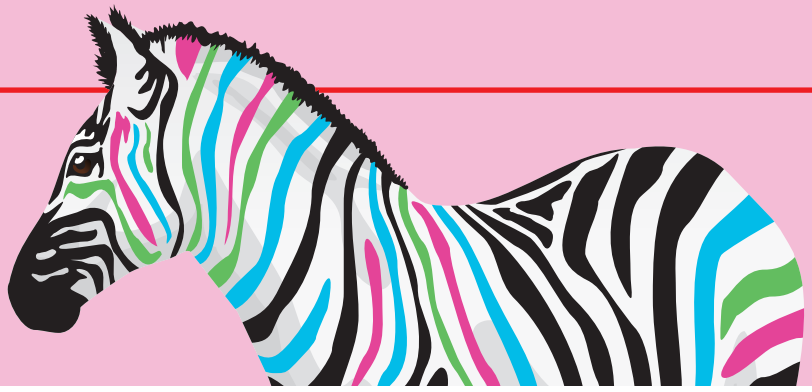
ECONOMIST IMPACT



One stripe at a time: raising awareness of rare diseases in Latin America

Supported by AstraZeneca

Introduction

Despite advances in innovative therapies and the adoption of more contemporary strategies for managing rare diseases (RDs), significant disparities in access to effective and timely care for a crucial, yet often overlooked, category of diseases persists in Latin America. This briefing article, commissioned by AstraZeneca, raises awareness around existing barriers to care for RDs in the region and explores opportunities for improvement.

The editorial team at Economist Impact would like to thank the following individuals (listed alphabetically) for generously contributing their time and insights, which have been critical to the creation of this briefing article.

- Valentina Goldschmidt Plate, Hematologist, Hospital Padre Hurtado, Fundación Arturo López Pérez, Chile
- Jacqueline Tovar, Director, Iniciativa Pensemos en Cebras, Mexico
- Gabriela Repetto, Clinical Geneticist, Director, Rare Disease Program, Centro de Genética y Genómica, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Chile
- Rafa Zimbaldi, State Representative, Legislative Assembly of the State of São Paulo, Brazil

This research was led by Kati Chilikova. The report was authored by Kati Chilikova and Alcir Santos Neto, and edited by Maria Ronald. Latifat Okara oversaw and directed the research program.

State of RDs in Latin America: trends of note

RDs are not so rare.

RDs are a group of poorly understood, predominantly heritable disorders that often manifest in childhood and have a significant impact on quality of life and life expectancy.[1] There is no universally accepted definition of RDs. According to the World Health Organization (WHO), a RD is one that affects less than 65 out of every 100,000 people.[2] While this definition is widely used, the minimum critical prevalence threshold of what constitutes a RD varies across countries. In Latin America, some countries like Brazil follow the WHO definition of an RD, while others, like Argentina, Chile, Mexico, Panama, and Uruguay have adopted lower prevalence thresholds, as set by the European Union (EU), which is 5 per 100,000 individuals.[3]

RDs are not uncommon. Research indicates that there are between 6,000-8,000 RDs, which affect approximately 350-450m people globally.[4,5,6,7,8,9] In Latin America alone, roughly 40-50m people are affected by a RD.[10] Estimates of the total disease burden vary due to the lack of a consistent definition of RDs across the region and patchy prevalence data,[10] but research suggests that the highest burden in the region is observed in Brazil (13m), Mexico (6m), and Argentina (3m).[7]

Measured in prevalence per 100,000 people, the most common RDs globally are narcolepsy (50), primary biliary cholangitis (40), Fabry disease (30), cystic fibrosis (25), hemophilia (20), spinal muscular atrophy (13), and retinal dystrophy (13).[10] While these diseases affect a very small number of people individually, taken together, they affect a significant proportion of the global population. Understanding their care pathways can therefore also identify promising approaches to better disease management more broadly.

