ABSTRACTS:

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

Maria T. Acosta, MD, Pediatric Neurologist, NIH-NHGRI-UDP, Bethesda, MD USA

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, free of charge 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 about how to pursue a diagnosis and sometimes therapy.

Since its inception in 2008, the UDP has received more than 6000 applications and has accepted around 30% of those applications; 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 are not solved with standard pipelines, data are reanalyzed and additional bioinformatic tools are employed. Sometimes establishing a molecular diagnosis requires multidisciplinary discussions and creating collaborations with other research groups inside and outside of 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, some illustrative cases that have already been published in fuller 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 around the world.

SII. "Buenos FAIRres": why and how you should apply the FAIR principles to your research project

Claudio Carta, Istituto Superiore di Sanità, Rome, Italy

Every day huge amounts of data is produced from different sources, data that needs to be analysed in order to answer different research questions. Research questions that require, often, access to different resources to be answered. Moreover, data is (i) sparse, (ii) heterogeneous, (iii) collected in different formats and, often, (iv) 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 integrated with data from other resources, requires a great effort in terms of human, economic resources and is time consuming. FAIR is an acronym that means that (meta)data is Findable, Accessible, Interoperable, Reusable for humans and machines and behind this acronym there are fifteen guiding principles.

FAIR data allows you to link data from different resources in compliance with the access restrictions of the data itself. The FAIRification of (meta)data at the source enables to optimize the use of data, thereby reducing costs and time. From the earliest stages of a research project it is necessary to allocate resources for the FAIRification of data which means, for example, staff with specific skills and the development and maintenance of a FAIR infrastructure.FAIR (meta)data allows you to respond quickly, efficiently and unambiguously to research questions complying with access restrictions. FAIR (meta)data optimises data

re-use, reduces data fragmentation and new data/results can be obtained from their integration and re/analysis.

SII. Beyond "One Disease at a Time" Platform Approaches for Rare Disease Gene Therapy/Gene Editing Clinical Trials.

P.J. Brooks, Deputy Director Division of Rare Diseases research Innovation (NCATS, NIH), USA..

Based on current estimates there are approximately 10,000 human diseases. A large fraction of these a monogenic diseases, i.e. they result from mutations in a single gene. Gene-targeted therapies, such as gene therapy, gene editing, and oligonucleotides are therapeutic platforms that are broadly applicable to monogenic diseases. However, the current approach to the clinical development of these technologies is to utilize them as treatments for individual diseases. In practice, the "one disease at a time" approach limits the clinical utility of these therapeutic platforms to the most common monogenic diseases of commercial interest. In my talk, I will discuss collaborative approaches involving NIH funding to support the development of these technologies as therapeutic platforms. Specifically, I will discuss two programs focused on gene therapy (https://pave-gt.ncats.nih.gov/, https://fnih.org/our-programs/AMP/BGTC) and one on gene editing (https://commonfund.nih.gov/editing).

SIII. Genomic Approaches to Undiagnosed Diseases: Lessons from International Collaborations

David R Adams, MD, PhD, Co-Director NIH Undiagnosed Diseases Program, United States

A person with an undiagnosed rare disease may be afflicted by a condition known to medicine but unrecognized, or a new disease. For known rare diseases, long diagnostic delays are well recognized. For new diseases, it is estimated that as few as 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—require the establishment of 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 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. Is only by working together that we will be able to break down the barriers preventing all persons with rare disease from benefiting from the best available knowledge.

SIII. Phase I/II Intravenous AAV9-GLB1 Gene Therapy for GM1 gangliosidosis

Precilla D'Souza[1], Jean Johnston[2], Cristan Farmer[3], Audrey Thurm[3], Anna Crowell[2] Amanda Gross[4], Maria T. Acosta[5], Cynthia J. Tifft[1,2,5]

[1]Office of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]Neurodevelpmental and Behavioral Phenotyping Service, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, [4]Scott Ritchey Research Center, Auburn University, Auburn, AL, [5]NIH Undiagnosed Diseases Program, National Institutes of Health, Bethesda, MD

GM1 gangliosidosis, caused by biallelic mutations in *GLB1* producing 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 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 was 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 activated without any thrombocytopenia and no detection of transgene or anti AAV9- antibody detection on immune modulation regimen. The Clinical Global Impressions Scale (CGI) showed mixed results with infantile onset patients having brief initial improvements followed by deterioration of 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 (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 identical 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 gangliosidosis are durable and promising, (2) that treatment of patients prior to 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.

