



Meeting Abstracts from the XVI International Collaboration on Rare Diseases and Orphan Drugs (ICORD): Incentivizing Science and a Comprehensive Program for Rare Diseases

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Meeting conferences

1.1. The XVI international collaboration on rare diseases and orphan drugs (ICORD)

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The 16th Annual International Collaboration on Rare Diseases and Orphan Drugs (ICORD) Meeting once again took place in Latin America, reaffirming its growing importance as a regional driver of action on rare diseases. The venue of this year was the Faculty of Pharmacy and Biochemistry at the University of Buenos Aires (FFyB-UBA), located in the Autonomous City of Buenos Aires, and the event was held on July 24-25, 2024. Following the meeting, participants contributed their insights and initiatives, which were compiled and reviewed by the conference committee. The resulting compilation showcases a diverse range of efforts currently underway across Latin America to support individuals living with rare diseases. By sharing these regional experiences, ICORD continues to serve as a vital platform for fostering cross-border collaboration and strengthening ties with the global community dedicated to rare diseases and orphan drugs. The Meeting aims to: (1) Promote the implementation of comprehensive health programs for the care of rare diseases and the development of orphan drugs in accordance with international models adapted to Latin American realities. It emphasizes the need for programs to

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prioritize based on local health conditions and to be developed in alignment with the social and economic conditions of each country; (2) Suggest working models and incentives for local scientists and the health industry to generate orphan diagnoses and treatments in collaboration with other countries worldwide and at the highest standard possible.

1.2. Fostering multisectoral collaboration in rare diseases: perspectives from Argentina and CERYDH

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The 16th International Conference on Rare Diseases and Orphan Drugs (ICORD 2024) was inaugurated in Buenos Aires, Argentina, with the participation of Collaboration for Rare and Orphan Diseases Foundation (CERYDH), a non-profit organization dedicated to fostering collaboration among stakeholders in the field of rare diseases and orphan drugs at local, regional, and international levels. CERYDH was founded on the recognition of numerous initiatives developed by individuals, institutions, and organizations across Argentina, united by the conviction that cooperation can accelerate shared goals, optimize resource use, address local priorities, and support policies that promote equity and integrity. Guided by its motto “*Semper et Ubique*” (Always and Everywhere), CERYDH seeks to be present wherever collaboration is needed. ICORD 2024 brought together international experts, researchers, and policymakers to exchange knowledge and strengthen global cooperation in rare diseases. The Faculty of Pharmacy and Biochemistry of the University of Buenos Aires hosted the event, contributing the expertise of its specialists in rare diseases and orphan drugs. The congress reaffirmed the importance of intersectoral collaboration, knowledge exchange, and institutional commitment to advancing equity, innovation, and policy development in the field of rare diseases.

1.3. Research, innovation, and policy challenges in rare diseases: insights from ICORD 2024

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The 16th International Conference on Rare Diseases and Orphan Drugs (ICORD 2024) Congress in Buenos Aires was conceived to foster interdisciplinary dialogue and advance research and policy development in the field of rare and orphan diseases. The event featured thirty-three invited lectures, free paper presentations, and an overview of the current situation and impact of rare diseases in Argentina. Discussions highlighted that rare diseases represent not only a medical issue but also a challenge for science and public health policy, underscoring the need to transform this challenge into an opportunity for innovation and collaboration. Two central areas were identified as essential for progress: promoting research incentives to generate new scientific knowledge and strengthening engagement with the pharmaceutical industry to enhance prevention strategies and reduce treatment costs. It was noted that approximately 8,000 rare diseases have been classified worldwide, most of which lack effective diagnosis or treatment. In Argentina, an estimated two million people are affected, often facing underdiagnosis and delays averaging five years before an accurate diagnosis is reached. Limited local production of orphan drugs leads to high treatment costs and forces many patients to seek care abroad. The congress discussions emphasized the importance of developing regional strategies to foster accessible therapeutic options derived from local scientific innovation. Proposals included repositioning existing treatments for common diseases into therapies for rare conditions. The strong foundation of Argentina in genetics education was recognized as a potential driver for significant progress within the next decade, provided that supportive policies, incentives, and regulatory frameworks are implemented. ICORD 2024 thus served as a platform to generate competitive ideas, develop an implementation roadmap, and explore emerging technologies applicable to the diagnosis and treatment of rare diseases.

1.4. Global collaboration and patient-centered perspectives in rare diseases: opening remarks at ICORD 2024

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The opening session of the International Conference on Rare Diseases and Orphan Drugs (ICORD) 2024 underscored the foundational mission of the organization and its ongoing contributions to advancing the global rare disease community. Established in 2007, ICORD was conceived as a collaborative platform that unites governments, patient organizations, researchers, healthcare professionals, industry representatives, and other stakeholders with the shared goal of strengthening international cooperation in the field of rare diseases and orphan drugs. The session emphasized the importance of integrating patient perspectives to deepen understanding of the burden, complexity, and social implications of rare diseases. Recognizing patient experiences serves as a driving force for accelerating research, improving equitable access to therapies, and reinforcing international networks. ICORD 2024 reaffirmed that global meetings of this nature are essential spaces for dialogue, interdisciplinary learning, and the development of coordinated strategies to advance collective action in research, care, and policy related to rare diseases.

1.5. Innovation and public-private collaboration in rare disease research: perspectives from Argentina

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The National Scientific and Technical Research Council (CONICET) of Argentina emphasized the importance of promoting research and innovation as key drivers for addressing the challenges posed by rare diseases. As a national institution dedicated to supporting scientific development, CONICET aims to

strengthen technology transfer and ensure that research outcomes directly contribute to societal well-being. During the International Conference on Rare Diseases and Orphan Drugs (ICORD) 2024, discussions highlighted the strategic role of public-private partnerships in fostering innovation in rare diseases. These collaborations were identified as essential mechanisms for translating scientific knowledge into tangible therapeutic solutions and enhancing accessibility for affected populations. The mature scientific system of Argentina was recognized as a significant advantage in this context. The country has a strong foundation in diagnostics, biomedical research, and advanced technologies. Its experience in areas such as transgenics, animal genome editing, and molecular biology has been internationally acknowledged, providing a platform for further scientific and industrial development. The Argentine research community was encouraged to leverage these strengths to promote pharmaceutical investment and the development of new treatments for rare diseases. The discussions also underscored the potential for international collaboration to expand research networks, share technological innovations, and accelerate progress in this field. ICORD 2024 provided an opportunity to reaffirm the commitment of Argentina to science-driven innovation and to encourage the development of products and solutions that directly benefit society. (*Adapted from CONICET website*).

1.6. Academic contributions and cross-sector collaboration in rare disease research: the role of the University of Buenos Aires

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The participation of the Faculty of Pharmacy and Biochemistry of the University of Buenos Aires (UBA) in the International Conference on Rare Diseases and Orphan Drugs (ICORD) 2024 Congress highlighted the commitment of the institution to advancing research, innovation, and education in the field of rare and orphan diseases. The opening remarks emphasized the importance of fostering a dynamic forum for exchanging experiences, knowledge, and best practices among academia, the productive sector, and patient organizations. The congress was envisioned as an opportunity to strengthen interdisciplinary and cross-sector collaborations that can bridge scientific expertise with real-world applications. The faculty expressed its aim to translate academic knowledge into the development of diagnostic tools and therapeutic strategies to address the complex challenges posed by rare diseases. By promoting collaboration among researchers, industry representatives, and patient associations, UBA seeks to enhance national and regional capacity for innovation in biomedicine and the pharmaceutical sciences. The broad expertise of the faculty in areas such as molecular biology, biochemistry, and pharmacology provides a solid foundation for contributing to the development of accessible and effective health solutions. The session reaffirmed the relevance of academic institutions as drivers of scientific advancement and social progress. Through active participation in global initiatives such as ICORD, the UBA continues to strengthen its leadership in promoting research, knowledge transfer, and collaborative innovation for the benefit of patients and society at large. (*Adapted from the National Scientific and Technical Research Council (CONICET) website*).

1.7. The Undiagnosed Diseases Program (UDP) at National Institute of Health

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The Undiagnosed Diseases Program (UDP) was established at the National Institutes of Health (NIH) in 2008 to help patients end this diagnostic journey through multidisciplinary clinical evaluations, exome and

genome sequencing, and basic science research. A second important goal was to facilitate disease discovery that could provide insights into biochemical, physiological, and cellular mechanisms. Many UDP participants have seen specialists at other major medical centers throughout the United States and the world. Patients can apply to the UDP by providing a referral letter from their physician, along with medical records, laboratory results, and imaging studies. UDP team members review applications to determine if a case is suitable for the program, based solely on clinical manifestations and regardless of geographic location. Approximately one-third of applicants are accepted into the program and receive a comprehensive clinical evaluation at the NIH Clinical Center, at no cost to the patient. In addition to extensive personalized phenotyping, patients and their families generally undergo genetic studies that include single-nucleotide polymorphism (SNP) microarrays to determine copy number variants and regions of homozygosity, exome, genome sequencing, RNA sequencing, and functional studies where indicated; these investigations are beyond what is available in a constrained clinical setting. Among those not accepted, approximately 25% receive recommendations on how to pursue a diagnosis and, sometimes, therapy. Since its inception in 2008, the UDP has received more than 6,000 applications and has accepted approximately 30%; in addition, ~160 non-accepted patients have been referred to other NIH services. Of those individuals accepted into the UDP, 39% were children, and more than 50% had neurological symptoms. Despite the clinical complexity of the participants, the program has successfully diagnosed approximately a third of the cases. Diagnoses have been made using the genomics, phenotyping, and functional tools described above. For cases that cannot be solved with standard pipelines, data are reanalyzed, and additional bioinformatic tools are employed. Sometimes, establishing a molecular diagnosis requires multidisciplinary discussions and collaborations with other research groups within and outside the NIH. Furthermore, there is an ongoing iterative process of reanalysis as new genomic technologies emerge. Discoveries made through UDP investigations have resulted in more than 200 peer-reviewed publications. Here we present the UDP program, and some illustrative cases that have already been published in greater detail. They highlight the value of the Program in identifying new diseases and novel disease mechanisms and enhancing our understanding of biochemistry, cell biology, and pathophysiology. They also emphasize the importance of deep phenotyping of rare diseases, genetic diagnostics as a necessary prelude to treatment, and collaborations with experts worldwide.

