfer disease knowledge from the expert centre to the patient's care network for informed care
		• Use of AI for personalised support
		• Utilising big data and AI enables more personalised care by identifying individual risks and tailoring advice
• **Post-diagnosis pathway**	• Access to and treatment or therapies + challenges	• Access to management and therapy is a common need
		• In some countries, access to care depends on ability to pay
		• Innovation in rare disease treatments eventually benefiting broader patient populations
		• Key role of medical advisory team from patient associations and clinicians in national enzyme therapy approval
		• Lack of treatment availability and evidence for treatment
		• Limited access to therapies in lower-income countries
		• Need for therapy development for rare diseases
		• New treatment access system – improved but lagging behind other countries
		• Recognition that multidisciplinary care and symptomatic treatment can improve outcomes even without available therapy
		• Treatment Approval Process
		• Treatment can be quite expensive
		• Treatment delays depend on drug approval
	• Challenges faced by everyone involved	• Distributed care coordination risks being overtaken by acute clinical demands (2)
		• Increased uncertainty for patients and healthcare professionals in ultra-rare diseases
		• Individual clinician challenges in post-diagnostic management due to lack of resources and pathways
		• Individual vs systems-level challenges in rare diseases
		• Need for high-quality disease-specific information
		• Risk of incorrectly assigning new or unrelated symptoms to the rare disease diagnosis
	• Challenges faced by patients and families after diagnosis.	• Absence of formal care pathways resulting in individualised, unsupported patient management
		• Care odyssey due to lack of expert-driven approach
		• Challenge of adjusting to assumptions about the condition's nature and progression
		• Challenges in employment and (social) relationships for patients and families
		• Common challenge of accessing expertise and specialised care
		• Common challenge of communicating diagnosis to family, social network, and community
		• Constant need for preparedness and loss of spontaneity in daily life due to illness management
		• Difficulty finding experts for ultra-rare diseases
		• Disruption in care chain due to ER physician's refusal to consult specialists
		• Feeling not taken seriously and opting to leave ED due to poor coordination and exhaustion
		• Geographical barriers to accessing care
		• Healthcare accessible but travel time requires energy and time
		• Hospitals and private healthcare systems sometimes refuse complex rare disease patients
		• Inadequate emergency care actions lead to patient deterioration and prolonged recovery
		• Inadequate medical support and delayed action during patient crisis situations
		• Inadequate personalised treatment approach and guidance post-diagnosis
		• Inadequate primary care support for complex patients leading to treatment delays and health deterioration
		• Lack of empathy and solutions from professionals leaves a negative impact on patients or families
		• Lack of expert-group-based treatment recommendations in some cases
		• Lack of patient associations and support affects daily life and disability levels
		• Limited knowledge and experience with ultra rare diseases leading to lack of clear care pathways and reliance on personal experience (2)

		● Medical care adequately managed; greater challenges in home situation and support
		● Mismatch between professional advice and patient's real medication needs forces continuous self-monitoring
		● Multiple single hospital visits disrupt work, school and family routine
		● Navigating systems (education, disability, social services) are common challenges
		● Necessity of recognition interventions in emergency rooms for rare disease patients
		● Ongoing daily medication adjustments instead of fixed treatment approach
		● Out-of-pocket expenses remain significant despite gratuity
		● Patients struggle with worsening symptoms during treatment approval process
		● Self-management between expert centre visits carries risks
		● Self-management due to insufficient medical information provision by professional
		● Switching drugs caused a severe allergic reaction with unknown cause
		● Unequal access to coordinated multidisciplinary care for rare disease patients
	● Connection between diagnostics and treatment	● Advancements in diagnosis to treatment through initiatives like MAxO and Treatabolome
		● Diagnosis as an integrated intervention, directly linked to personalised treatment and post-diagnosis care
		● Earlier diagnosis improves treatment efficiency and outcomes