Approximately 80% of RDs are genetic in origin, and the majority (75%) manifest during childhood, with children aged 0-5 years being most impacted.[7] RDs are responsible for approximately 35% of deaths in the first year of a child's life; approximately 30% of children die before reaching their fifth birthday.[10,11]

Approximately 80% of RDs are genetic in origin, and the majority (75%) manifest during childhood, with children aged 0-5 years being most impacted.

The economic burden on both patients and health systems is high, but grossly underestimated.

The economic burden of RDs is estimated to be high; however, it should be noted that the availability of reliable and consistent data on costs is limited, especially in resource-constrained settings.[10] The high economic burden is closely associated with the hefty price tag that accompanies the cost of drugs and care.

Treatment of RDs is some of the most expensive on the market; orphan drugs,[12] developed to treat RDs, can cost as much as five to 25 times the cost of non-orphan drugs.[2,10] It is estimated that 88% of orphan drugs cost more than US$10,000 a year per person.[2] The high cost of these drugs is due to the lack of production and commercialization in Latin America.[2] While the cost of developing orphan drugs is equally high as any other drug, the buyer pool is substantially smaller. As very few countries in Latin America have incorporated orphan drugs into their public health schemes, this presents a significant accessibility and reimbursement challenge for patients. It is also a risky economic investment for pharmaceutical companies.[6]

It is estimated that 88% of orphan drugs cost more than US$10,000 a year per person. [2]

Research has yet to explore the total economic cost of RDs in Latin America; however, in 2019, the total economic cost of just 379 RDs was estimated at approximately US$1trn — in the United States alone.[13] An estimated US$449bn accounted for direct medical costs and an additional US$548bn accounted for indirect, non-medical and healthcare costs not covered by insurance. In Mexico, the total cost per patient for hemophilia, a rare bleeding disorder, alone was estimated at US$332,458 in 2019, and in Ecuador, it was US$156,064 in 2017.[10]

This financial burden not only affects individuals but also significantly impacts national health budgets. For example, in 2019, the Peruvian Ministry of Health spent US$33m in care for 42,000 people living with a RD, and in Colombia, the economic burden of atypical hemolytic uremic syndrome treatment was nearly US$4m for only 18 patients, in the same year.[10] Even in the context of just one RD, these costs are significant and pose challenges and concerns for the sustainability of health systems in Latin America.

The social burden of RDs on patients and caregivers is significant.

The chronic and disabling nature of RDs severely impacts patients' quality of life, as well as their mental health and personal well-being, and social and economic opportunities. Research indicates that those living with a RD often experience behavioral problems, strong feelings of isolation, depression, and violent outbursts that prevent them from maintaining an active and healthy social and/or professional life.[10,14] Often, these feelings result from difficulties in accessing timely and accurate diagnosis and treatment and/or due to a perceived lack of political visibility, prioritization, and support for their condition.[10,15]

Patients often rely on family members for care. In Latin America, there are twice as many caregivers as RD patients; there are approximately 80m RD caregivers, most of whom are disproportionately women and typically mothers of someone living with a RD.[16] The taxing and time-intensive nature of caregiving for a patient with a RD leaves many caregivers struggling physically, mentally, and professionally. A Brazilian survey revealed that caregivers of those living with a RD experience: bodily pain (79%), poor sleep quality (60%), and insufficient energy to complete daily activities (82%). The majority of caregivers also report feeling lost (72%) and emotionally isolated (68%).[16] Additionally, many are forced to stop working or reduce their hours to care for their loved ones. This puts additional financial pressure on households, which are often already grappling with the high costs associated with RD treatment and care.