1.8. “Buenos FAIRres”: why and how you should apply the FAIR principles to your research project

Claudio Carta

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Every day, huge amounts of data are produced from various sources, which need to be analyzed to answer different research questions. Research questions that require, often, access to different resources to be answered. Moreover, data is (1) sparse, (2) heterogeneous, (3) collected in different formats, and, often, (4) sensitive, for example, data from patients with rare diseases. The integration of the different types of data produced in a project, which often need to be combined with data from other sources, requires significant effort in terms of human and economic resources and is time-consuming. FAIR is an acronym indicating that (meta)data are Findable, Accessible, Interoperable, and Reusable for both humans and machines; it is supported by fifteen guiding principles. FAIR data enable the linking of data from different resources while complying with applicable access restrictions. FAIRification of (meta)data at the source optimizes data use, thereby reducing costs and time. From the earliest stages of a research project, resources should be allocated for data FAIRification, including personnel with appropriate expertise and the development and maintenance of FAIR-compliant infrastructure. FAIR (meta)data enable rapid, efficient, and unambiguous responses to research questions while respecting access constraints. They also optimize data reuse, reduce data fragmentation, and enable the generation of new data and results through integration and re-analysis.

1.9. Beyond “One Disease at a Time” platform approaches for rare disease gene therapy/gene editing clinical trials

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Based on current estimates, there are approximately 10,000 human diseases. A large fraction of these are monogenic diseases that result from mutations in a single gene. Gene-targeted therapies, such as gene therapy, gene editing, and oligonucleotide-based approaches, represent therapeutic platforms that are broadly applicable to monogenic diseases. However, the current approach to the clinical development of these technologies is to deploy them as treatments for individual diseases. In practice, this “one disease at a time” approach limits the clinical utility of these therapeutic platforms to the most common monogenic diseases with commercial viability. In this talk, I will discuss collaborative approaches supported by National Institutes of Health (NIH) funding that aim to advance the development of these technologies as shared therapeutic platforms. Specifically, I will highlight two programs focused on gene therapy (<https://pave-gt.ncats.nih.gov/>, <https://fnih.org/our-programs/AMP/BGTC>) and one program focused on gene editing (<https://commonfund.nih.gov/editing>).

1.10. Genomic approaches to undiagnosed diseases: lessons from international collaborations

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A person with an undiagnosed rare disease may be afflicted by a condition recognized by medicine but not yet diagnosed, or by a new disease. For known rare diseases, long diagnostic delays are well recognized. For new diseases, it is estimated that only half of all Mendelian disorders have been discovered. Given the large number of rare disorders, these challenges are further complicated by the expanding body of information needed to both identify and manage rare conditions. For these reasons, the rare disease community - both providers and patients - needs global networks to reinforce local medical systems. These networks may include forums for consultation about difficult cases as well as automated systems for aggregating and sharing phenotypic, genotypic, and clinical management knowledge. This presentation will present case examples of the successful implementation of international collaborations, tools, and strategies. Examples will include work being done by both national and international programs to expand global rare disease infrastructure. Only by working together will we be able to break down the barriers that prevent people with rare diseases from benefiting from the best available knowledge.

1.11. Phase I/II intravenous AAV9-GLB1 gene therapy for GM1 gangliosidosis

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GM1 gangliosidosis (GM1), caused by biallelic mutations in *Galactosidase Beta 1 (GLB1)* that result in b-galactosidase enzyme deficiency, is a rare, relentless neurodegenerative multisystem disorder with heterogeneous onset and variable disease progression. There is no approved therapy. Using intravenous delivery of vector adeno-associated virus serotype 9 (AAV9)-GLB1 in a phase 1/2 first-in-human study, we have treated 12 individuals, including 2 infantile onset, 4 late-infantile onset, and 6 juvenile onset patients. No vector-related serious safety concerns have been noted. In 7 type II patients for whom longitudinal data were available, b-galactosidase activity in cerebrospinal fluid (CSF) was increased $> 5 \log^2$ fold above baseline and stable for at least 24 months post-dosing, and GM1 ganglioside in CSF was decreased. The terminal complement complex was activated without thrombocytopenia or detection of the transgene or anti-AAV9 antibody during the immune modulation regimen. The Clinical Global Impressions Scale (CGI) showed mixed results, with infantile-onset patients demonstrating brief initial improvements followed by deterioration in skills consistent with disease progression. In contrast, 3 of 4 late-infantile and 3 of 5 juvenile patients showed sustained improvement over 36 and 24 months, respectively. Interim results on the Vineland III (Vineland Adaptive Behavior Scales, VABS) showed a greater number of patients with stabilization or improvement in the gross motor and personal care domains as compared with domains in fine motor and receptive communication. Notably, a juvenile patient, presymptomatic at the time of treatment, has maintained age-appropriate development in all domains 36 months following treatment. Identical twins treated together have shown nearly similar and stable clinical outcomes on the CGI and VABS. We conclude: (1) that biochemical and clinical outcomes up to 3 years following gene therapy for GM1 are durable and promising, (2) that treatment of patients before the onset of symptoms has a better chance for favorable outcomes, and (3) that variability in symptom onset and disease progression across a small cohort makes data analysis challenging.

1.12. Access to CNS rare diseases innovative therapies

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Brain access is still nowadays a challenge for specific treatments in rare diseases with neurological involvement. Our central nervous system is well protected by multiple layers forming the blood-brain barriers (BBBs) although the BBB is permeable to different substances and cells in a very controlled way. Several brain delivery technologies have been proposed and experienced. On the one hand, invasive approaches such as intrathecal brain delivery, direct brain injections, or intracerebral grafts. In the other non-invasive techniques, including nanoparticles, intranasal administration, and larger groups using biological mechanisms such as receptor-mediated transcytosis, cell-mediated brain delivery, or neurotrophic viruses. There are no curative treatments available for rare neurological diseases due to the inability of systemic treatments to cross the BBB and the potential risks versus benefits of direct CNS delivery. Research is focused on overcoming the BBB to increase the concentration of treatments in CNS cells, as well as exploring different gene therapy approaches. Clinical experience now shows that crossing the BBB alone is not always sufficient, so improving access to neurons and targeting secondary pathogenic pathways, such as inflammation or autophagy, is also being considered.

1.13. The International Rare Disease Research Consortium (IRDiRC): making rare disease research efforts more efficient and collaborative, around the world

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The International Rare Disease Research Consortium (IRDiRC) is a global consortium of key stakeholders from diverse areas of rare disease research that together seek to advance diagnostics, therapeutics, and patient outcomes. The consortium facilitates global, cross-disciplinary exchange of ideas to tackle key issues in rare diseases by developing recommendations, data standards, tools, and guidelines that harmonize research efforts and improve efficiency. While IRDiRC has made significant contributions to the development of new therapies and diagnostics since its founding in 2011, much work remains to alleviate the burden of rare diseases. The consortium has demonstrated its success in providing a global platform to advance rare disease research through collaborative efforts worldwide, continuing to identify and address barriers to health equity for all rare disease patients.

1.14. Pluto program (living no one behind)

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As of today, fewer than 6% of rare diseases have approved treatments, and most drug development efforts are concentrated on a limited number of conditions. Therefore, there are many rare diseases with little or no research activity, the so-called “disregarded rare diseases”. Many technical and social reasons may account for this: lack of disease knowledge and academic interest, the pathophysiological complexity of many diseases, cellular localization of the defective protein (for genetic diseases), diagnostic complexity, and - possibly above all - extreme rarity. Although the existence of a large group of “disregarded” rare diseases is unanimously acknowledged by the rare disease research, patient, and development communities, no specific analysis has been conducted so far to characterize specific commonalities amongst these diseases, with the potential secondary aims to identify removable roadblocks that may foster future research and development. The PLUTO project (PLUTO is a project focused on ultra-rare diseases) addresses this gap by employing an integrated database-driven approach to (1) identify and classify rare diseases that are under-represented in both academic research and industrial development, (2) determine their common characteristics, and (3) elucidate the key roadblocks that limit progress toward effective treatments. Based on these analyses, PLUTO aims to generate evidence-based recommendations for policymakers, funders, and developers to help overcome existing limitations and accelerate research and therapeutic development for disregarded rare diseases.

1.15. The IRDiRC drug repurposing guidebook: creating an efficient and visible pathway for rare diseases

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Drug repurposing is an exciting topic in the world of rare diseases, and it has often been suggested as a key approach for developing more therapies for the estimated 6,000–8,000 rare diseases. This strategy can be an attractive option because it often involves developing therapies in an efficient, potentially cheaper, and innovative way, building on previous knowledge and experience. Drug repurposing can be defined in several ways. Still, in broad terms, it can be considered the development of an existing drug in an indication outside its original scope, with the ultimate purpose of obtaining a new, regulator-approved indication. Several tools and incentives have been developed to facilitate and ease the repurposing of treatments for rare diseases. Nevertheless, the field still faces several challenges, such as intellectual property issues, limited understanding of regulatory requirements, the need for additional (re)formulation or for obtaining additional safety-efficacy data that may be difficult to collect, and difficulties in commercialization due to the lack of sustainable business models. Consequently, repurposing approaches for rare diseases have, until now, not been as impactful as anticipated. We will present the work of the Therapies Scientific Committee Task Force of the International Rare Diseases Research Consortium (IRDiRC), following the Orphan Drug Development Guidebook that was previously launched. We set out to develop a Drug Repurposing Guidebook. This Guidebook is developed for researchers and developers involved in drug repurposing in the rare disease space, specifically academics, startups, small and medium enterprises, and patient-led groups. This Drug Repurposing Guidebook gathered and reviewed tools and created a roadmap to help deliver an efficient development program. This roadmap is integrated with a Gantt chart, highlighting the key repurposing activities for each development phase, with checklists outlining the necessary steps to complete before starting a repurposing project. As such, this Guidebook can help researchers and developers who want to optimize a repurposing project for rare diseases. By providing an understanding of the available tools, asking the developer essential questions at different stages, and directing them to available resources, repurposing for rare diseases can be faster, more efficient, and better aligned with regulatory processes.

