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From the rare to the essential: analyzing the needs of physicians and families managing rare diseases

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Abstract

Background This study aims to identify the social and healthcare needs of patients with rare diseases (RD) and their physicians within a Universal Health Care System. It seeks to provide valuable insights for policymakers, patient organizations, and healthcare professionals while informing about these diseases, raising awareness, and designing strategies to improve access to quality, timely medical care, including therapies and medication at a local and regional level.

Methods Two semi-structured surveys were conducted between May 2023 and August 2024, targeting family members of patients with RD ($N=64$) and physicians ($N=56$) in Uruguay. Surveys were self-administered via email or conducted by an interviewer, and were disseminated through healthcare professionals, RD associations, and social media, using "snowball" methodology and word-of-mouth references.

Results Uruguay faces significant deficiencies in access to diagnosis and treatment for rare diseases, leading to a prolonged "diagnostic odyssey" for families and multiple barriers for physicians, ranging from lack of training to limited access to specialized tools. The low reporting rate to the National Registry of Congenital Defects and Rare Diseases and the lack of updates to the Comprehensive Health Care Plan exacerbate inequities in access to diagnosis and treatment. A key finding is inequality in access to whole-exome sequencing (WES), despite its proven effectiveness in reducing diagnostic times and improving accuracy. Its use remains restricted due to high costs and lack of universal coverage, highlighting the need for a national genomic medicine strategy and medical training in molecular diagnosis.

Conclusion The survey results indicate that RDs have a significant physical, emotional, and economic impact on patients and families. The main concerns raised include diagnostic delays, partly due to difficulties accessing specific tests and treatments. The medical community also acknowledges these issues. The healthcare system needs to update its coverage to include genomic diagnostics, improve medical training, strengthen coordination, and ensure equitable treatment access. These results mimic what is seen in other countries in Latin America and the Southern

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Cone. They call for a comprehensive, formalized framework for diagnosis, treatment, and care of rare diseases at local and regional levels, accounting for family experiences and prioritizing family wellbeing.

Keywords Rare diseases, Diagnostic odyssey, Physicians, Families, Semi-structured survey

Introduction

According to the World Health Organization (WHO), rare diseases (RD) are defined as those affecting fewer than five individuals per 10,000 inhabitants [1]. An estimated 7,000 RD have been identified worldwide, although this figure varies by source and ranges from 5,500 to 10,000 [2, 3]. While each condition is uncommon on its own, collectively they affect a significant share of the population—approximately 3% to 8% of people globally, totaling more than 300 million individuals [4]. Notably, about 80% of RD have a recognizable genetic origin, and over 70% present during childhood [5].

RDs affect 40–50 million people in Latin America, but the region faces significant challenges including a lack of standardized definitions for a RD, delayed diagnoses, limited access to treatments, and disparities in national policies and funding [6–8]. The numbers for Uruguay are similar in terms of burden, with an estimated 8% of the population affected by a RD, equating to approximately 280,000 individuals. Approximately 1 in every 4–5 infants who die before the age of one has a congenital defect as the cause [9–11].

RD significantly impacts quality of life and life expectancy, as they are typically chronic and progressive, and the majority have no specific treatment, but needs to be tailored to the patient, sometimes on a trial-and-error basis [12]. However, due to Uruguay's small population and universal healthcare system, access barriers to diagnosis and treatment may require systematic evaluation. This is due to the direct costs and pressure these specific diseases could put into the system. Examples include the lack of and high cost of medication and treatments, the shortage or unavailability of specialist consultations (locally and globally) for patients with RDs. The diagnosis process itself—delays and misdiagnoses—leads to both inappropriate care and increased costs, sometimes at 10 times the amount of a mass market disease like arthritis or diabetes [13]. In Uruguay, previous work has documented the development of a national framework for congenital anomalies and rare diseases, including the establishment of a neonatal screening program and a National Reference Center (CRENADECER), as well as the creation of the National Registry of Congenital Defects and Rare Diseases [9, 10, 14]. The RNDCER mandates the reporting of all congenital defects, irrespective of age, birth outcome (live or stillbirths > 500 g), or timing of diagnosis, to support epidemiological surveillance, research, healthcare planning, service evaluation, policy development, and awareness raising. More recent descriptive analyses of congenital anomaly trends using RNDCER data have underscored both the epidemiological burden and the importance of a robust registry to guide health-system planning and resource allocation [15] an outline of the Uruguayan healthcare system and relevant legislation on RD is presented as an Online Appendix).

International research consistently highlights similar challenges across health systems. Studies describe prolonged diagnostic odysseys, repeated consultations, and high rates of misdiagnosis, often linked to limited professional knowledge of RDs and fragmented care coordination [16–18]. Families frequently become primary coordinators of care and information, relying heavily on informal networks and online sources [19, 20]. Financial burden is also a recurrent theme, encompassing direct medical costs, travel, administrative delays, and lost productivity [21]. Evidence underscores the importance of robust registries, early access to genomic diagnostics, and integrated care networks to reduce delays and improve outcomes [22–24]. These findings frame the relevance of the present study and highlight the persistent gap between international recommendations and real-world patient and physician experiences.