		● Missed window for curative treatment
		● The need to systematically link genetic diagnostics to treatment options for improved care in rare diseases
	● Factors influencing pathways and care infrastructures	● (Psychiatric) comorbidity makes organising proper care more difficult
		● Care pathways differ depending on the disease and established care (infra)structures
		● Challenge of cultural and linguistic diversity in accessing care and support
		● Easier access to care pathways for paediatric rare diseases; more complex for adult-onset
		● Gender-related challenges, especially for females during pregnancy as the disease may worsen
		● Lack of knowledge as a key obstacle to achieving the ideal care pathway
		● Lack of resources as a key obstacle to achieving the ideal care pathway
		● Language barriers in communication during diagnosis and care
		● Rare disease care infrastructure is improving but remains limited, as systems focus on common diseases
		● Social, financial, and educational factors influencing care access
		● Stigma complicates care management and treatment adherence (2)
		● Triple impact of rare disease, remote location, and cultural/linguistic diversity
	● Follow-up care	● Annual monitoring (e.g. blood test, MRI) for long-term medication use
		● Biweekly infusions as part of long-term enzyme therapy
		● Enzyme therapy reduced symptoms, allowing less frequent monitoring (from quarterly to yearly)
		● Follow-up care is tailored according to the specific diagnosis (2)
		● Frequent (weekly) healthcare interactions for multi-morbidity management
		● Implementation of a standardised monitoring protocol including quarterly consultations, blood tests and MRI
		● Lack of continuity and transparency in appointment scheduling: no clear reason for cancelations
		● Mixed methods of follow-up care (in-person, online, email)
		● Periodic check-up frequency based on stability
		● Scheduled alternating biannual consultations with neurologist and metabolic specialist
		● Set up regular structured consultations in hospital
		● Shift from seeking medical guidance to routine monitoring due to loss of trust in healthcare system's ability to provide solutions
	● Initial reaction to diagnosis	● Diagnosis brings clarity, but loneliness due to disease rarity.
		● Emotional impact and fear related to uncertain prognosis and life expectancy
		● Emotional impact of delayed and impersonal delivery of rare disease diagnosis
		● Initial focus on child's diagnosis often overshadows family support needs
		● Patient experience shock due to lack of information and guidance from professionals after initial diagnosis

		● Post-diagnosis adjustment phase and lots of uncertainties about the next steps
	● Involved healthcare professionals and institutions	● Ambiguity and limitations in the role of general practitioners in rare disease care
		● Complexity of condition(s) limits care to academic hospitals only
		● GP informed but no active role in care for the rare disease
		● GP unaware of patient's rare disease
		● Involvement of a clinical geneticist
		● involvement of an endocrinologist
		● Involvement of an internal medicine specialist
		● Involvement of an internist-endocrinologist
		● involvement of a metabolic specialist
		● Involvement of a neurologist
		● Involvement of a paediatrician
		● Involvement of a psychologist
		● Involvement of occupational and insurance physicians
		● Involvement of social worker in providing psychosocial support to families
		● Involvement of specialised client support workers in assisting families navigating support and communication.
		● Referral and follow-up within centres of expertise
		● Use of regular and academic hospitals (for admissions)
	● Patterns in post-diagnostic care pathways	● Diverse initial pathways in rare diseases narrowing and converging over time
		● Patterns of common and specific needs in post-diagnostic pathways
	● Treatment options	● Chaperone therapy (small molecules) as part of the patient pathway
		● Clinical trial as part of the patient pathway
		● Dietary treatment as part of the patient pathway
		● Disease-modifying treatments as part of the patient pathway
		● Enzyme (replacement) therapy as part of the patient pathway
		● Occupational therapy for symptomatic treatment
		● Physiotherapy for (symptomatic) treatment
		● Primarily symptom-based care for ultra-rare diseases due to lack of evidence and knowledge
		● Symptomatic treatment as part of the patient pathway
		● Diverse initial pathways in rare diseases narrowing and converging over time
● Psychological and social support	● (Role of) peer support and patient advocacy groups	● Active patient advocacy and peer support role beyond personal care
		● Collaboration between patient associations could be a valuable initiative.