1.16. Primary prevention of Rare Diseases and the new one health vision

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Primary prevention of congenital anomalies is feasible because scientific evidence points to several risk factors (e.g., obesity, infectious and toxic agents) and protective factors (e.g., folic acid status and glycaemic control in diabetic women). A number of specific communities are envisaged, such as promoting healthy lifestyles, developing policies for vaccination and the treatment of chronic disorders such as diabetes, and implementing regulations on workplace and environmental exposures. Yet, how to integrate into a consistent plan such a range of actions across different domains? The One Health (OH) vision can be a powerful tool. The operational definition adopted in 2021 by four international agencies - World Health Organization (WHO), Food and Agriculture Organization (FAO), World Organization for Animal Health (WOAH), and United Nations Environment Program (UNEP) - defines OH as an integrated and unifying approach: it recognizes that the health of humans, animals, plants (and therefore food), and ecosystems is interconnected and interdependent. Consequently, OH involves multiple sectors, disciplines, and components of society. A key OH concept is complexity: the OH vision provides a comprehensive “landscape” of a complex issue, enabling the identification of both priority areas and aspects that might otherwise be overlooked but remain important. The “landscape” vision then allows for the mobilization of the relevant range of skills. Building up a primary prevention plan for congenital anomalies is a transdisciplinary enterprise, an ideal field to implement an OH approach. Some examples of OH vision: the prevention of congenital anomalies induced by arthropod-borne viruses, such as Zika virus, calls for contributions by skills in ecology, zoology as well as eco/toxicology, in order to ensure a safe use of insecticides; prevention of neural tube defects calls for communication and nutrition skills in order to assess and improve the folate status as well as the characterization of environmental factors involved in folate-unresponsive defects; the reduction of exposure to the widespread neurodevelopmental toxicant methylmercury calls for a OH-driven “water-to-fork” approach, from environmental emissions through to fish farming and the empowerment of consumers awareness; prevention of birth defects related to common risk factors such as diabetes should include the careful management of the disease, as well as the broader living environment. Finally, multifactorial congenital anomalies -and rare diseases in general- are particularly liable to have a significant uncertainty burden: the OH vision may provide a comprehensive identification of priority knowledge gaps. Strengthening primary prevention of congenital anomalies with an OH vision calls for scientific evidence as well as governance. A critical aspect is the consistent involvement of institutional domains other than “health” according to the principle of “health in all policies”, which is, indeed, a component of the OH vision. In practice, a national plan for the primary prevention of congenital anomalies should be steered by domains such as welfare, environment, agriculture, *etc.* Another practical consequence of great importance for all OH-driven action is the integration and interoperability of diverse data sources, collected for different purposes: in its turn, this requires both technical and institutional steps. Increasing cases show that the initial efforts to establish an OH approach are amply rewarded in terms of cost-effectiveness, rational use of resources, and impact. Thus, why not develop an OH vision to support the primary prevention of congenital anomalies?

1.17. Extended newborn screening for rare diseases: the Italian system

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Newborn screening (NBS), also called neonatal screening, is an important public health secondary prevention measure. NBS identifies shortly after birth pre-symptomatic conditions that can affect the long-term health or survival of a child. Thus, early detection, diagnosis, and intervention can prevent death and disability or ameliorate the clinical manifestations of diseases, enabling children to reach their potential for health and well-being. In Italy, during the years 2016-2017, a combined legislative framework established a nationwide NBS for more than 45 disorders. Accordingly, the NBS is funded and supported by the Italian National Health System and is included among the essential levels of assistance provided by the State. The framework defines the requirements to achieve the maximum uniformity in the national-level regional implementation of NBS. In this context, the NBS Coordination Center was established at the Istituto Superiore di Sanità (ISS) and is coordinated by the ISS director. The center includes experts and representatives from central and regional institutions, as well as three representatives from patient associations. The regional-level screening program is organized into four main functional components: a screening laboratory, a confirmatory diagnosis laboratory, clinical centers, and a regional coordination/supervision center. The legislation also defined the panel of screening conditions, the timing for specimen collection, the screening methodology, the confirmatory tests, and the clinical follow-up. A periodic review of the list of conditions/diseases to be screened is set up by a working group coordinated by the Ministry of Health, in collaboration with other government agencies and organizations. This working group also has the mission to elaborate an operational protocol, including procedures for the management of positive NBS, positive diagnosis, and access to therapies. In conclusion, the NBS in Italy is an organized, structured secondary prevention program funded by the National Health System.

1.18. Rare diseases in Bulgaria

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Bulgaria has made notable progress in managing rare diseases through the establishment of the Information Centre for Rare Diseases and Orphan Drugs, a key initiative of the Institute for Rare Diseases - Bulgaria. This center, which began operations in 2004, offers comprehensive educational and information services in both Bulgarian and English, serving a diverse clientele, including patients, families, and medical professionals. Importantly, these services are provided free of charge, ensuring broad accessibility. The center provides personalized responses to inquiries with support from a dedicated team of volunteers and medical consultants. These consultants specialize in various disciplines, including genetics, pediatrics, internal medicine, and surgery, allowing for expert guidance tailored to specific medical needs. The multidisciplinary approach ensures that inquiries are forwarded to the appropriate specialists, enabling accurate and relevant responses. However, response times to inquiries average 4.37 days, with some responses taking as long as 196 days. The website attracts around 330 visitors daily, totaling approximately 83,000 visitors annually, indicating strong demand for the center's resources. A milestone in the history of the center was the organization of the First Eastern European Conference on Rare Diseases and Orphan Drugs, held on May 27, 2005. This event marked a significant step in fostering regional collaboration and knowledge exchange on rare diseases. Additionally, the website has undergone three major updates between 2004 and 2018, reflecting a commitment to evolving and improving its digital resources. Legislation plays a crucial role in Bulgaria's strategy for managing rare diseases. At the national level, the 2009-2013 National Plan for Rare Diseases and Ordinance No. 16 (2014) established the regulatory framework for the registration of rare diseases and the creation of expert centers and reference networks. At the European Union (EU) level, Recommendation 2009/C 151/02 and Directive 2011/24/EU are pivotal, focusing on ensuring patient rights in cross-border

healthcare, promoting collaboration across member states, and enhancing the overall quality of care for patients with rare diseases. A significant development was the establishment of the Commission on Rare Diseases on February 13, 2015. Situated within the Ministry of Health, the commission includes four representatives from the ministry, seven medical professionals, and two patient representatives. Its functions are comprehensive and multifaceted: defining a list of rare diseases, recommending the official designation of centers of expertise, evaluating the activities of the national registry and designated centers, advising on prevention, diagnosis, treatment, follow-up, and rehabilitation of rare diseases, and collaborating with European and international organizations. The national list of rare diseases managed by the commission has grown over time and is used strategically for several purposes: designating centers of expertise, managing the national registry for rare diseases, planning medical services, supporting European and international collaboration, developing tailored rare disease training programs, and establishing expert clinical trial sites. Bulgaria's comprehensive approach to managing rare diseases underscores the importance of coordinated efforts involving legislation, collaboration, and dedicated support services. The Information Center for Rare Diseases and Orphan Drugs, part of the Institute for Rare Diseases, serves as a model for providing critical resources and support to those affected by rare diseases, facilitating improved patient outcomes and fostering a collaborative environment for medical professionals and researchers. The evolution of Bulgaria's strategies and resources reflects a robust commitment to addressing the unique challenges posed by rare diseases, ensuring that patients receive timely and effective care.

1.19. Indian organization for Rare Diseases - initiatives in India

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Indian Organization for Rare Diseases (IORD) was established in 2005 and registered in the USA and India as a not-for-profit umbrella organization representing 90 million Rare Disease Patients suffering from 7,000 rare diseases. IORD is the first patient organization to bring to the public's attention and popularize the phrases "Rare Disease" and "orphan drugs" in the country. Its vision is that all rare disease patients should have the same opportunities as those with common diseases. Its mission is to raise awareness, advocate for public policy, and promote diagnosis, treatment, and medical and social services. IORD provides free membership and disease-specific organizations. Here are some accomplishments for which IORD is directly responsible: National Policy for Rare Diseases Treatment was drafted in 2017, 2019, and 2022; Amended clinical trial rules for orphan drugs in 2019; Import license and compassionate use privileges for new orphan drugs; Orphan drugs included are included in the production-linked incentives; Medical devices for rare diseases are included in the National Health Plans; Rare Diseases have been eligible for CSR funds since 2022; Indian Council of Medical Research (ICMR) requests research proposals to develop drugs for rare diseases in 2022; Delhi High Court ordered the release of Rs5.35 crores for clinical trials in 2022; several pharma companies are investing in the manufacturing of orphan drugs; All approved orphan drugs are manufactured in India (~450). Historical facts of patient organizations will be highlighted.

1.20. European model and the Catalan model of care for Rare Diseases

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The European Parliament directive of 9 March 2011 included, for the first time, information on European Reference Networks (ERNs). In 2014, the European Union (EU) workgroup on ERNs established the criteria and conditions that ERNs and healthcare providers must meet, as well as the requirements for the creation and evaluation of networks and their members. In 2016, the designation of the first accredited centers for the 24 different ERNs began. This model of care has the following main objectives: improving patients' access to highly specialized healthcare; facilitating European cooperation in rare disease patient care; enhancing diagnosis and treatment for conditions where knowledge is limited; assisting states with an insufficient number of patients to access specialized services; and sharing knowledge, disseminating innovations, and promoting training and research. Some aspects of these eight years of experience will be reviewed. In Catalonia, the Advisory Commission on Rare Diseases was created in 2009 to assess and address patient needs. In 2014, a proposal was launched for a networking system connecting centers of expertise with professionals across the region. This system, the Networks of Units of Clinical Expertise (XUEC), enables multidisciplinary team care with two main levels: centers of expertise and territorial assistance divided by units of knowledge. One of the most relevant contributions has been strengthening the role of case managers, who coordinate between patients, their environment, and the professionals involved in their care.