The objective of this study is to identify the social and healthcare needs of people affected by rare diseases (RD) and to examine physicians' experiences with diagnosis and management in Uruguay. The aim is to provide evidence for policymakers, patient organizations, and healthcare professionals to improve knowledge, awareness, and access to appropriate care, both locally and across countries with similar healthcare systems.

Methods

Survey design

Two surveys were designed, one for physicians and another for family members of patients with rare diseases of genetic origin that begin in childhood or are diagnosed during childhood.

The physician questionnaire contained 34 questions addressing demographic data, employment details, experience in diagnosing and treating RD, interactions with families, knowledge of RD and genomic analysis techniques (especially whole-exome sequencing), sources of diagnostic information, and RNDCER awareness.

The family member questionnaire contained 49 questions, gathering demographic information about both the respondent and the patient, disease type, caregiving experiences, changes in family dynamics following

symptom onset, perceived social and financial support, and the use of genomic sequencing (exome or whole genome sequencing) during diagnosis.

Both questionnaires use both quantitative and open ended (of qualitative nature) question types to analyze the experience of RD diagnosis and treatment. Eighty percent of family members data were collected through self-completed questionnaires (via a link to the form), and 20% through interviewer-administered online sessions with one of the researchers. For physicians, the percentages were 96 and 4%, respectively. Both surveys can be found in the Online Appendix, as well as the consent form provided to respondents.

Data collection

The surveys were disseminated through healthcare professionals, the Uruguayan Foundation for the Promotion and Research of Rare Diseases (FUPIER), the Association "Todos Unidos Enfermedades Raras Uruguay" (ATUERU) and a public roll out through social media on Rare Disease Day. A snowball sampling strategy was also used, allowing respondents to refer to other potential participants. While this method may introduce selection biases, particularly by overrepresenting physicians more involved with RD and the fact that not all the target population families had the same probability of being selected, it was considered a valid approach given the lack of access to the RNDCER. The surveys were conducted between May 2023 and August 2024, yielding responses from 64 family members of patients with RD and 56 physicians.

The surveys were distributed either via email or conducted through interviewer-administered online sessions (see Annexes A1 and A2 for the full questionnaires). Informed consent was obtained from all participants prior to data collection. The choice of data collection method was determined by participants' availability and preference. To maximize participation and account for the logistical challenges faced by families of patients with rare diseases, participants were given the flexibility to complete the survey at their convenience or do it through an interviewer-administered online session. For those who completed the survey through an online session, only the questions included in the questionnaire were asked, with no additional discussion beyond its scope.

Data analysis

The collected data were anonymized, coded, and exported to STATA version 18 and NVivo version 14. The quantitative questions were analyzed using descriptive statistics, to summarize participants characteristics and responses. Data quality checks were performed to identify any missing or inconsistent responses.

For the open-ended question data, a tree of themes, codes, and subcodes relevant to the RD diagnosis and treatment process—as experienced by physicians and family members—was developed and used for coding in NVivo, as the questions were qualitative in nature. Codes and subcodes were generated using a codebook thematic analysis (CTA) approach rather than reflexive one. CTA is suited for studies with multiple coders and for analyses embedded in mixed-methods or post-positivist frameworks [25]. This approach allows for the development of a shared coding structure, the assessment of consistency across coders, and the generation of themes that reflect recurrent patterns in the data. Our analytic process was inductive, meaning that codes and themes were derived from the data rather than from pre-existing theoretical frameworks. We followed general steps described by Braun and Clarke [26] but operationalized them through a structured codebook procedure aligned with coding-reliability traditions. The complete coding tree can be found in Online Appendix A3. In addition, a word cloud on physicians' experiences with treatment and diagnosis were used to inform the tree of codes (the word cloud, in Spanish can be found in the Online Appendix). Two of the researchers (IM, PT) then coded the responses independently and subsequently cross-checked their analyses to ensure consistency and validity before collaboratively writing the results section. Discrepancies were discussed until consensus was reached, ensuring reliability in the interpretation of the data.

From a more general perspective, the study was conducted within a post-positivist and pragmatic research paradigm [27, 28], appropriate for qualitative analyses integrated into a quantitative survey. From this perspective, the use of multiple coders, cross-checking procedures, and consensus meetings serves to enhance the credibility and transparency of the analytic process.