Assessing challenges across the patient care journey in Latin America

Research has highlighted a significant lack of awareness and knowledge regarding the care pathway for RDs, spanning from early diagnosis to treatment, among patients, healthcare professionals, and political decision-makers, indicating a need for urgent action. While the majority of RDs are genetic and hereditary, patients are often unaware of their genetic predisposition; unfamiliar with the signs and symptoms, many also do not seek timely medical attention.[17] Given the low prevalence of RDs, healthcare professionals, including primary care providers (PCPs), equally lack sufficient knowledge about RDs.[17] As a result, PCPs often incorrectly assess and attribute RD symptoms to more common diseases, thereby misdiagnosing RD patients.[17] The scarcity of critical knowledge, guidelines, and training on RDs for healthcare professionals impedes the referral and diagnosis process, and therefore impacts access to timely and adequate treatment and care.[10]

A correct RD diagnosis can take four to five years and require multiple healthcare consultations. However, the diagnostic pilgrimage can sometimes span decades.

On a public health policy level, RDs are often overlooked. Public health funding, especially in resource-constrained settings, is limited; many countries in Latin America struggle to put RDs on the policy agenda.[10] RDs are often deprioritized in environments where several political priorities compete for national funding. Rafa Zimbaldi, State Representative in the Legislative Assembly of the State of São Paulo, Brazil, affirms this reality, stating that often policymakers "leave out [of the policy agenda] important discussions [like rare disease…] because they do not reach or benefit many people". This is why patient advocacy groups, like Mexico's Iniciativa Pensemos en Cebras, continuously seek an audience with policy and decision makers at the national and local level, regardless of changes in power and political administration. This, confirms Jacqueline Tovar, the Director of Iniciativa Pensemos en Cebras, allows for "continuity [and ensures that rare diseases remain] a public policy priority".

While policies on RDs do exist across the region, Latin American countries have come "relatively late to the game" in comparison to other countries.[7] Colombia was the first Latin American country to pass a comprehensive RD healthcare policy (Ley 1392) in 2010. Since then, other countries in the region have followed suit. However, RD policies across these countries vary greatly, in terms of comprehensiveness, level of public funding, and patient financial protection. Research[10] shows that countries like Argentina, Brazil, Colombia, Ecuador, and Panama have comprehensive RD policies that support and enable disease management for patients and access to dedicated health facilities. Conversely, other countries in the region, such as Guatemala, Mexico, Peru, and Uruguay, have only basic protective policies codified into law, and have yet to finance treatment or regulate access to RD care. Some countries, such as Venezuela and Cuba, have yet to develop any laws that respond to the needs of patients living with RDs. Meanwhile legislative efforts to move the needle in Congress have been ongoing in Chile and Costa Rica.[18,19]

The patient advocate community in Latin America is not only key to filling knowledge gaps for PCPs and connecting patients and families with resources and support, but also for driving the development and adoption of legislation and programs to improve RD research, care, and therapeutic access.[10] Their role is critical in ensuring that RD patients have a voice, especially given that approximately 50% of RDs do not have disease-specific foundations/research groups or communities.[10] Ms Tovar confirms the importance of building a patient advocate community, explaining that "we are the hand

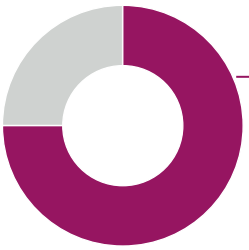
that accompanies [patients] and guides them throughout their care process, empowering and advocating for them".

Patient advocate groups have been particularly active and successful in moving the needle on regulation in countries, such as Argentina, Colombia, Panama, Peru, and Mexico, and working closely with decision-makers to ensure adequate care for those living with an RD.[20] For Ms Tovar, success relies on ensuring that decision-makers understand that actions taken to benefit the patient community are "an investment, [...] and that disease sequelae, disability, and admissions to intensive care will always carry a higher cost". Examples of patient advocacy efforts in the region include Argentina's Pituitary Disease Association, which has provided medical guidance to PCPs on how to diagnose pituitary diseases in new patients, and Mexico's Lysosomal Storage Disease Patient network, which has created a comprehensive care model for lysosomal storage disease that has garnered high-level political attention and financial endorsement.[21]