1.21. Initiatives for Rare Diseases in Colombia

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Colombia was the first Latin American country to enact a law in favor of patients with orphan/rare diseases (HD/RD) and their caregivers, Law 1,392 of 2010. It recognizes these diseases as being of special health interest, it states. The creation of a system for negotiating medicines and incentivizing research drives the establishment of reference centers for diagnosis, treatment, and pharmacy, as well as mechanisms for social integration, international cooperation, and the development of prevention, education, and dissemination programs. It is a comprehensive law; it had to be regulated and implemented in its entirety in less than two years, but in substantial aspects, it is still being implemented. With it, significant advances have been achieved in visibility, financing by the state for the diagnosis and treatment, in education, and in the dissemination of these diseases. The law establishes the preparation of a list that must include all diseases that are accepted as HD/RD in Colombia; there are 2,046 that are entitled to the benefits of the law. The diagnosed cases are mandatory to report; as of today, there are nearly one hundred thousand reported patients, a very low figure for a country of fifty million inhabitants. Patients who benefit from the law have strong protection; in fact, the law provides that benefits cannot be restricted for economic or administrative reasons. The out-of-pocket cost to the family is considered very low compared to developed countries. But Colombia is a large country, with few specialized RD personnel, concentrated in the 5 largest cities. Half of the country is very distant, difficult to access, and where there are only first and second-level health services. For adequate care, it is necessary to organize networks and subnetworks of reference centers with national coverage, an essential but pending task. Patient associations, more than 50 according to the Ministry of Health registry, have played a vital role in the development of legislation, education, dissemination, and protection of the rights of patients and their caregivers. In Colombian law, an orphan disease was defined as one with a prevalence of less than 1 in 5,000. The terms orphan and rare are used interchangeably in official documents on these diseases. This inaccuracy also appears in the legislation of other Latin American countries, so to try to resolve those misunderstandings that are creating problems for transnational programs and policies on these diseases, the World Health Assembly in May 2022 proposed the following universal definition: A rare disease is a medical condition with a specific pattern of signs, symptoms, and clinical findings that affects < 1 in 2,000 people living in any region. Even though it is not easy to change legislation to standardize matters related to RD, it is advisable to seek mechanisms to create a common language that facilitates cooperation and joint transnational work in RD.

1.22. Development of a potentially therapeutic bacterium for the treatment of trimethylaminuria

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Trimethylamine (TMA) is a volatile tertiary amine with a strong odor of rotting fish, even at low concentrations. In the human body, TMA is produced by the gut microbiota from dietary precursors such as choline, carnitine, and trimethylamine N-oxide (TMAO). Usually, the TMA generated in the intestine enters the bloodstream and is converted in the liver into the odorless compound TMAO. The enzyme responsible for this reaction is flavin-containing monooxygenase 3 (FMO3). In some individuals, the FMO3 enzyme is nonfunctional or has reduced activity, leading to a rare condition called trimethylaminuria (TMAU). In this pathology, TMA is not metabolized, leading to its accumulation in the body and excretion in urine, sweat, exhaled breath, and other bodily secretions, giving the person a body odor resembling that of rotting fish. Consequently, patients may suffer severe psychosocial impacts. In this study, we analyzed the potential use of a bacterial flavin-containing monooxygenase (FMO) to reduce the TMA odor. The coding sequence of a bacterial FMO was synthesized using codons optimized for expression in *Escherichia coli* (*E. coli*), with a His-tag at the C-terminal end. Overexpression of FMO in *E. coli* BL21(DE3) enabled the production of large amounts of protein, which was purified by immobilized metal affinity chromatography (IMAC). The activity of the purified FMO (*in vitro*) was evaluated by spectrophotometry, using TMA as the substrate. It was determined that the purified FMO is active with TMA as substrate, and its kinetic parameters were obtained. To evaluate its activity *in vivo*, the FMO sequence was cloned into vectors suitable for expression in the probiotic strain *E. coli* Nissle 1917 (EcN). These vectors allowed the expression of FMO in the probiotic strain, and the ability of these bacteria to oxidize substrates under aerobic and microaerobic conditions was confirmed. Additionally, the transport of TMA and TMAO in these bacterial strains was evaluated. It was established that both TMA and TMAO freely enter the cell. Furthermore, it was demonstrated that the TMAO produced by the FMO does not accumulate within the cell but is released into the culture medium. Finally, to improve the efficiency of this potentially therapeutic bacterium, a mutant strain with the TMAO reductase gene (EcN Δ TorA) was constructed. The mutant strain showed a marked decrease in TMAO reductase activity compared to the wild-type EcN strain. Additionally, it was demonstrated that the mutant strain transformed with plasmids for FMO expression is capable of consuming TMA. The potential use of these bacteria as a complementary therapy for TMAU will be discussed.

1.23. Synthesis and supramolecular study of an amphiphilic compound for the delivery of idebenone

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Idebenone (IDE) is a synthetic compound analogous to coenzyme Q10 (CoQ10) and is used in the treatment of neurodegenerative diseases, Leber's hereditary optic neuropathy, and Friedreich's ataxia. Its physicochemical characteristics make IDE a water-insoluble molecule with low bioavailability. The objective of this work was to synthesize a low-molecular-weight amphiphilic molecule capable of self-aggregating into supramolecular structures that internalize IDE, increasing its apparent solubility. Electron microscopy and dynamic light scattering studies were performed, which allowed verifying the existence of two types of superstructures when the amphiphilic compound is dissolved in water. Molecular dynamics studies were conducted and were consistent with the experimental data. The synthesized amphiphile was found to have

very low toxicity when tested in cells, and allowed the apparent solubility of IDE to increase 20 times.

1.24. Familial chylomicronemia syndrome: case reports in Argentina and the role of clinical biochemistry laboratory in its diagnosis

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Familial Chylomicronemia Syndrome (FCS) is a rare autosomal recessive disorder with a prevalence of around 1/1,000,000. It is characterized by impaired hydrolysis of intestinal triglyceride (TG)-rich lipoproteins, the chylomicrons (CM), leading to their accumulation in plasma. This increase in CM levels in the circulation causes severe hypertriglyceridemia (sHTG), milky serum, and many clinical symptoms such as eruptive xanthomas in the chest and limbs, *lipemia retinalis*, recurrent abdominal pain, hepatomegaly, splenomegaly, and acute or recurrent pancreatitis, which is the main cause of mortality in these patients. CM hydrolysis is primarily determined by lipoprotein lipase (LPL), an extracellular triglyceride hydrolase (TG-hydrolase) that is expressed by the parenchymal cells of many tissues and then anchored to the endothelial cell surface of the tissue that synthesized it. LPL activity is determined by a delicate balance among many transcriptional and post-translational regulators, including Peroxisome proliferator-activated receptors (PPARs) as one of the main transcription factor that stimulates LPL expression, apolipoproteins (apo) CII and AV as positive post-translational regulators, and glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1), as the necessary factor to anchor LPL to the endothelium, thereby allowing its activity. On the other hand, among negative post-translational regulators, it is worth mentioning apoCIII and Angiopoietin-like proteins (ANGPTLs), such as ANGPTL3 and ANGPTL4. In this regard, mutations in the above-mentioned genes impair TG- and CM-hydrolysis, in some cases leading to FCS. Loss-of-function (LOF) mutations in the LPL gene account for 80% of mutations responsible for FCS, but other homozygous mutations involve the GPIHBP1, apoCII, apoAV, and Lipase Maturation Factor 1 (LMF-1) genes. It is worth noting that some FCS patients harbor double heterozygous mutations involving LPL and other canonical genes. Nevertheless, in approximately 30% of the cases of sHTG, where FCS is strongly suspected, no mutations in the five mentioned genes are detected. In this scenario, the diagnosis becomes difficult, and the distinction between FCS and Multifactorial CS (MCS), a disorder resulting from multiple genetic and environmental factors, becomes less clear. Some scoring systems have been proposed to diagnose FCS, such as the Moulin and Brisson scores. These scores include clinical and biochemical features of sHTG patients, and, according to the final score obtained, patients can be classified as very unlikely, probable, possible, or definitive FCS. In cases of negative genetic tests and a strong suspicion of FCS, the measurement of plasma LPL activity arises as a promising diagnostic tool. LPL activity is determined in post-heparin plasma (PHP), and methods for its assessment are often difficult to standardize due to the high heterogeneity across techniques and laboratories. Globally, there are few laboratories that perform this determination, and the Lipids and Atherosclerosis Laboratory from the Faculty of Pharmacy and

Biochemistry (University of Buenos Aires) represents the only one in Latin America. In our laboratory, we evaluate PHP-LPL activity by an *in vitro* radiometric assay, using an artificial radioactive micelle. We established our own reference value for LPL activity, determined in PHP from 30 normotriglyceridemic patients, which ranges from 18.7–70.3 mIU, with a median of 33.3 mIU. From August 2021 to June 2024, we studied 39 sHTG patients referred to our laboratory from health centers in Argentina and Colombia, who had probable FCS based on clinical and familial features. In some cases, genetic data were available. In most cases, LPL activity was below the lower reference value. In some cases, it accounted for less than 20% of the median LPL activity in normotriglyceridemic patients, indicating a very likely FC. When available, a strong correlation was verified between LPL activity levels and the detected genetic variants. Taken together, the available data and our expertise demonstrate that the measurement of plasma LPL activity in patients with sHTG could be an additional diagnostic tool to detect FCS or MCS, especially in those patients where mutations in the sought-after genes are not detected. This also highlights the role of the specialized clinical biochemistry laboratory in supporting the diagnosis of these rare diseases, thereby assuring access to treatment and, finally, improving the quality of life of these patients.

1.25. X-chromosome inactivation, its impact in female hemophilia expression

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X-chromosome inactivation (XCI) is a paradigm of epigenetics, involving typically heritable clonal changes that do not correspond to DNA sequence differences and are inheritable at all levels. XCI leads to the massive silencing of one of the two X chromosomes, balancing the dosage of X-linked genes between males (XY) and females (XX). The initiation and maintenance of this process are associated with expression of the non-coding RNA X-inactive specific transcript (XIST), resulting in females being mosaic with two cell lines: one with the maternally inactivated X chromosome and the other with the paternally inactivated X chromosome, theoretically distributed 50:50 in each tissue. Once established, this inactivation is inherited unchanged in every somatic cell throughout adult life. Skewed XCI is a significant deviation from the 50:50 inactivation, leading to tissues/organs or the entire organism predominantly expressing one active X chromosome (either maternal or paternal). Hemophilia is a sex-linked hereditary disorder caused by defects in either the Factor VIII (*F8*) or Factor IX (*F9*) coagulation genes, associated with Hemophilia A (HA) or Hemophilia B (HB), respectively. The clinical severity of the condition correlates with the levels of factor activity (*F8*, *F9*), categorized as severe hemophilia (*F8* or *F9* < 1%), moderate (1%–5%), or mild (5%–40%). In this context, affected individuals are hemizygous males, while carrier females heterozygous for the affected allele rarely exhibit severe symptoms. Hemophilia primarily affects males due to X-linked inheritance, introducing a bias as carrier females are typically asymptomatic. Recently, there has been a report of increased bleeding tendency in hemophilia carriers (HCs). A new classification considers personal bleeding history and initial factor levels, categorizing HC as: females/girls with mild, moderate, or severe hemophilia (FVIII/IX > 5% and < 40%, 1%–5%, and < 1%, respectively); symptomatic and asymptomatic HC (FVIII/IX ≥ 40% with and without bleeding phenotype, respectively). This new classification aims to enhance diagnosis and clinical management. Heterozygous HCs may have standard or intermediate levels of FVIII/FIX activity, influenced among other factors by epigenetic mosaicism of the X chromosome in their somatic cells, where alternatively the X chromosome carrying the pathogenic or non-pathogenic variant may be active. Most symptomatic women are heterozygous for HCs with complete skewing in X chromosome inactivation for *F8/F9* variants. Molecular genetic studies of the pathogenic variant in males help determine the causal variant of hemophilia in the family. In contrast, studies in females investigate genetic and epigenetic causes of phenotype expression in affected women.