Lastly, for the presentation of the open-ended data, the quotes presented in this manuscript were anonymized when referring to a specific doctor or patient. Spelling errors were also corrected whenever needed. The following descriptors are used to refer to the characteristics of the participants: the age of the family member who answers the patient survey (generally father or mother), *P* for age of the patient, age of the physician, and medical specialization based on the groupings in Table 1. The quotes were selected after the data was coded into the categories of the tree of themes and codes in Online Appendix A3. Quotes were agreed by the researchers who coded the open-ended question responses (IM, PT) and were selected to illustrate the most frequently mentioned or salient themes identified in the responses. If a discrepancy was raised, it was discussed until consensus was reached to present the quote, making sure that the quotes presented were reliable and consistent with the

Table 1 Characteristics of the surveyed physicians

Variable	Average (± st. dev.)
Age (years)	49 (11.5)
Gender, %	
Female	59
Male	41
Employment, %	
Public sector only	60.8
Private sector only	29.4
Both public and private sectors	9.8
Medical field, %	
Internal medicine	12.5
Pediatrics	19.6
Genetics	17.9
Neurology	8.9
Nephrology	19.6
Gastroenterology	5.4
*Others**	16.1
Years of medical experience	19.7 (11.4)
Years of experience treating RD	10.4 (10.7)

Note: Author's calculations based on physician survey. Standard deviation (st. dev.) in parentheses. Other medical fields category include single responses for cardiology, hematology, dermatology, infectious disease specialist, pneumology, rehabilitation, otolaryngologist and rheumatology

findings. The quotes are presented in English for clarity purposes, but the original ones in Spanish can be found in the Online Appendix.

Results

Physician surveys

Individual characteristics

The diagnosis and care of patients with RD require the combined efforts of a group of healthcare professionals, including general physicians and specialists, physical therapists and nursing services. Because physicians are the ones who coordinate the process, we chose to survey only this group of healthcare professionals in this first stage.

The average age of the surveyed physicians who completed the survey was 49 years (standard deviation - SD – 11.5 years), and 59% were women. Regarding job placement, 60.8% reported working only in the public sector, 29.4% only in the private healthcare sector, while the remainder had dual employment (Table 1). Almost 60% of the physicians surveyed were unaware of the existence of the RNDCER, only two physicians reported uploading data to the national registry, and seven physicians reported registering their RD patients in other systems, such as the renal health program, the Latin American immunodeficiency registry, and ClinVar.

Initial experience of RD diagnosis and treatment

Focusing on the treatment of RD, 71% of physicians identify access to medication as the main barrier to providing treatment, 48% the ability to consult with other specialists, 39% psychological care, and 30% physiotherapy, prosthetics, or patient assistance devices (Fig. 1).

Regarding the experience of diagnosis (see Table 2), although 77.8% consider RD to be a public health problem, 53.7% indicate that their knowledge about them is insufficient and 13% poor. In terms of the treatment of RD, 16% feel very insecure and 16% insecure in the treatment of these diseases, needing support both in the diagnosis process and in the treatment.

Difficulties to diagnose, the need for specialist consultations, and more information about the disease and the

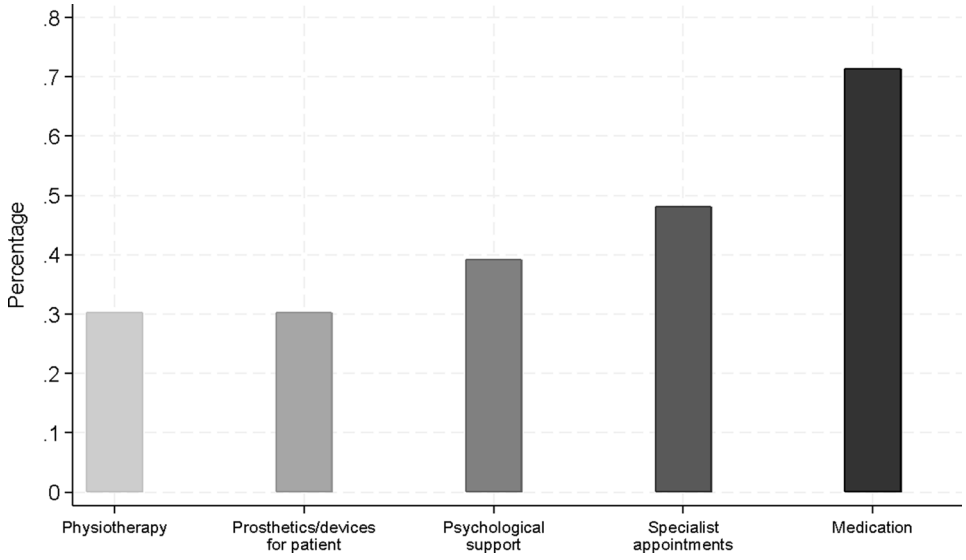

Fig. 1 Barriers to treatment provision, %. Note: Author's calculations based on physician survey. Since more than one option is possible, the alternatives do not add up to 100%

Table 2 Experience in RD diagnosis

	%
Considers RD to be a public health problem	77.8
Knowledge about RD	
Very good	1.8
Good	31.5
Poor	13.0
Insufficient	53.7
Main sources of information for diagnosis	
Education	71.4
Experience	32.1
Colleagues	66.1
Confidence in treating patients with RD	
Very confident	4.0
Confident	22.0
Neither confident nor insecure	36.0
Insecure	16.0
Very insecure	16.0
I don't know	6.0
Support in the diagnostic process	
Support for the diagnosis itself	71.4
More information (clinical trials)	28.7
More information (about RD)	48.2
Support for treatment	
Better public health services	62.5
Availability of medication	66
Cost of medication	55.4
All physicians should be trained in the diagnosis of RD	57.1
Knowledge about parent`s and patient`s support	56.6

Note: Author's calculations based on physician survey

family (including the patients themselves) are essential parts of the discussion (Figure A5.1, Appendix A5).