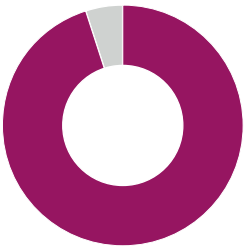
The diagnostic odyssey

The road to diagnosis for RD patients in Latin America is long. In Brazil, Colombia and Argentina, patients experience substantially long wait times to get a diagnosis. Research shows that RD patients in these countries have multiple interactions with the healthcare system before an accurate diagnosis is achieved and treatment is initiated.[10] In Colombia for instance, patients report enduring at least eight consultations and receiving at least three wrong diagnoses before reaching an accurate diagnosis.[10] Mr Zimbaldi also confirms that patients and their caregivers in Brazil "end up having to go to several doctors, sometimes an infinite number of them" before receiving a correct diagnosis and access to care. This experience of delayed and inaccurate diagnoses is also seen in Chile. "RDs are diagnosed late...if diagnoses are confirmed at all," affirms Valentina Goldschmidt Plate, Hematologist at the Hospital Padre Hurtado in Chile.

Generally, in Latin America, 75% of RD patients lack a definitive diagnosis.[3] One factor contributing to mis- and underdiagnosis is the significant knowledge gap among healthcare professionals, especially PCPs, caused by the rarity and complexity of these diseases and the absence of standardized criteria for diagnosis.[10,17] Gabriela Repetto, Clinical Geneticist and Director of the Center for Genetics and Genomics at Facultad de Medicina Clínica Alemana Universidad del Desarrollo, in Chile emphasizes this critical issue, stating, "We have to admit our lack of knowledge and the difficulty in acquiring and maintaining the [necessary] clinical skills... [education and training] really depends on personal interest and time." This knowledge gap often results in delays in both diagnosis and the initiation of appropriate treatment. Delayed and/or inaccurate diagnosis can lead to inappropriate disease management and disease progression, and significantly impact a patient's health, well-being, and, ultimately, their survival.[10] This, coupled with the lack of treatment options (close to 95% of RDs lack approved medical treatment), can have significant ramifications for patients' path forward in the care journey.[11]



75% of RD patients lack a definitive diagnosis in Latin America.[3]



Close to 95% of RDs lack approved medical treatment.[11]

"RDs are diagnosed late... if diagnoses are confirmed at all."

Valentina Goldschmidt Plate, Hematologist, Hospital Padre Hurtado, Fundación Arturo López Pérez, Chile.

The diagnostic delay for RDs varies depending on the patient's phenotype, age, and available resources.[22] On average, receiving the correct diagnosis can take four to five years and require multiple healthcare consultations and referrals to different specialists.[22] However, the diagnostic pilgrimage can sometimes span decades. Research across Europe shows that approximately 25% of patients endure lengthy diagnostic odysseys ranging from five to 30 years, whereas others experience frequent misdiagnosis (40%), often as a product of low medical knowledge and/or a lack of genetic testing tools and counseling.[10,11,23] Additional research is required to explore this trend across Latin America. It is, however, probable that the diagnostic odyssey is even longer given the resource constraints and the lack of public policy in the region.

Research shows that knowledge gaps often stem from a lack of education and training, and that there is inadequate investment in medical training for the specialized knowledge necessary for diagnosis at the primary care level. To further exacerbate the problem, there is an insufficient number of specialists, such as clinical geneticists and genetic counselors, available to provide guided diagnosis and treatment.[10] "Professionals are needed in the field, namely genetic counselors, laboratory scientists, and bioinformaticians who can perform tests," asserts Ms Repetto. As a result, patients face difficulties in locating healthcare professionals who can provide precise diagnoses, thereby contributing to longer wait times.[10] This phenomenon is echoed by the Brazilian experience. Despite the Ministry of Health's launch of the Brazilian Policy of Comprehensive Care for People with Rare Diseases in 2014, which sought to ensure public access to genetic testing and specialized RD centers, access to early and accurate diagnosis and treatment remains a challenge.[2,5] This is largely because specialized centers remain concentrated in university and public hospitals in large urban areas. Given Brazil's large population, these specialized centers are not only insufficient in number, but often lack the necessary laboratories and healthcare professionals to perform the genetic tests required for diagnosis.[5]