1.26. The journey toward therapy for GM1 gangliosidosis

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Eva and Franco are 11 and 8 years old. In June 2022, they both received a juvenile type B GM1 gangliosidosis (GM1) diagnosis. That date marked a turning point for us before we were preoccupied with Eva, mostly but that day, everything fell apart. Our dreams and hopes crashed. Eva began with motor skills difficulties at age 4. She got a dyspraxia diagnosis and started occupational therapy. She managed to complete preschool by herself, but when she started 1st grade, everything got worse. She began with speech difficulties and couldn't follow the teaching. We decided to reduce hours at school and reinforce therapies. Finally, we changed to a smaller school with a personal companion. That year, 2019, we had an initial consultation with a geneticist, and the first results came back normal. At the beginning of 2020, we were all prepared to succeed, but the coronavirus disease (COVID-19) pandemic kept us home for a full year. All medical exams were halted, and Eva's progress at school and in therapies was difficult to measure. That year, Franco started with speech difficulties, and we thought he was copying his sister or that maybe it was caused by the isolation. But when he finally could restart preschool in 2021, the teachers noticed he had fine motor skills difficulties as well. We rapidly reinforced therapies for him, and we returned to consult the geneticist doctor, this time regarding Eva and Franco as well. That is how we got to the diagnosis 2 years ago. To get there, we had to cross too many doctors, therapists, clinical studies, paperwork, absences at work, school changes with goodbyes and adaptations to new places and new groups, so sometimes family questioning and our own demands and interrogations. However, it is always best to know that there is an explanation for what is happening to our kids, the challenges that we face every day. Every consult we've done before the diagnosis was another source of uncertainty and now we learn from each specialist that we talk to. The next few months after the diagnosis were the hardest until we finally received the notice that Franco was eligible for gene therapy at the NIH. So, we traveled as fast as we could, and after all the exams and immune suppression, Franco received gene transfer in November 2022. Since the same date, Eva has been on Migalastat and a ketogenic diet, hoping that a new treatment or a better medication comes up, since she is not eligible for adeno-associated virus serotype 9 (AAV9) gene therapy. We all continue fighting GM1 and with the medical system because it is not prepared for people with rare diseases. Last year, we had to manage over 100 documents to approve therapies and medications. Despite having excellent health insurance, we had to request 3 judicial protections for our kids so far. Living with GM1 is an exhausting task from every point of view; many times, we feel alone. We have the means to access treatments, doctors, and communicate in other languages, but sadly, that is not the case in many other families.

1.27. Personal experience living with familial Mediterranean fever

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Familial Mediterranean Fever (FMF) is a genetic condition characterized by recurrent episodes of fever and inflammation affecting various systems in the human body. The symptoms are often nonspecific, which means the disease can go undiagnosed for years. Over time, it may progress to amyloidosis, a severe complication that significantly impacts both quality of life and survival. My story reflects that of many others living with FMF. Some of my relatives suffered from the condition without ever receiving a diagnosis, which ultimately affected their life expectancy. In my own case, I was misdiagnosed with various rheumatic diseases and received ineffective treatments for years. Perhaps my background as a health journalist and my interactions with medical professionals helped me begin to question whether I had ever truly received an

accurate diagnosis. This growing doubt led me to research information online, and by reflecting on my own symptoms and family history, I began to suspect that I might be living with FMF. Medical evaluations and laboratory tests confirmed my suspicions, and eventually, I found a specialist who provided a treatment specifically designed for FMF. This changed not only my own prognosis but also that of my relatives, as several were subsequently diagnosed as well. This process of self-diagnosis, while unusual, is more common than we might think among those living with rare diseases. It inspired me to start addressing FMF in my radio and television programs and to join with others in founding the Argentine FMF Association. The path - from uncertainty and untreated symptoms to diagnosis and effective treatment, and ultimately to media advocacy and patient organization - has been a transformative journey. It is a positive experience I now share with others. People living with rare diseases often begin their fight by simply refusing to accept the initial, unsatisfying reality. They dare to explore lesser-known options. I hope that this effort becomes a smart, empowered one - one that motivates others to push for diagnostic alternatives beyond common pathways and everyday medical practice.

1.28. Phelan-McDermid syndrome (PMS): features and challenges in Argentina

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The Phelan-McDermid Syndrome (PMS) is a rare genetic condition caused by a deletion of genetic material on chromosome 22, specifically in the 22q13.3 region, or by mutations in the SH3 and multiple ankyrin repeat domains 3 (SHANK3) gene, located in that same region. This deletion can involve a loss of various parts of the chromosome, but the loss of the SHANK3 gene is associated with the main symptoms of the syndrome. The SHANK3 gene is crucial for the development and function of neuronal synapses, which are the connections between neurons. Therefore, loss or mutation of this gene interferes with neuronal communication, leading to problems in brain development and function. The symptoms of PMS can vary widely among individuals. Most people with PMS experience a significant delay in motor development, such as sitting, walking, or speaking. Many children with this syndrome do not develop verbal language skills or have a very limited vocabulary. Intellectual disability is a common feature of PMS, and its severity can range from mild to profound. Individuals with PMS may show symptoms that overlap with autism spectrum disorders, such as problems in social communication, repetitive behaviors, and hypersensitivity to sensory stimuli. Some physical characteristics may include hypotonia (low muscle tone), abnormally large fingers and toes, and distinctive facial features such as low-set ears or drooping eyelids. People with PMS may also have a higher incidence of medical problems such as seizures, sleep disorders, and feeding difficulties. Diagnosis of PMS is usually made through genetic testing, such as chromosome microarray or SHANK3 gene sequencing. Due to the rarity of the syndrome, it is common for the symptoms to be confused with other neurological or genetic disorders until specific genetic testing is performed. There is no cure for PMS, and treatment focuses on symptom management. This may include physical, occupational, and speech therapy to help children develop motor and communication skills. Additionally, medications may be used to control associated symptoms, such as seizures or behavioral problems. Families and caregivers of people with PMS often face significant challenges due to the complexity of the syndrome. It is crucial to have a multidisciplinary healthcare team that understands the patient's specific needs. Additionally, connecting with support groups and online communities, such as the PMS in Argentina, can provide valuable resources and emotional support for affected families. Although there is no cure, early intervention and ongoing support can improve the quality of life for people with PMS. Research continues in the search for more effective treatments, and knowledge about this condition continues to grow, offering hope for the future. The community in the country is calling for local clinical trials as a model to enhance the quality of sanitary support for the affected.

1.29. Education for Rare Diseases in Argentina

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Rare Diseases (EPF) are a growing Public Health problem in Argentina. Part of the difficulty in this area is the lack of knowledge across all the disciplines involved in caring for the health of the people. One of the crucial moments to incorporate EPF detection and management tools is undergraduate university education. The Subject “Rare Diseases in Medicine” was created in 2021, and since then, many students have enrolled each year. Part of the activity of a group of students is carried out at the Reference Center for Rare Diseases and Difficult Diagnosis (CERyD in Spanish) of the San Juan de Dios Hospital in La Plata. The interest that students show in each course represents the importance of generating these academic spaces, since they increase the possibilities of choosing this area of medicine as a specialty and create more health professionals dedicated to an area in which they are scarce. The experience of the EPF Chair of the UNLP Faculty of Medicine is shared.

1.30. RIBERSER program for Latin America

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The Spanish Agency for International Development Cooperation (AECID) opened the NTERCONNECTA 2023 call for proposals in June 2023. The State Foundation, Health, Childhood and Social Welfare, F.S.P. (CSAI), sent a proposal, which included two of the three main objectives approved by the International Rare Disease Research Consortium (IRDiRC): (1) The analysis of the impact of policies on rare diseases, and (2) to promote access to the diagnosis of rare diseases. After a long phase of co-creation of this proposal in joint work with the AECID, the program called Ibero-American Network of Health Experts in Rare Diseases (RIBERSER - La Red Iberoamericana de Salud en Enfermedades Raras) Program [report_Conv23_Resolucion_aprob_program.pdf](#) was approved in February 2024. A complete list of participants is in the annex to this summary. The RIBERSER program will develop 6 activities in the next two years. Two of the activities will be online training courses, one aimed at rare diseases as a global problem and another more focused on genetic diagnosis. The first of them is scheduled for the month of September this year, and the second for 2025. The other four activities are described below: The first took place online on June 25-27 (<https://intercoonecta.aecid.es/programaci%C3%B3n-de-actividades/an-lisis-y-propuestas-de-pol-ticas-de-salud-en-las-enfermedades-raras>). The second will be held in February 2025 and will be organized as a ministerial conference. This will be held in Montevideo, Uruguay, at the AECID headquarters. The third will be online and will focus on the genetic diagnosis of complex cases. The format of this meeting will be a hackathon of undiagnosed rare disease cases. Finally, the programming will conclude with a congress to present the results in person, and it will take place in Montevideo, Uruguay, at the AECID headquarters, probably at the beginning of 2026. The challenge to be solved by RIBERSER is the creation of a network of health experts with the capacity to advise, lead, and manage training processes, develop methods to implement interoperable information systems, evaluate needs and resources, and implement innovative methods in the area of genetic diagnosis in the field of rare diseases in the Latin American and Caribbean region. The aim is to influence the development of public policies aimed at equitable access to diagnostic services for Rare Diseases and the management of information and needs of patients and their families affected by rare diseases. The impact we try to achieve is to optimize socio-health resources and harmonize policies for the promotion of innovative methods in genetic diagnosis, thus enabling the use of specific