Overarching barriers to diagnosis and treatment

The central problem, according to physicians, lies in the time it takes to diagnose, the delays in the process, costs, and access options to different treatments. In most cases, the cost of diagnosis and treatment is not included in the PIAS, which creates access problems.

> *Every person has the right to receive the treatment they need. Therefore, from that perspective, it's a matter of public health. (70 years old, Nephrology)*
> *Due to the limitations and obstacles families encounter, especially when it comes to accessing high-cost treatments … (43 years old, Internal Medicine)*
> *Although they are a small group of patients, they are patients who, if not treated promptly, often generate enormous healthcare expenses, because they are dealing with more advanced pathologies with less chance of rehabilitation. They also generate an emotional and economic cost for families whose members suffer from rare diseases. (36 years old, Nephrology)*

The process of reaching a diagnosis and long-term treatment for rare diseases is identified as a true "diagnostic odyssey, not only for physicians but also for families, generating great uncertainty in the diagnosis and subsequent treatment.

> *Odyssey is a good word. Getting a patient to genetics is already difficult, but then the limitations of consultation times with other specialties, the clinical history, diagnostic tests, and costs make the already long and intellectually difficult process even more complicated. (38 years old, Clinical Genetics)*
> *Odyssey. Often, I don't think about rare diseases after the first symptoms appear. Then, if I suspect it or if initial symptoms appear, other odysseys begin. (41 years old, Pediatric Neurology)*

The process is emotionally demanding, characterized by uncertainty, complexity, and, in many cases, resignation. Numerous barriers hinder obtaining a prompt and effective diagnosis, including limited access to tests and specialists, long wait times, lack of institutional support, a limited available services, and high costs associated with the entire process.

Furthermore, physicians identify several "negative" interactions during the diagnostic process. They note that family members, faced with a lack of concrete answers, may express confusion, distrust, and pressure toward physicians. From the healthcare team, these situations are exacerbated by a lack of resources and timely responses. This situation not only generates intense anxiety about seeking a diagnosis and potential treatment plan but also distress due to the difficulties in accessing therapies and rehabilitation services.

> *Challenging, frustrating, sometimes you don't get there in time. You do what you can with what you have. Achieving a diagnosis is a substantial change in care. (28 years old, Infectious Diseases)*
> *It's a difficult challenge when the doctor is faced with this type of patient. In Uruguay, there are many barriers that prevent things from flowing quickly and efficiently, as these children deserve. (36 years old, Pediatrics)*

On the other hand, "positive" interactions are also highlighted, such as the bond between the doctor and parents, and the development of trust, expectations, and security within the family. Among these interactions are providing certainty and information to the family regarding symptoms and test results.

Table 3 Characteristics of the family members surveyed

Variable	Average (± st.dev)
Age (years)	43 (8.7)
Female, %	
Female	89
Male	11
Education of the surveyed family member, %	
Primary school	7.8
Middle school	18.8
High school	23.4
Technical school	1.6
Tertiary non-university degree	15.6
Bachelor's degree and above	32.8
Surveyed family member works?, %	81.2
Married or in a common-law relationship, %	71.8

Note: Author's calculations based on family member survey. Standard deviation (st. dev.) in parentheses. Education categories include complete and incomplete for each type

> *A good experience. Over time, I learned to ration the information I provided and never be categorical … (36 years old, Nephrology)*
> *It depends on the disease. Some patients feel special relief because their symptoms have a name, an objective and treatable explanation. (55 years old, Nephrology)*

Organized support around RDs

Fifty-seven percent of the physicians surveyed emphasized their awareness of support groups available for parents and patients. These include disease-specific groups, recommended on a case-by-case basis as well as broader organizations such as FUPIER Uruguay and the Latin American Association of Pediatrics and Adults with Rare Diseases and Congenital Anomalies (ALAPA, based in Argentina). In general, support groups are more easily found through social media or the Internet, and physicians recognize that this facilitates access for families.

Physician views on exome sequencing

Regarding exome sequencing—a technique that has significantly reduced diagnostic confirmation times and has been in clinical use for over a decade [29, 30]—healthcare professionals identify both opportunities and challenges. Physicians highlight the need for expanded medical training, particularly in interpreting results and applying them to local populations. They also stress the importance of academic spaces for discussing complex cases, such as medical conferences and multidisciplinary working groups.

However, professionals also point to key limitations: the high cost of the technique, limited local availability, and barriers to universal access. These issues are closely tied to ethical concerns around equity in healthcare. There is consensus on the importance of establishing safeguards for managing and storing the data generated by exome sequencing, ensuring confidentiality and respecting patient privacy.