In Latin America, the healthcare systems not only grapple with a shortage of healthcare workers specialized in RDs, but they also lack the resources necessary to ensure widespread access to essential services such as screenings, diagnoses, and treatments. These challenges for the healthcare sector exacerbate the difficulties in offering comprehensive care for all, particularly for those with rare or complex conditions.

The high cost and accessibility challenges of treatment

Equitable access, coverage, and reimbursement

The challenges of high costs and limited accessibility to RD treatments are increasingly evident and can have a profound economic impact on healthcare systems in Latin America. Adding to these challenges is the reluctance of insurance companies and governmental bodies to reimburse RD drugs due to the high costs of these medications.[6,14] High costs and lack of public policy can hinder the development and commercialization of new treatments, despite their potential to make groundbreaking contributions to medicine and healthcare.[10] However, there are countries in Latin America that are taking steps to ensure that these medications become more cost-effective.

The Chilean healthcare system operates under the Ricarte Soto Law, which utilizes specific criteria established by legislation to determine which health conditions and interventions are eligible for coverage. These criteria

include disease burden, budget impact, social preferences, cost-effectiveness evaluations, and treatment costs that exceed a legal threshold.[24] However, this framework presents challenges for RD interventions. Often, interventions for RDs fail to meet the standard cost-effectiveness thresholds. Traditional economic evaluation methods do not fully capture the complete social value and societal preferences, resulting in a lack of coverage and inadequate healthcare for patients with RDs.[24] The prioritization criteria, coupled with limited resource allocation, create barriers to diagnosis and treatment, further exacerbating the financial burden on patients, families, communities, and the overall health system.[24] Without a legal framework specifically tailored for RDs, these conditions must compete with more common high-cost diseases that more easily meet the established criteria.

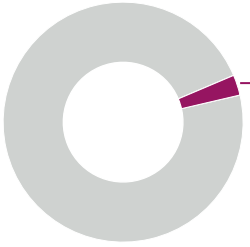
"There is very limited access to therapies... but I think that this reality has to do with socioeconomic factors and health, science, and research expenditures, [with Latin America] being lower than high-income countries," says Ms Repetto. In this context, Ms Repetto's analysis of Chile's healthcare system offers a clear example of the hurdles in ensuring equitable access to high-cost medications. Ms Goldschmidt Plate agrees, explaining that "In the case of paroxysmal nocturnal hemoglobinuria, for example, [healthcare professionals] have good access to diagnosis; however, the problem is that it is difficult to ensure treatment because the patients in the public system do not have access to treatment, and in the private system they have to fight [and sue to get access]."

Despite the existence of laws designed to cover expensive therapies for certain diseases, the narrow focus of these laws often excludes many rare conditions, leaving many families to face severe financial hardships. As Ms Goldschmidt Plate reiterated, "There is a lack of coverage and generalized public policies in Latin America [...] they are still diseases that are extraordinarily neglected due to their infrequency and from a cost-benefit point of view." This underscores the pressing need for broader healthcare policies that address the diverse, and often overlooked, needs of patients with RDs.

Yet, there are signs of progress. Policies in countries like Mexico and Brazil are evolving to improve access to RD drugs. Mexico's and Brazil's public health systems, for instance, have made notable efforts to include treatments for RDs within their healthcare frameworks.[7] These steps represent a growing awareness and acknowledgment of the need for inclusive healthcare policies. However, the journey towards equitable access and affordability for all RDs patients is far from complete, underscoring the need for policy reprioritization and cost-effective innovation. Therefore, cost is only one of the components that must be considered in the pursuit of better access to RD care.