treatments and research in the framework of rare diseases. The problems to be solved arise on two different fronts: (a) the absence of training/information, and (b) the difficulty of accessing a correct diagnosis. The absence of training within the training itineraries of health professionals and social agents, and of socio-health information, makes adequate decision-making difficult. On the other hand, the difficulty of access to diagnosis is due to several different types of determinants, such as the structural problems of health systems, the fact that many rare diseases are at the limit of current scientific knowledge, and access to the diagnostic tools currently available. RIBERSER will address problems related to the ability to lead and manage future developments, such as a definition of a rare disease agreed upon for the region, information systems and registries aimed at rare diseases, including integration with other registration systems for congenital anomalies and systems aimed at understanding intellectual and physical disabilities, always in relation to rare diseases and 2) Facing the challenge of the first objective of the IRDiRC consortium. To achieve this challenge, it is necessary to significantly involve experts in the genetic diagnosis of rare diseases. Throughout the process there will be the support of the Ibero-American Alliance for Rare, Orphan or Infrequent Diseases (ALIBER) Network, which represents many of the associations and federations of rare diseases in Latin America (LATAM) and the Caribbean; the collaboration of the International Conference on Rare Diseases and Orphan Drugs (ICORD), an international society with activity in the countries of the work area of the project, as well as the possibility of incorporating groups from these countries into the international network of undiagnosed cases (UDNI <https://www.udninternational.org/>). The proposed project begins with partners and collaborators belonging to LATAM and Caribbean countries that are signatories of the proposal, but the objective is to involve most of the countries in the region, both in the network of experts of partners and collaborators and in those proposed activities with a scope beyond the signatories of the proposal. Therefore, the development results to be achieved after addressing these two major problems have to do with health promotion, equitable access to existing diagnostic resources, the possibility of family counseling, and the reduction of the burden of disease, and all this from the promotion of knowledge, information, and awareness about the need to implement health policies for rare diseases, through networking.

1.31. Duchenne muscular dystrophy: molecular confirmations and its impact on precision medicine

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Muscular dystrophies (MDs) comprise a heterogeneous group of over 60 genetic and hereditary diseases that cause progressive muscle degeneration and present with various patterns of weakness and modes of inheritance. Duchenne muscular dystrophy (DMD) is the most common and severe form of MD in the pediatric population, caused by pathogenic variants in the DMD gene. This X-linked recessive disease primarily affects males, though some females may also exhibit clinical manifestations. DMD is characterized by the complete absence of functional dystrophin protein, progressive muscle weakness leading to a gradual loss of motor functions, and severe disability. There is significant clinical variability among affected males, even among those with the same mutation. Diagnosing MDs is challenging when based solely on patient clinical presentation, due to overlapping signs and symptoms between different MDs, making a molecular approach essential for achieving a differential diagnosis. Even though there is still no cure for these severe diseases, unprecedented advances are being made in the development of therapies, especially for DMD. Notable advances include exon skipping, premature stop codon read-through, and gene therapy, among

others. Our primary research focus is DMD. Over the 30 years dedicated to studying these diseases, we have analyzed approximately 3,000 samples from patients and families with MD. We have a molecular diagnostic program for affected families in Argentina that identifies disease-associated variants. Early diagnosis is crucial for establishing care standards that help delay disease progression and improve patient quality of life. Additionally, it is essential to provide genetic counseling and determine eligibility for specific treatments within the framework of precision medicine. To achieve molecular diagnosis, we implement a diagnostic algorithm utilizing multiplex ligation-dependent probe amplification (MLPA), next-generation sequencing (NGS) (in silico panels), polymerase chain reaction-sanger sequencing (PCR-Sanger), messenger RNA studies, and bioinformatics tools. This work aims to present the molecular algorithm used for diagnosing MDs and its utility in determining the variant/gene-dependent therapeutic protocol. Furthermore, we will summarize the results of recent research on the muscle involvement in female carriers of DMD alterations and the study of modifier genes affecting the clinical progression of DMD.

1.32. Development of a new therapeutic strategy for CoQ₁₀ deficient newborns

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Coenzyme Q₁₀ (CoQ₁₀) is an endogenous lipophilic antioxidant compound that participates in many critical cellular pathways and is an essential component of the mitochondrial respiratory chain. CoQ₁₀ deficiency can be classified according to its origin as primary or secondary. Clinical manifestations can occur either from birth or even into late adulthood. Therefore, having an adequate treatment that adapts to each type of patient is of utmost importance. In all associated pathologies, the clinical condition improves and/or is reversed through CoQ₁₀ supplementation. Therefore, it can be said that the effectiveness will be greater if both the diagnosis and the start of treatment are carried out early. The complexity of CoQ₁₀ is widely known regarding its physicochemical characteristics, such as high lipophilicity, great instability, and limited solubility. These characteristics result in easy degradation and difficulty in intestinal absorption and, therefore, low bioavailability. For these reasons, the design of an adequate formulation that corrects these difficulties positively influences the success of the treatment. As there is no pharmaceutical form that meets the requirements for patients such as newborns, neonates, and infants, a formulation with a high CoQ₁₀ content was developed and characterized, which, based on the method of preparation, resulted in an oil-in-water (O/W) emulsion with the size and characteristics typical of a nanoemulsion. Both the type and quantities of excipients to be used were optimized, as was the maximum load of CoQ₁₀, obtaining a final concentration of 9.5% w/v. It is important to highlight the achievement of solubilizing large quantities of said molecule in a high aqueous content (75%), considering its high hydrophobicity. The formulation was physicochemically stable for at least 90 days. In turn, CoQ₁₀ remained unchanged under the different conditions of use. Other parameters, such as density and pH, were evaluated at the said study time. The nanoemulsion manages to disperse in a dairy matrix without modifying its organoleptic characteristics, making it the most favorable form of administration for newborns. On the other hand, this formulation did not demonstrate *in vitro* cytotoxicity. The bioavailability of the CoQ₁₀ nanoemulsion was evaluated by supplementing infant formulas with said formulation in healthy volunteers. The results obtained demonstrated that the CoQ₁₀ in the milk matrix supplemented with the nanoemulsion is absorbed well and faster, making it more bioavailable than the same infant formula supplemented with CoQ₁₀ powder. In summary, the results indicate that future supplementation with the novel CoQ₁₀ nanoemulsion in infant formula could facilitate individualized administration and significantly improve the child's quality of life. At the same time, it may enhance therapeutic efficacy, which should be confirmed in subsequent studies.

1.33. Role of the SLC35A3 transporter in congenital disorders of glycosylation

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Congenital disorders of glycosylation (CDGs) comprise a group of inherited human diseases related to a deficiency in the synthesis of glycoconjugates that occur mainly in the Golgi apparatus (Golgi) and the endoplasmic reticulum (ER). The identification of more than 160 CDG-associated genes and the characterization of the corresponding biochemical phenotypes in patients have been driven in recent years by advances in massive sequencing and mass spectrometry. Many of these disorders are related to mutations in genes that encode proteins that are known to play a role in the synthesis of nucleotide sugars (NS) in the cytosol or nucleus, in the transport of NS to the lumen of the Golgi or ER, or in the use of NS by glycosyltransferases that add sugars to glycoproteins, glycolipids and proteoglycans. In this presentation I will focus on discussing the role of the Solute Carrier Family 35 Member A3 (SLC35A3) transporter in CDGs. In particular, the relevance of the study of substrate specificity to understand the biochemical phenotypes observed in SLC35A3-CDG patients, the characterization of pathogenic variants and the use of animal models.

Poster presentations

2.1. Rare diseases in Ecuador: a vision from the public health

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Rare diseases in Ecuador, as defined by Ministerial Agreement 1829 dated since 2012, are potentially lethal, long-term, debilitating disorders with low prevalence and high complexity, affecting 1 in 10,000 people, and ultra-rare diseases affecting 1 in 50,000 people. In Ecuador, about 5%-6% of the population, i.e., approximately one million people, suffer from rare diseases. The Ministry of Health has identified 106 rare diseases from the 8,000 known globally. These conditions significantly impact individuals and the healthcare system, with limited and expensive therapeutic resources, some still experimental. There is a need for comprehensive and equitable healthcare services, strengthening governance towards universal health coverage, and improving financing to eliminate barriers to access. Key strategies include better regulation to ensure access and quality, efficient financial organization, transparent acquisition processes, and addressing social determinants of health through intersectoral action. Real-life case studies highlight the diagnostic challenges patients face, including misdiagnosis and delayed diagnosis. The Neonatal Screening project, which began in December 2011, has studied over 2.25 million children by March 2023. Limited awareness among healthcare professionals and access to specialized diagnostic tests contribute to these issues. Treatment options for rare diseases in Ecuador are scarce due to limited research and funding. Advocacy groups play a crucial role in providing community support, emotional aid, and vital information. They also push for better access to treatments, research funding, and awareness campaigns. Despite challenges, significant progress has been made in understanding the genetic basis of these diseases and developing targeted therapies. Collaborations among researchers, healthcare professionals, and patient advocacy groups are essential for advancing research and improving the lives of those affected by rare diseases in Ecuador.

2.2. Brucella infection affects functionality of decidua stromal cells and trophoblasts

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The ability of trophoblasts to migrate, form tubes, and invade the decidua is essential for a successful pregnancy. These processes are modulated by cytokines produced by decidual cells. *Brucella* infections are associated with reproductive complications in humans and animals. We evaluated whether *Brucella* could impair the functions of decidual cells and trophoblasts, which are relevant to a successful pregnancy. The effect of *Brucella* infection on trophoblast migration was evaluated with the scratch test using the human trophoblastic cell line Swan71. Wound closure was significantly reduced in trophoblasts infected with *Brucella abortus* (*B. abortus*) (multiplicity of Infection (MOI) 50:45%; MOI 500: 36% vs. 83% in uninfected controls), and with other *Brucella* strains. Human endometrial stromal cells (THESC) were infected with different *Brucella* species (*B. abortus*, *B. suis*, *B. melitensis*) before or after decidualization with medroxyprogesterone and cyclic adenosine monophosphate, and conditioned media (CM) were used to stimulate Swan71 cells during the scratch test. Wound closure was reduced in Swan71 cells treated with CM from *Brucella*-infected decidualized THESC as compared to uninfected CM (20% vs. 86%). Similarly, wound closure was inhibited by CM obtained from THESC cells infected before decidualization (8.5% vs. 72.8%). Inflammatory signals are known to promote trophoblast functions. Trophoblast migration (wound closure) improved when CM from *B. abortus*-infected THESC (different multiplicities of infection, MOI) was treated with neutralizing antibodies against specific chemokines before addition to the scratch test (Human C-X-C motif chemokine ligand 8 (CXCL8) Antibody MOI 50: 59%; MOI 500: 45% vs. same MOI untreated; C-C motif chemokine ligand 2 (CCL2) Human Antibody MOI 50: 62%; MOI 500: 38% vs. same MOI untreated; Human CXCL8 Antibody plus Human CCL2 Antibody MOI 50: 55%; MOI 500: 52%). Moreover, tube formation assay with same experimental conditions was more successful in uninfected controls (NI), as revealed by the number of master junctions (NI: 88; MOI 50: 33.2; MOI 250: 42; MOI 500: 19), master segments (NI: 152; MOI 50: 28; MOI 250: 62; MOI 500: 46.5) and meshes (NI: 56; MOI 50: 16; MOI 50: 20; MOI 500: 13.5). In addition, when THESC were infected, the attachment area of trophoblast spheroids (invasion) was affected (NI: 0.98; MOI 50: 0.71; MOI 250: 0.53; MOI 500: 0.47). Overall, the normal functions of trophoblasts and decidual cells, as well as the crosstalk between them, can be affected by *Brucella* infection.