Table 4 Characteristics of the patient with rare disease

Variable	Average (± st.dev)
Age (years)	11.1 (6.9)
Female, %	
Female	45.3
Male	54.7
Education, %	
Not enrolled in school	12.5
Pre-school	21.9
Home-schooling	1.6
Primary education (complete or incomplete)	45.3
Health coverage, %	
Public	31.7
Private	68.3

Note: Author's calculations based on family member survey. Standard deviation (st. dev.) in parentheses

Surveys to family members of RD patients

Individual characteristics

Eighty-nine per cent of the relatives of ER patients who responded to the survey were women, which may reflect gender bias in caregiving, despite the vast majority (81.2%) reporting that they were employed at the time of the survey. Nearly half of the family members achieved completed or incomplete tertiary education (bachelor's and above and technical non-university education), and approximately 72% were married or in a common-law relationship (Table 3).

Regarding patients, the majority are in pre-school or primary school, with 1.6% being home- schooled, and 68.3% having private health coverage (Table 4).[1]

As shown in Fig. 2, the majority of those family members(63%) stated that the patient's illness is physical, that is, it affects some part of the body, 57% cognitive (affects learning or language), 49% affects some sense, and 38.5% emotional or related to behavior.

Initial experience of RD diagnosis and treatment

Regarding support in the RD diagnosis and treatment process, 79.7% report a lack of coordination among health services, with limited information provided about rights and coverage, and potential financial assistance. Forty one percent of children received psychological support. Forty six percent of households have gone into debt to pay for the costs associated with the patient's treatment (see Table 4).

[1] For the total Uruguayan population, based on the JUNASA [54] Accountability Report, as of December 2023, 75% had coverage through the IAMC (National Health Insurance System), 21% through the ASSE (National Health Insurance System), and 3% through private insurance.

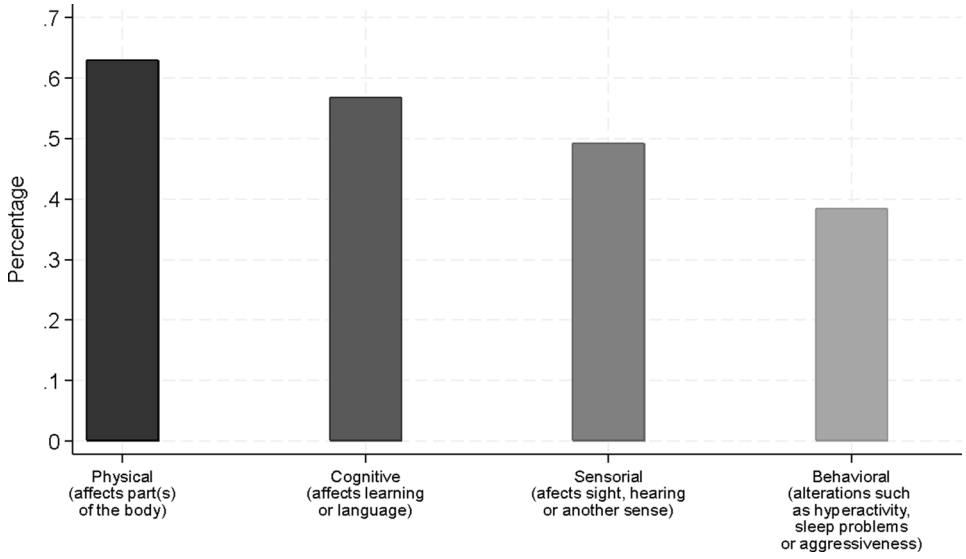

Fig. 2 Type of disease, %. Note: Author's calculations based on family member survey. The classification corresponds to the respondent's self-reported diseases. Since selecting multiple options is possible, the alternatives do not add up to 100%