		● Empowerment through peer support
		● Foundation's role in providing updated, accessible (practical) information to the patient community
		● Key role of medical advisory team from patient associations and clinicians in national enzyme therapy approval (2)
		● Lack of patient groups due to small population size and disease rarity
		● Online community as only source of real support following diagnosis
		● Parent-led initiative to establish patient support organisation due to lack of existing one and dispersed community
		● Realisation that, despite the support of online communities, each child's condition and needs remain unique
		● Relying on patient associations for support when social support is lacking
		● Role of patient advocacy and awareness campaigns in reducing stigma
		● Seeking peer community for shared experiences, guidance, and disease progression insight
	● Assistance in social services	● Access to assistance is a common need
		● Barriers to accessing social services due to lack of guidance and patient-initiated navigation
		● Challenges with prolonged and frustrating processes in accessing social services, despite having client support
		● Inaccessible facility requiring lifting patient in wheelchair during disability assessment
		● Inadequate recognition of patient's medical complexity by social services despite comprehensive clinical documentation causing profound family frustration
		● Involvement of specialised client support workers in assisting families navigating support and communication. (2)
		● Lack of integrated social services forces families into private arrangements
		● Lack of social support experienced by many patients and families.

		• Limited state financial support insufficient for holistic care needs
		• Medical care adequately managed; greater challenges in home situation and support (2)
		• Need for clearer overview and assistance with social and municipal support for families
		• Need for knowledge and skills to navigate complex social support systems
		• Parent's persistent advocacy achieves disability recognition, highlighting systemic inadequacies in support
		• Provision of adapted equipment by municipalities early in the care process
		• Relying on patient associations for support when social support is lacking (2)
		• Social services are not in-house of the expertise centre and must be arranged externally
		• Variation in municipal social care provision creates inequities in support for families
		• Youth health physician coordinating family-centred support and navigating municipal services through local networks
	• Mental health support	• Access to psychological support is a common need
		• Common challenge of accessing mental health support
		• Common challenge of accessing mental health support (2)
		• Confidence in being able to access psychosocial support if needed
		• Early onset of rare disease leading to learned self-management and adaptation
		• Follow-up care is tailored according to the specific diagnosis
		• Integration of a psychologist during the diagnostic phase
		• Integration of psychiatric or psychosomatic care during the diagnostic phase
		• Involvement of social worker in providing psychosocial support to families (2)
		• Limited (public) mental health resources
		• Limited access to psychological support due to long waiting times
		• Limited and impractical psychological support exacerbates patient burden
		• Need for mental health support and tailored attention for families and siblings of children with complex care needs
		• Ongoing efforts to improve mental health access post-diagnosis
		• Positive impact of occupational physicians on mental and practical support
		• Privacy concerns regarding extensive information sharing for psychological care
		• Psychological care provided based on observed need within expertise centre
		• Psychological support experienced as brief, superficial, and unhelpful
		• Recognises importance of psychological support despite system shortcomings
		• Role of physiotherapist in supporting mental health through encouragement of active self-management
	• Professionals perspective on mental health support	• A well-being approach is preferred over a mental health-only focus, as it's more palatable to families (2)
		• Paperwork for financial and social support by clinician takes time
		• Psychological and comorbid mental health needs
• Technology and orphan devices	• Examples of technologies or orphan devices	• Sensor-based devices provide objective feedback on disease status in daily life and clinical trials
		• Use of gamification to promote home exercise for patients
		• Use of telemonitoring in rare disease healthcare processes
		• Using information technology to find, use, and deploy the best available knowledge in care
		• Vagus nerve stimulator for drug-resistant epilepsy treatment
	• Implementation and perspectives on technology in practice	• Access to historical patient healthcare data can improve statistical models and patient outcome predictions
		• Accuracy in home monitoring is essential for trust and timely care
		• Combining digital technologies including AI with traditional approaches
		• Data sharing across sources is essential for creating accurate predictive models and improving research
		• Effective, accurate, and cost-effective integration of technology can benefit both patients and healthcare but must preserve human interaction.
		• Ensuring the use and right adoption of technology is key to optimising healthcare
		• Equity consideration: value of paper-based tools in remote or low-income areas with limited digital access
		• International collaboration is essential for validating, personalising, and integrating global technologies into local healthcare practices

		• Need for new physicians to quickly adopt and master digital health technologies
		• Technology must be validated, effective, and easy to integrate into care without burdening clinicians
		• Value of simple, paper-based solutions alongside digital technologies
	• The role of technology use: post-diagnosis	• Technology as a supportive tool to empower home care by providing reassurance and early signals between contact moments
		• Technology enables home-based monitoring, making care less intrusive and more integrated into daily life
		• Use of technology for remote monitoring and supporting decision-making in treatment planning
	• The role of technology use: pre-diagnosis	• Use of growth charts for detecting growth disorders