2.3. Molecular diagnosis of thyroid hormone resistance syndrome

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Thyroid hormone resistance (THR) is a rare pathology characterized by decreased sensitivity to thyroid hormones, which leads to elevated serum thyroid hormone levels and inappropriately normal or slightly elevated thyroid-stimulating hormone levels. The incidence is estimated at 1 in 40,000 to 50,000. This syndrome is mainly caused by alterations in the thyroid hormone receptor beta (THRB) gene, which maps to chromosome 3 and spans 378 kb, including 10 exons. 270 variants have been described in THRB (9 missense, 247 missense, 9 deletions, 4 duplications, and 1 indel). 14 families with a clinical-biochemical diagnosis of resistance to thyroid hormone (RTH) were studied. To identify the variants responsible for the pathology,

genomic DNA was isolated, exons 6-10 (containing the variants hot spots) including the flanking intronic regions were amplified and sequenced. 11 variants were found (10 missense and one insertion) of which 2 (c.917A>C [p.Lys306Thr] and c.1276_1277insTGA [p.425_426insMet]) turned out to be novel variants. Pathogenicity prediction and molecular modeling studies indicated that the identified variants would be responsible for RTH. This work contributes to the study of RTH and its molecular characterization, thereby enabling accurate diagnosis and specific treatment.

2.4. Identification of a novel variant in SLC6A8 through clinical exome sequencing in a family with Creatine Transporter Deficiency (CRTR)

Micaela Barbieri

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Creatine Transporter Deficiency (CRTR) is an X-linked inherited metabolic disorder caused by variants in the solute carrier family 6 member 8 (SLC6A8) gene, leading to reduced cerebral creatine levels. It primarily affects males, who present with severe symptoms such as developmental delay and epilepsy, while female carriers may exhibit variable symptoms. In this study, we describe a 10-year-old boy who underwent targeted clinical exome sequencing due to a phenotype including developmental delay, seizures, lack of language acquisition, incontinence, behavioral disorders, and distinctive facial features. His magnetic resonance imaging and electroencephalogram showed abnormalities, whereas array comparative genomic hybridization and karyotype were normal. Clinical exome sequencing identified a likely pathogenic novel variant in the SLC6A8 gene (c.222_226del; p.Asn74LysfsTer113) in hemizyosity, associated with CRTR. Segregation studies confirmed that the mother is a heterozygous carrier of the variant and that his older affected brother also carries the variant in hemizyosity. This finding is crucial for treatment and family counseling, as CRTR can be managed with oral supplementation of creatine, arginine, and glycine. Being a rare disease with a broad phenotypic spectrum, next-generation sequencing technologies play a key role in diagnosis.

2.5. National cooperation efforts to develop an antivenom for a rare but fatal envenomation in Argentina

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Lononism is an orphan disease in Argentina caused by accidental contact with the venomous caterpillar *Lonomia obliqua*. This envenomation is characterized by a wide range of systemic complications that can even lead to death. Forty cases were recorded in Argentina between January 2014 and May 2020. Aware of the national need for specific treatment and taking into account sustainability in antivenom development, in this work, we produced the recombinant form of the two major toxins of *L. obliqua* venom (Lopap and Losac) by using a biotechnological platform based on an insect. Both recombinant toxins were used as immunogens in rabbits. Specific antibodies against both the recombinant and native forms of Lopap and Losac, respectively, were detected by Western blot analysis. To understand the immunoreactivity observed, both recombinant toxins were subjected to an exhaustive analysis using bioinformatic tools to describe their three-dimensional structures, identify potential active sites and relevant epitopes, and examine the structural implications of amino acid residues involved in interactions. This work provides a preliminary framework for having access to an effective and sustainable treatment for *Lonomia* envenomation.

2.6. Identification of a novel variant in SLC6A8 through clinical exome sequencing in a family with Creatine Transporter Deficiency (CRTR)

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Creatine Transporter Deficiency (CRTR) is an X-linked inherited metabolic disorder caused by variants in the solute carrier family 6 member 8 (SLC6A8) gene, leading to reduced cerebral creatine levels. It primarily affects males with severe symptoms such as developmental delay and epilepsy. Female carriers may exhibit variable symptoms. In this study, we describe a 10-year-old boy who underwent targeted clinical exome sequencing due to a phenotype including developmental delay, seizures, lack of language acquisition, incontinence, behavioral disorder, and distinctive facial features. His magnetic resonance imaging and electroencephalogram showed abnormalities, while array comparative genomic hybridization and karyotype were normal. Clinical exome sequencing identified a likely pathogenic novel variant in the SLC6A8 gene (c.222_226del; p.Asn74LysfsTer113) in hemizyosity, associated with CRTR. Segregation studies confirmed that the mother is a heterozygous carrier of the variant and that his older affected brother also carries the variant in hemizyosity. This finding is crucial for treatment and family counseling, as CRTR can be managed with oral supplementation of creatine, arginine, and glycine. Being a rare disease and due to its broad phenotypic spectrum, next-generation sequencing technologies play a key role in diagnosis.

2.7. Development of benznidazole orally disintegrating tablets for pediatric patients

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Chagas disease, or American trypanosomiasis, is a parasitic infection caused by *Trypanosoma cruzi*. It is considered a neglected tropical disease by the World Health Organization (WHO) and a rare disease by the Food and Drug Administration (FDA). After years of infection, the disease can cause serious heart illness, and it can also affect swallowing and digestion. Chagas disease primarily affects people living in rural parts of Latin America. The first-line treatment is benznidazole, designated as an orphan drug by the FDA. Although children are highly affected by this disease, there are no specific commercial pharmaceutical preparations for this age group in Argentina. This research aims to develop a benznidazole pediatric orally disintegrating tablet. Co-milling was applied to the production process, and then direct compression. X-ray diffraction studies showed that benznidazole remained in its original crystalline state (form I) in the tablets. Taste masking experiments were conducted with a test panel of adult volunteers. The resulting tablets complied with all quality control requirements; their disintegration time was less than 1 minute, and the benznidazole dissolution rate was much faster than that of the conventional tablets for adults.

2.8. Pseudohypoparathyroidism: presentation of a case with established molecular diagnosis

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Pseudohypoparathyroidism (PHP) is a rare hereditary disorder characterized by normal renal function and resistance to parathyroid hormone (PTH). It is classified as Type 1, with subtypes a, b, and c (PHP IA, IB, IC)^[1-3], and Type 2 (PHP II)^[4]. Type 1 PHP is associated with reduced or absent expression/function of the alpha subunit of the stimulatory G protein (G α), encoded by the GNAS locus, which may result from various genetic or epigenetic alterations^[5]. We report a patient with clinical suspicion of PHP whose molecular cause was determined using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). Genomic DNA was extracted from peripheral blood (MagNA Pure 96, Roche), and the GNAS locus was analyzed for methylation and copy number using the MS-MLPA technique (ME031 GNAS, MRC-Holland). MS-MLPA products were analyzed using the SeqStudio capillary electrophoresis system (Thermo Fisher), and Coffalyser.Net software (MRC-Holland) was used for bioinformatics analysis.

Results: An altered methylation pattern was detected at the GNAS locus.

Conclusion: Establishing a molecular diagnosis in clinically suspected PHP can be challenging due to the diversity of underlying genetic alterations. In this case, we identified the molecular mechanism responsible, confirming a diagnosis of PHP IB.

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2.9. Development of a high-dose coenzyme Q₁₀ emulgel for chronic oral therapy of deficient patients with dysphagia

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Coenzyme Q10 (CoQ10) is a cofactor in the electron transport chain and an endogenous antioxidant. In patients with severe CoQ10 deficiency, an early treatment with high oral doses (50 mg/kg/day) may avoid renal disease and neurological manifestations. CoQ10 is extremely lipophilic, water-insoluble, and poorly absorbed in the gut, which reduces its bioavailability, especially in solid forms. In addition, CoQ10-deficient patients generally present with swallowing difficulties (dysphagia), which affects the treatment acceptance of solid oral dosage forms. From a pharmaceutical technology perspective, the apparent low density of CoQ10 powder limits the development of high-dose solid oral formulations. To facilitate administration, an oral emulgel (20/80 w/w oil-in-water) was developed. This emulgel allows the delivery of a high dose of CoQ10 (4 g/100 g of emulgel), which is dissolved in the oil phase, dispersed in an aqueous phase using sodium alginate as a gelling agent. Also, the physical and chemical stability of the emulgel was evaluated for 12 months at 25 °C. In conclusion, it was possible to formulate an oral emulgel with high doses of CoQ10 that is stable for 12 months, which would help in reducing the rejection of treatment, leading to its abandonment in patients with dysphagia due to severe CoQ10 deficiency.