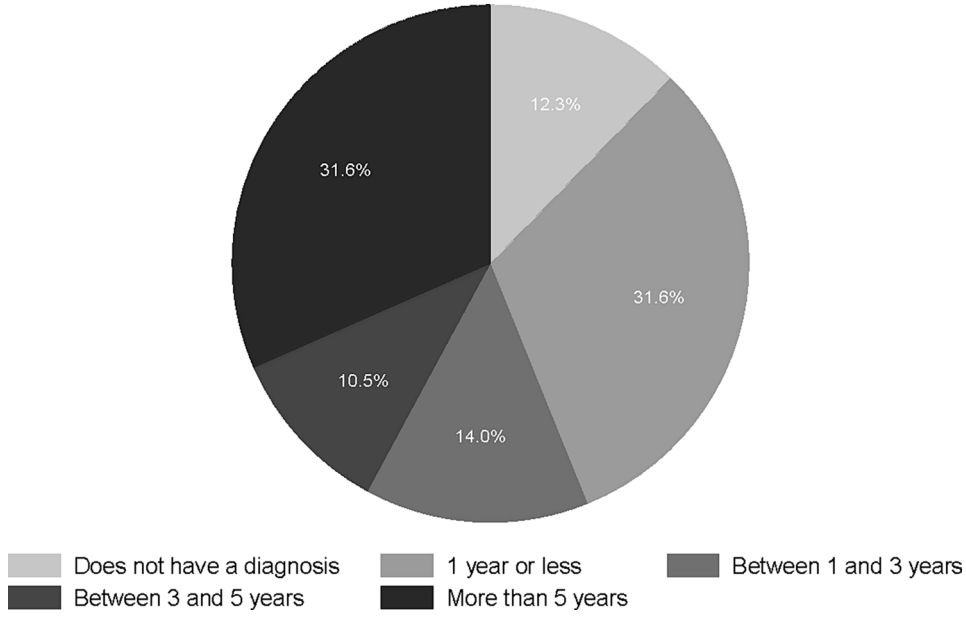

Fig. 3 Time between the patient's first symptoms and the final diagnosis. Note: Author's calculations based on family member survey

The average time between the first symptoms and the final diagnosis is 1 to 3 years (14%). Nearly a third took 1 year or less to obtain a diagnosis, 10.5% took between 3 and 5 years, a third more than 5 years, and 12.3% stated that the patient still does not have a final diagnosis, although RD is strongly suspected (see Fig. 3). For those diagnosed, the average time reported by family members until reaching it was 2.5 years, similar to the maximum reported by physicians (average 1.34 years with SD 1.08 years). These data are lower than those reported in the literature; for example, 4.7 years are reported in Europe [31], and 6 years for the Latin American average [32].

The experience of family members of children with RD is described as painful, complicated, and marked by a lack of empathy from healthcare professionals. Many parents report that they are not adequately listened to, forcing them to research the disease on their own and facing bureaucratic barriers to access diagnoses and treatments (Table 5).

A lack of information about rare diseases (RD), as well as patients' rights and available assistance (e.g., social security), is a recurring concern. Parents are often

Table 5 Rare disease support

Variable	%
Support groups	
When diagnosed, were you provided with any information about parent support groups?	15.6
Participates in support groups	54.7
Sought support from other international online groups	57.8
Lack of coordination of health services regarding the patient's care plan	79.7
Received information about specific rights and coverage from a health professional	39.3
Information about financial assistance is accurate and sufficient	10.9
Information about medical services is accurate and sufficient	22.2
Information about rights (legal and social) is accurate and sufficient	12.5
The patient received psychological support from the time of diagnosis	41.2
Went into debt to pay for health-related costs	46.0
Patient has undergone genomic sequencing	67.7

Note: Author's calculations based on family member survey. Support category does not add to 100 as respondent could choose multiple options

primarily responsible for managing treatment within the healthcare system.

> *It was very distressing because in our country he wasn't diagnosed despite private consultations. It was finally in [country] that we learned the diagnosis, and it was confirmed by genetic testing in [country]. Here, he was hospitalized unnecessarily and underwent unnecessary invasive tests, such as a lumbar puncture, MRI, etc. (53 years old, P23 years old)*
>
> *The diagnostic process was a difficult stage because reaching a possible diagnosis took a long time. Many years from the onset of symptoms until the true diagnosis was given. So many invasive studies, tests, and operations along the way … (34 years old, P15 years old)*
>
> *Reaching the diagnosis wasn't difficult. After the diagnosis, we were left "alone," lost, and where we realized that it basically depends on us, the parents. We've been waiting for an appointment with CRENADECER for a year. Everything we know about the disease is because we made our own moves. (39 years old, P3 years old)*

There is consensus that the diagnostic process is more straightforward in the private sector, though it comes at a higher cost. In contrast, the public sector offers a more satisfactory experience overall, especially due to better access to geneticists. Additionally, having personal connections within the health system can improve the experience by introducing discretion into the process.

Financial and time constraints of families

Financial barriers include costs for tests, medication, emergency services, therapies, and specialists—particularly when diagnosis occurs outside the National Integrated Health System, whether funded by parents locally, abroad, or through academic research. Many parents are unaware that CRENADECER can cover these expenses. Institutions like Pereira Rossell Children's Hospital, Teletón, and BPS/CRENADECER [33] are associated with positive experiences, although accessing BPS/CRENADECER can be challenging. Geneticists contribute positively to the experience, unlike other health professionals.

> *Many tests were required to arrive at a diagnosis, but I couldn't afford them. Tests not covered by the mutual insurance company were performed by the BPS (National Health Service), but the diagnosis was made through a study project by Dr. […] through the faculty. The BPS procedures were very cumbersome; some tests were denied. (41 years old, P4 years)*
>
> *Very complicated and stressful because it wasn't easy to access more in-depth tests to find out what was really going on until the geneticist performed tests that provided a diagnosis, though not definitive … but that process took about 7 or 8 years. (50 years old, P19 years)*

Parents often describe patient care as a "drastic" shift in daily life due to the time needed to establish treatment routines—combining medication, physical therapy, and alternative therapies like hippotherapy—along with economic strain and limited caregiving support. Typically, mothers leave their jobs to become primary caregivers. In many cases, parental separation adds further financial stress. The caregiver's responsibilities include scheduling and transporting the child to specialist appointments, exams, and ongoing care, depending on the illness and level of disability. Support networks vary and may include grandparents, children, friends, and neighbors.