Socioeconomic status and geographic disparities

In Latin America, access to RD diagnosis and treatment is influenced by socioeconomic status and geographic disparities.[10] Many RD patients are forced to travel long distances, often outside of their countries of origin, to access care; yet, less than 3% of the Latin American population is financially able to travel for medical treatment.[3] The majority of patients who can access diagnosis and treatment are members of the middle- and upper-class, who can afford to absorb the travel costs associated with medical tourism.



Many RD patients are forced to travel long distances, often outside of their countries of origin, to access care; yet, less than 3% of the Latin American population is financially able to do so.[3]

In general, urban centers, especially those with university or public hospitals, are better equipped with medical services required for RDs, in particular due to the concentration of private genetics laboratories and clinical services.[5] On the other hand, rural areas suffer from a significant lack of such facilities, highlighting a broader issue of health inequities in the region. The quality of care for RDs also largely depends on the socioeconomic standing of patients, revealing a critical need for more equitable healthcare policies and infrastructure improvements. Ms Repetto further underscores this issue of geographic disparities by drawing attention to the substantial gaps in access to genomic diagnosis across Latin America. She points out that outside of the metropolitan cities in Chile, rural and indigenous populations are particularly underserved. This uneven access not only lengthens the diagnostic journey but also increases healthcare expenses.

Many who cannot afford medication and need coverage seek legal routes.

The care journey for RD patients differs significantly between the public and private healthcare sectors. In the public system, there are limitations to diagnosis and therapy access, leading to long, resource-intensive medical journeys; this disproportionately impacts access for low-income patients.[10] On the other hand, although the private sector offers faster diagnosis and treatments, high costs still restrict access, highlighting systemic challenges in both sectors. Many who cannot afford medication and need coverage seek legal routes.

Judicialization of access

To overcome disparities imposed by socioeconomic status, the judicialization of access to medicines in Latin America, particularly in countries like Colombia, Brazil, Argentina, and Chile, is a growing phenomenon. Judicialization is often a patient's only recourse to access treatment and is increasingly used to obtain medications in the region despite differences in socioeconomic conditions, legal frameworks, and health systems in these countries.[25] While these countries have made efforts to expand health system coverage and access to medicines since 2000, coverage remains uneven and largely dependent on individual socioeconomic factors, such as labor and health status, and the ability to pay.

In Brazil, judicialization has influenced research and development (R&D) policies, leading to initiatives like public-private partnerships (PPPs) for local production of drugs that are considered a priority for the public health system.[2] This approach is partly in response to limited access to RD diagnostics and treatment, driving patients to seek judicial remedies based on constitutionally guaranteed rights.[2] Despite Brazil's approval of around 100 drugs for RDs, legal action against the government and health plans has become a common phenomenon with significant financial implications, costing the country nearly R$5.2bn between 2010 and 2017.[26]

Conclusion and looking forward

Impacting nearly 7.5% of the Latin American population, RDs are a public health priority. While recent years have seen advances across the treatment and reimbursement landscape, diagnostic challenges hamper progress and adversely impact patients and caregivers living with RDs. Addressing the years-long diagnostic odyssey is key to ensuring RD patients live healthier, longer, and more fulfilling lives. Yet, this challenge cannot be addressed in silos by any one entity. Instead, patient advocates, healthcare professionals, regulators, policymakers, payers, and other relevant actors, must work together to ensure a supporting environment for RD care in the region.

To truly disrupt the status quo and change patients' lives, an emphasis must be placed on the need for more reliable data, knowledge, and awareness. This is critical not only for better public health surveillance, but also for effective and efficient public health policy and services. Patient advocacy groups have a critical role to play in this. They must continue to support and educate patients and their caregivers, as well as advocate for the development of new therapies and more favorable policy environments for RDs. Meanwhile, the efforts of local patient advocate organizations should be complemented at the regional level by scientific and clinical research partnerships.