2.10. Post-heparin lipoprotein lipase activity in severe hypertriglyceridemic patients: case reports in Argentina

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Severe primary hypertriglyceridemia (sHTG) (triglycerides-TG- >880 mg/dL) represents a rarely diagnosed disease, and in many cases, patients lack treatment. Among these disorders, it is possible to identify the Familial Hyperchylomicronemia Syndrome, characterized, until now, by mutations in five canonical genes, with the lipoprotein lipase (LPL) gene being the most frequent; and the Multifactorial Hyperchylomicronemia Syndrome, a disorder resulting from multiple genetic and environmental variables. The measurement of plasma LPL activity has been proposed as a diagnostic tool for these diseases. However, the methods for its assessment are difficult to standardize due to the high heterogeneity across techniques and laboratories. Globally, there are few laboratories that perform this determination, and our Laboratory represents the only one in Latin America. Our objective was to evaluate LPL activity in post-heparin plasma (PHP) for patients with sHTG, in association with gene variants, and to propose this measurement as a diagnostic tool for these diseases. PHP (post-injection of 60 units of heparin/Kg) from 12 patients with a history of sHTG were obtained, and LPL activity was evaluated by a radiometric assay, with and without the addition of activators, such as apolipoproteins (apo) CII and AV. Lipid profile was measured in serum.

Genetic data were available for a subgroup of patients. Genetic variants in LPL and ApoAV were detected in two patients, in whom LPL activity was almost null. Likewise, the increase in LPL activity upon exogenous ApoCII addition in one patient was coincident with the detection of variants in the apoC2 gene. Conclusion: measuring plasma LPL activity in patients with sHTG could be an additional diagnostic tool to detect these familial diseases, especially in patients in whom mutations in the sought-after genes are not detected.

2.11. Lynch-like syndrome and male infertility

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Lynch-like Syndrome (LLS) manifests as a deficiency in DNA mismatch repair (MMR) genes, typically "sporadic but occurring at early ages." However, biallelic germline variants in minichromosome maintenance complex component (MCM)8 have been reported in this pathology. We hypothesized that mutations in MCM8/9 might also affect meiosis in men.

Patients and Methods: A couple, aged 27 and 33, who had consulted for infertility for four years, underwent clinical and laboratory studies at the Gastroenterology Hospital "Dr. C. B. Udaondo."

Results: The woman showed normal results, pending hysterosalpingography. The man, previously diagnosed with rectal cancer-LLS and treated with chemotherapy and immunotherapy for two years, underwent three semen analyses, which revealed severe teratozoospermia (2% normal forms) and germ cell exfoliation above the cutoff value ($1.7 \times 10^6/\text{mL}$).

Conclusion: Although there is significant evidence of spermatogenesis failure, we cannot rule out the iatrogenic effects of cancer treatment as a confounding factor. This hypothesis should be further investigated using molecular biology tools, including complete exome sequencing on DNA from peripheral blood, tumor tissue, and semen samples.

Reference: Golubicki M. *et al.* Comprehensive Genomic Characterization of Fifteen Early-Onset Lynch-Like Syndrome Colorectal Cancers. *Cancers (Basel)*. 2021 Mar 12;13(6):1259.

2.12. Current status and promising pharmaceutical development of coenzyme q10 paediatric formulation

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Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipophilic substance with redox activity found in the lipid bilayer of all cellular membranes. It plays a crucial role in the electron transport chain of mitochondrial respiration, promoting adenosine triphosphate (ATP) production. CoQ10 deficiency, whether primary (associated with mutations in genes that are involved in its biosynthesis) or secondary (more prevalent), leads to neurodegenerative, mitochondrial, and muscular pathologies. Symptoms can include progressive motor degeneration, memory loss, swallowing difficulty, fibromyalgia, cardiovascular disease, and varying degrees intellectual disability, among others. Due to limited expertise in this field, underdiagnosis and misdiagnosis of CoQ10 deficiency, and a lack of accurate data on its incidence, are very common. Treatment with CoQ10 offers significant therapeutic benefits by reversing pathologies and improving patient quality of life especially if started during childhood. CoQ10 is not commercially available in the Argentinian market as a pharmaceutical formulation, except for small-scale manufacturing of solid CoQ10 preparations (capsules or tablets). As paediatric patients have swallowing difficulties, their parents are compelled to disperse the tablet or capsule contents in water for administration. However, due to the insolubility of CoQ10 in water, this practice significantly reduces its bioavailability. Therefore, there is a critical need to develop new pharmaceutical formulations to address the needs of this population. In this context, the objective of our work is to develop and characterize orally disintegrating CoQ10 tablets (ODTs) using direct compression, with appropriate dosing for paediatric pharmacotherapy as a promising alternative due to the lack of pharmaceutical formulations containing CoQ10. ODTs are ideal for paediatric patients or those with swallowing difficulties as they disintegrate in the oral cavity in less than 30 s after placement. In preliminary studies, the interaction between excipients and powder blend and rheological parameters (angle of repose, Carr's index, and Hausner ratio) was evaluated to predict their possible use as mixtures for direct compression. This future development will provide an improved administration, dosing, and consequently, the efficacy of CoQ10 treatment in paediatric patients.

2.13. Beyond the DMD GENE: molecular modifiers that alter disease progression in patients with dystrophinopathy

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There is great variability in the progression of the disease between Duchenne muscular dystrophy (DMD) patients, even affected males with the same alteration lose the ability to walk at very different ages. Recent studies point to different single nucleotide variants (SNVs) as the cause of these phenotypic variations. This work focused on characterizing these genetic modifiers in the Duchenne or Becker muscular dystrophy (DMD/BMD) Argentinian population and validating their prognostic value. Two groups of extreme phenotypes were formed. The first contained 30 patients with loss of ambulation (LoA), ages = 15years (mild phenotype). Previously reported SNVs in Secreted Phosphoprotein 1 (SPP1), Latent Transforming Growth Factor Beta Binding Protein 4 (LTBP4), CD40, and Actinin Alpha 3 (ACTN3) were evaluated using polymerase chain reaction (PCR) followed by Sanger sequencing. The only SNV showing significant differences between groups was ACTN3. These results indicate that the SNV in ACTN3 acts as a modifier of

DMD, whereas the SNVs in the other genes do not. The significance of this analysis lies in elucidating the origins of variability in clinical manifestations among affected individuals. This understanding can improve the design and evaluation of clinical trials, enhance patient prognosis, support personalized treatment strategies, and guide the development of new molecular targets for gene therapy.

2.14. Characterization of genetic alterations in the TANGO2 gene

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The Transport And Golgi Organization 2 Homolog (TANGO2) gene encodes a protein essential for the distribution of secretory proteins to the endoplasmic reticulum. Alterations in TANGO2 cause a rare autosomal recessive disorder affecting approximately 100 individuals worldwide. The first case of TANGO2 deficiency in Argentina was recently reported. Based on this report, we aimed to characterize the molecular alterations in TANGO2 described in the ClinVar database. Pathogenic and likely pathogenic variants reported to date were analyzed, revealing a total of 166 structural variants (> 50 bp) and 30 small variants. Deletion of exons 3-9 was the most frequently observed structural variant and was homozygous in the Argentinian patient. Among the small variants, 23 were substitutions, 6 were deletions, and 1 was a duplication. In conclusion, the majority of molecular alterations in this gene are large rearrangements. Accurate characterization of disease-causing genes is essential for establishing diagnostic guidelines and supporting the development of targeted therapies.

2.15. Molecular diagnosis of partial thyroxine-binding globulin deficiency

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Thyroxine-binding globulin (TBG) is the primary transporter of thyroid hormones. The TBG gene is located on the X chromosome (Xq21-q22), spans 5.5 kb of genomic DNA, and contains 5 exons. TBG defects result in three phenotypes based on serum TBG concentration: complete deficiency (TBG-CD), partial deficiency (TBG-PD), and excess (TBG-E). To date, 54 variants in the TBG gene have been identified and characterized. TBG-PD is the most common phenotype, occurring in 1 in 4,000 newborns. Twelve families with a clinical-biochemical diagnosis of TBG-PD were analyzed. Genomic DNA was isolated, and exons 0-5 of the TBG gene, including flanking intronic regions, were amplified and sequenced. Eight variants were identified (3 missense, 2 nonsense, 1 frameshift, and 2 splicing variants), seven of which were novel: c.520A>T (p.Asn174Tyr), c.622G>A (p.Ala208Thr), c.770T>G (p.Leu257Arg), c.783C>A (p.Tyr261*), c.826C>T (p.Gln276*), c.-18+2delT, and c.-18+6T>C. Pathogenicity prediction and molecular modeling indicated that

these variants are responsible for TBG-PD. Since affected patients are clinically euthyroid but show abnormal thyroid function test results, these findings contribute to improved diagnosis and help avoid unnecessary therapies.

2.16. Role of *Pantoea* spp. as an etiological agent of catheter-associated bloodstream infection

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Pantoea spp. are facultative anaerobic, Gram-negative bacilli of the Enterobacteriaceae family. They are widely distributed in nature, inhabiting plants, water, and soil. Because their biochemical profile is similar to that of closely related genera, misidentification is possible, and their true pathogenic role and clinical impact are often unclear. This study aimed to evaluate the clinical and microbiological characteristics of *Pantoea* spp. isolates associated with bloodstream infections. Eleven blood isolates were analyzed, and clinical information - including underlying disease, predisposing factors, diagnosis, antibiotic treatment, and clinical outcome - was collected from medical records. The patients included 7 men and 4 women, aged 0-72 years. All isolates were broadly sensitive to antibiotics, and catheter-associated bloodstream infection was diagnosed in 9 cases, highlighting *Pantoea* spp. as an emerging pathogen in this setting. Seven patients had solid tumors or onco-hematological neoplasia as underlying conditions. All patients were treated with beta-lactam antibiotics and showed favorable clinical outcomes.

2.17. Characterization of genetic alterations in the TANGO2 gene

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The Transport And Golgi Organization 2 Homolog (TANGO2) gene encodes a protein that plays a fundamental role in the distribution of secretory proteins to the endoplasmic reticulum. Alterations in TANGO2 cause a rare autosomal recessive disease affecting approximately 100 people worldwide. The first case of TANGO2 deficiency in Argentina has been reported. Based on this report, the aim of this study was to characterize the molecular alterations in TANGO2 described in the ClinVar database. To achieve this, all pathogenic and likely pathogenic variants reported to date were analyzed using ClinVar. A total of 166 structural variants (> 50 bp) and 30 small variants were identified. Deletion of exons 3-9 was the most frequent variant and was found in homozygosity in the Argentinian patient. Among the small variants, 23 were substitutions, 6 were deletions, and 1 was a duplication. In conclusion, the majority of molecular alterations in TANGO2 correspond to large rearrangements. Characterizing the gene underlying this pathology is essential for establishing diagnostic guidelines and supporting the development of targeted therapies.

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