> *I had to stop working. We all have to coordinate so that someone is always with her, even at night, because she only sleeps 4 or 5 hours. One day in the morning she has an assistant. (53 years old, P14 years old)*
>
> *My father couldn't keep his job because he was supporting me during hospital stays, so he had to change jobs. (35 years old, P9 years old)*

Discussion

Diagnostic odyssey and family burden

The experiences reported in this study, characterized by multiple consultations, tests, and misdiagnoses, are consistent with previous findings [21, 34], which highlight the emotional, social, and practical challenges patients and their caregivers face. Parents are often primarily responsible for managing treatment within the healthcare system, and the internet remains the most important and widespread source of information globally [20].

These findings align with broader evidence on the lack of humanization in healthcare and limited knowledge of RDs among medical professionals [16–18, 34]. Consequently, parents and patients often become the experts, actively seeking information and managing care [19, 35]. Parents also report unnecessary testing, which prolongs diagnosis, increases stress, and adds financial costs [19, 21]. Additional barriers include limited access to specialized testing and financial constraints, reducing the likelihood of timely diagnosis and treatment. These challenges are consistent with physician survey findings citing resource shortages and system fragmentation as major obstacles in RD care [24, 36].

The "diagnostic odyssey" documented in our study is widely reported in the literature [17, 18]. While the average time to diagnosis in Uruguay appears shorter than in some countries, the high costs associated with diagnosis generate uncertainty and profoundly affect families, similar to findings elsewhere [37]. This process impacts quality of life and represents a significant burden for health systems, potentially exacerbating health inequities [21, 38].

Health system gaps and registry utilization

A critical weakness of the current health care system is the lack of awareness of the National Registry of Congenital Defects and Rare Diseases (RNDCER), which remains unknown to 59% of surveyed physicians, and although the registry of patients with RDs is mandatory by law. This undermines epidemiological surveillance and health planning. The population covered by the National Integrated Health System (75%) has access and can choose between public and private providers, who must offer a Comprehensive Health Care Plan (PIAS). The absence of updates to the PIAS and limited coverage under the National Resource Fund (FNR, which finances high-complexity procedures, devices, and high-cost medicines based on pre-approved lists) create inequities, leaving access to diagnosis and treatment dependent on financial capacity or personal connections within the system.

Access to RNDCER, live since 2011 and part of the National Statistical System (Law 16.616; Centro de Informacion Oficial IMPO [38]), is an immediate concern. A comprehensive, high-quality, dynamic registry would enable better coordination between health system actors, facilitate access to services, improve knowledge of rights and benefits, reduce delays [23, 39], and support follow-up of diagnostic and treatment changes based on new evidence [36, 40]. It would also enhance assessment of patient, family, and caregiver quality of life [21, 35]. Centralized data integration has proven essential for international research and evidence-based clinical decision-making [22, 24, 41].

Information access and research networks

Online information is a common source for patients, caregivers, and healthcare professionals, highlighting the need for portals that provide free, timely, high-quality, up-to-date, and nationally adapted information [18, 42]. It is also crucial to promote local research and medical groups and their collaboration with international networks, enabling training, knowledge transfer, and participation in multicenter projects on RD [24, 43]. International collaboration is key to advancing diagnosis, treatment, and understanding of rare diseases [44, 45].

Awareness and training campaigns for medical institutions, patient organizations, health professionals, and families are necessary, focusing on the importance of providing epidemiological and socio-economic information while ensuring strict statistical confidentiality.

Genomics and capacity building

Strengthening genetic literacy, alongside education in medical, biological, regulatory, and social dimensions of RDs, has been emphasized for both healthcare professionals and the public [46] Skirton et al. [47]). Developing these capacities is essential to maximize the impact of genomic medicine on public health policies, ensuring technologies are used effectively, equitably, and sustainably [48, 49]. Ongoing education and training help reduce barriers to diagnosis and treatment, translating scientific advances into tangible benefits for patients [24, 44].

Despite these efforts, significant obstacles remain in accessing consultations, tests, and therapies. Unequal access to WES is particularly concerning. Evidence shows WES reduces diagnostic delays and improves accuracy, yet availability in Uruguay is scarce and universal coverage is absent. Direct costs range from US$300 to US$850 per test depending on sequencing methods, data processing, labor, and whether analyses are commercial or academic. With an estimated 1000–1800 children born annually with an RD (MSP [50]), the cost of offering WES would range from US$300,000 to 1.53 million. Future research should weigh these costs against those of the diagnostic odyssey to assess cost-effectiveness. Additionally, the shortage of professionals trained to interpret genomic data underscores the need for capacity building and a national strategy for equitable access.