There is also a pressing need to standardize a regional definition of RDs and improve the collection, quality, and use of data, which the aforementioned collaborations can facilitate and champion. Only by mapping the true, real-world disease burden (e.g., epidemiological, social, economic) on patients and their caregivers, can relevant policymakers be made to understand the urgent call for actions that respond to the needs of the RD community.

The future is bright for people living with RDs if Latin American countries foster a supportive environment for innovation to thrive. While progress has been made in countries like Mexico, Brazil, and Colombia the availability of, and access to, cutting-edge genetic testing technologies and RD treatment is far from comprehensive. This highlights the need for policy prioritization and cost-effective innovation to ensure that cost is not a deterrent to RD diagnosis, treatment, and care. Only through concerted efforts can we end the diagnostic odyssey and transform the medical management of RDs in Latin America.

References

1. Honavar SG. Uncommon ophthalmology – care for the rare. Indian J Ophthalmol. 2022;70(7):2213.

2. Lopes-Júnior LC, Ferraz VEF, Lima RAG, Schuab SIPC, Pessanha RM, Luz GS, Laignier MR, Nunes KZ, Lopes AB, Grassi J, Moreira JA, Jardim FA, Leite FMC, Freitas PSS, Bertolini SR. Health policies for rare disease patients: a scoping review. Int J Environ Res Public Health. 2022;19(22):15174.

3. Wainstock D, Katz A. Advancing rare disease policy in Latin America: a call to action. Lancet Reg Health Am. 2023;18:100434.

4. Cunico C, Vicente G, Leite SN. Initiatives to promote access to medicines after publication of the Brazilian Policy on the Comprehensive Care of People with Rare Diseases. Orphanet J Rare Dis. 2023;18(1):259.

5. de Oliveira BM, Neiva MB, Carvalho I, Schwartz IVD, Alves D, Felix TM; Raras Network Group. Availability of genetic tests in public health services in Brazil: data from the Brazilian Rare Diseases Network. Public Health Genomics. 2023;26(1):145-158.

6. Pierzynowska K, Kamińska T, Węgrzyn G. One drug to treat many diseases: unlocking the economic trap of rare diseases. Metab Brain Dis. 2020 Dec;35(8):1237-1240.

7. Arnold RJ, Bighash L, Bryón Nieto A, Tannus Branco de Araújo G, Gay-Molina JG, Augustovski F. The role of globalization in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America. F1000Res. 2015;4:57.

8. Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: a systematic review of cost of illness evidence. Health Policy. 2015;119(7):964-979.

9. Ferreira RL, do Nascimento IJB, de Almeida VIA, de Oliveira VRL, Marangne LG, Dos Santos Gameleira F, Dutra TRC, de Oliveira Santos D, Dias Afonso MP, Dos Santos PEA, de Oliveira HN, Vilhena Dias FM. The utilisation of primary health care system concepts positively impacts the assistance of patients with rare diseases despite limited knowledge and experience by health care professionals: a qualitative synopsis of the evidence including approximately 78 000 individuals. J Glob Health. 2023;13:04030.

10. Adachi T, El-Hattab AW, Jain R, Nogales Crespo KA, Quirland Lazo CI, Scarpa M, Summar M, Wattanasirichaigoon D. Enhancing equitable access to rare disease diagnosis and treatment around the world: a review of evidence, policies, and challenges. Int J Environ Res Public Health. 2023;20(6):4732.

11. Sequeira AR, Mentzakis E, Archangelidi O, Paolucci F. The economic and health impact of rare diseases: a meta-analysis. Health Policy Technol. 2021;10:32-44.

12. Orphan drugs and rare disease drugs are often used interchangeably in published literature. For the purposes of this research, Economist Impact uses the definition in the US Orphan Drug Act (1984), which classifies an orphan drug as one with "efficacy against a disease affecting fewer than 200 000 people... or one that... will not be profitable for seven years".

13. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis. 2022;17(1):163.