Policy and health system recommendations

From a policy perspective, several measures are urgent. Updating and expanding PIAS coverage to include advanced diagnostics and innovative treatments, strengthening medical education in RD and genomics, improving coordination across health system levels to ensure systematic RNDCER reporting and timely referrals, guaranteeing equitable access to therapies through regional cooperation for high-cost medicines and technologies, and incorporating psychosocial and financial support for families are all critical. Establishing a publicly funded national genomic diagnostic program would reduce diagnostic uncertainty, improve patient outcomes, and optimize system resources by preventing misdiagnosis and ineffective care. Uruguay must advance toward a robust national strategy that secures equity, access, and quality in RD care.

Uruguay's challenges are reflected in other countries in the region. In Chile, financial coverage for high-cost diagnoses and treatments has been established (Law 20.850, "Ricarte Soto," [36]), alongside Law 21.743, which creates a specific RD framework, defines prevalence, mandates a national list and registry, and establishes a Technical Advisory Commission (BCN; Superintendency of Health). Previous evidence in Chile documented gaps in diagnosis and coverage under a universal system, with concrete policy recommendations [51]. In Brazil, Ordinance 199/2014 instituted the National Policy for Comprehensive Care for People with Rare Diseases and organized the referral network, though evaluations describe both progress and persistent gaps in coordination and access to medications [52]. In Argentina, Law 26.689/2011 and its regulatory Decree 794/2015 established the Ministry of Health as the implementing authority and created the National Program for Rare Diseases. The official list was later approved (Res. 641/2021) and updated in 2023 (Res. 307/2023).

Taken together, these cases demonstrate regional convergence toward formal regulatory frameworks, but with heterogeneity in implementation, financing, and availability of diagnostic technologies. This underscores the relevance of our proposals for Uruguay and highlights the need for a robust, standardized framework for RD diagnosis, treatment, and long-term care, informed by family and healthcare personnel experiences with explicit consideration of family wellbeing. Fragmented healthcare systems, limited access to orphan drugs, inadequate registries, and socioeconomic disparities, particularly in underserved areas, exacerbate these challenges. Regional collaboration—including cross-border data sharing, joint procurement strategies, and centers of excellence—is critical. Rare diseases remain underrepresented in national health agendas, emphasizing the importance of advocacy, family-centered care, and integration of genomic medicine into public health strategies.

Limitations

This study has several limitations, including potential bias in physician and family member samples and lack of access to RNDCER data. Future studies should estimate the direct and indirect costs of the diagnostic odyssey and explore the implications of exome sequencing and other genomic techniques through extended cost-effectiveness analyses [53].

Conclusion

This study highlights the multifaceted challenges faced by families and healthcare professionals in managing rare diseases in Uruguay, reflecting broader regional and global patterns. The "diagnostic odyssey," characterized by delayed diagnoses, repeated tests, and significant emotional and financial burdens, underscores systemic gaps in information, access, professional training, and service coordination. Our findings demonstrate that families often become *de facto* experts, navigating complex healthcare pathways in the face of limited support, insufficient empathy, and bureaucratic barriers. Strengthening national registries, integrating genomic medicine, improving equitable access to diagnostics and therapies, and fostering regional and international collaboration emerge as critical priorities.

These measures not only have the potential to reduce diagnostic delays and associated costs but also to enhance patient and family wellbeing, inform health policy, and support evidence-based, equitable health service provision. By documenting these experiences and gaps, this research contributes essential knowledge to guide health system improvements, promote humanized care, and advance the management of rare diseases both nationally and regionally.

Abbreviations

ALAPA	Latin American Association of Pediatrics and Adults with Rare Diseases and Congenital Anomalies
ASSE	State Health Services Administration
ATUERU	Association "Todos Unidos Enfermedades Raras Uruguay"
BPS	Social Security Administration
CRENADECER	National Reference Center for Congenital Defects and Rare Diseases
FNR	National Resources Fund
FUPIER	Uruguayan Foundation for the Promotion and Research of Rare Diseases
IAMC	Collective Medical Assistance Institutions
JUNASA	Junta Nacional de Salud
MSP	Ministry of Public Health
PIAS	Comprehensive Health Care Plan
RD	Rare diseases
RNDCER	National Registry of Congenital Defects and Rare Diseases
SD	Standard deviation
WES	Whole-exome sequencing
WHO	World Health Organization

Supplementary Information

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Supplementary material 1

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Author contributions
Conceptualization and survey design: All authors. Survey administration: PC. Data analysis: IM, PT, MG. Review, writing, and editing: IM, PT, MG, LS, VR

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Data Availability
The datasets generated during the current study are not publicly available as they contain sensitive and identifying information (of patients with a diagnosis of a rare disease, where cases are few), but are available from the corresponding author on reasonable request. Survey analysis materials can be found in the online appendix.

Declarations

Ethical approval and consent to participate
This study was approved by the Ethics Committee of the Institut Pasteur de Montevideo on April 12, 2017 (Ref. IP011-17/CEI/LC/MB) and later extended. This research complied with the ethical principles of the Declaration of Helsinki. Informed consent to participate was obtained from all of the participants in the study before any information was collected.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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