14. Chung CCY; Hong Kong Genome Project; Chu ATW, Chung BHY. Rare disease emerging as a global public health priority. Front Public Health. 2022;10:1028545.

15. UN. General Assembly (76th session: 2021-2022). Addressing the challenges of persons living with a rare disease and their families: resolution / adopted by the General Assembly. New York (NY): United Nations;2022. Available from: https://digitallibrary.un.org/record/3953765?ln=+=+en&ln=ru.

16. Dias AG, Daher A, Barrera Ortiz L, Carreño-Moreno S, Hafez H SR, Jansen AM, Rico-Restrepo M, Chaparro-Diaz L. Rarecare: a policy perspective on the burden of rare diseases on caregivers in Latin America. Front Public Health. 2023;11:1127713.

17. Nestler-Parr S, Korchagina D, Toumi M, Pashos CL, Blanchette C, Molsen E, Morel T, Simoens S, Kaló Z, Gatermann R, Redekop W. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR Rare Disease Special Interest Group. Value Health. 2018;21(5):493-500.

18. Senado de la República de Chile. Proyecto de ley sobre enfermedades poco frecuentes. Senado; 2023. Available from: https://www.senado.cl/appsenado/templates/tramitacion/index.php?boletin_ini=7643-11.

19. Caja Costarricense de Seguro Social. ASUNTO: Proyecto de ley "PREVENCIÓN Y ATENCIÓN INTEGRAL DE LA SALUD DE LAS PERSONAS CON ENFERMEDADES RARAS PARA MEJORAR SU CALIDAD DE VIDA Y LA DE SUS FAMILIAS", Expediente legislativo No. 23257. Seguro Social;2023. Available from:https://www.ccss.sa.cr/arc/actas/2023/files/9388-52278.pdf.

20. Tudela JC, Díaz AA, Galkute M, Henao AMM. Study on socio-health needs of people with rare diseases in Latin America. [Internet]. Ibero-American Alliance for Rare Diseases (ALIBER); 2022. Available from: https://www.enfermedades-raras.org/que-hacemos/por-la-investigacion/investigacion-social/estudios/estudios-especificos/estudios/estudio-sobre-necesidades-sociosanitarias-de-las-personas-con-enfermedades-raras-en-america-latina.

21. Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis. 2017;12(1):63.

22. Marwaha S, Knowles JW, Ashley EA. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. Genome Med. 2022;14(1):23.

23. Nothaft W, Goldsmith C, Le Cam Y. It takes far too long for a rare disease to be diagnosed. Here's how that can change. Geneva: World Economic Forum;2020. Available from: https://www.weforum.org/agenda/2020/02/it-takes-far-too-long-for-a-rare-disease-to-be-diagnosed-heres-how-that-can-change/.

24. Encina G, Castillo-Laborde C, Lecaros JA, Dubois-Camacho K, Calderón JF, Aguilera X, Klein AD, Repetto GM. Rare diseases in Chile: challenges and recommendations in universal health coverage context. Orphanet J Rare Dis. 2019;14(1):289.

25. Vargas-Pelaez CM, Rover MRM, Soares L, Blatt CR, Mantel-Teeuwisse AK, Rossi FA, Restrepo LG, Latorre MC, López JJ, Bürgin MT, Silva C, Leite SN, Farias MR. Judicialization of access to medicines in four Latin American countries: a comparative qualitative analysis. Int J Equity Health. 2019;18(1):68.

26. Leal G. Doenças raras: Brasil é considerado "terreno fértil", mas desafios ainda são latentes (Rare diseases: Brazil is considered 'fertile ground and vanguard in Latin America', but challenges are still great). [Internet]. Brazil: Futuro da Saúde;2022. Available from: https://futurodasaude.com.br/especial-doencas-raras-brasil-e-considerado-terreno-fertil-e-vanguarda-na-america-latina-mas-desafios-ainda-sao-grandes/.