SIII. Access to CNS rare diseases innovative therapies

Mireia del Toro

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

David A. Pearce1,2,3
1 Sanford Research, 2301 E 60th Street N, Sioux Falls, South Dakota, USA
2 Sanford Health, 2301 E 60th Street N, Sioux Falls, South Dakota, USA
3 Sanford School of Medicine, 1400 W 22 nd St, Sioux Falls, South Dakota, USA
E-mail: david.pearce@sanfordhealth.org

The International Rare Disease Research Consortium, or IRDiRC, is a global consortium of key stakeholders from different facets of rare disease research that together seek to drive advances in diagnostics, therapeutics, and patient outcomes. The consortium facilitates a global and cross-disciplinary exchange of ideas to tackle key issues in rare diseases through the development of recommendations, data standards, tools, and guidelines that harmonizes research efforts and improves efficiency. While IRDiRC has made significant contributions to the development of new therapies and diagnostics since it's founding in 2011, much work remains to alleviate the burden of rare diseases. The consortium has demonstrated it's 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.

KEYWORDS: Rare Disease, patient advocates, orphan drug, clinical research

SIV. Pluto Program (living no one behind).

Anneliene Jonker

SIV. The IRDiRC Drug Repurposing Guidebook: Creating an efficient and visible pathway for rare diseases.

Anneliene Hechtelt Jonker[1,2], Daniel O'Connor[2,3], Michela Gabaldo[2,4], Simon Day[2,5], Martin de Kort[2,6], Heather Stone[2,7], Anna Maria Gerdina Pasmooij[2,8], on behalf of the IRDiRC Drug Repurposing Task Force

1. University of Twente, Enschede,The Netherlands
2. IRDiRC, Paris, France
3. MHRA, London, United Kingdom
4. Evotec, Verona, , Italy
5. Clinical Trials Consulting & Training, North Marston, United Kingdom
6. EATRIS, Amsterdam, The Netherlands
7. FDA, Washington DC, United States
8. CBG, Utrecht, The Netherlands

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 6000-8000 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 but in broad terms, can be considered as developing an existing drug in an indication outside

the scope of the original indication, with the ultimate purpose of obtaining a new regulator-approved indication. Several tools and incentives have been developed to stimulate and ease the approach for repurposing for rare diseases. Nevertheless, the field still sees quite some challenges, such as intellectual property issues, lack of knowledge on regulatory requirements, the need for additional (re)formulation or 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 IRDiRC's Therapies Scientific Committee Task Force, following the previously launched Orphan Drug Development Guidebook. 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 Gannt chart, highlighting the key repurposing activities for each development phase with checklists to consider the necessary steps to be implemented 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 allowing an understanding of the available tools, by asking the developer essential questions at different stages and directing them to the available resources, repurposing for rare diseases can be faster and more efficient, and more aligned with the regulatory processes.
References Jonker, A.H., Day, S. Gabaldo, M., Stone, H. de Kort, M., O'Connor, D.J. and Pasmooij, A.M.G. (2023). IRDiRC Drug Repurposing Guidebook: making better use of existing drugs to tackle rare diseases. NRDD, accepted.

SV. Primary prevention of Rare Diseases and the new One Health vision.

Alberto Mantovani, Former member of Technical Advisory Group – WHO Europe; Vice-President of Study Centre KOS-Science, Art, Society *alberto.mantovani1956@gmail.com*

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 glycemic control in diabetic women). A number of specific community are envisaged, such as promotion of healthy lifestyles, policies for vaccination and toward chronic disorders such as diabetes, regulations on workplace and environmental exposures.

Yet, how to integrate in a consistent plan such a range of actions pertaining to different domains? The One Health (OH) vision can be a powerful tool. The operational definition adopted in 2021 by the four international agencies WHO, FAO, WOAH and UNEP, OH is an integrated and unifying approach: it recognizes that the health of humans, animals, plants (hence food) and the ecosystems, are linked and interdependent. Hence OH involves multiple sectors, disciplines and components of society. A main OH keyword is *complexity*: the OH vision provides a comprehensive "landscape" of a complex issue, allowing to identify either the priority issues and the aspects that might remain overlooked but, nonetheless, should be considered. The "landscape" vision then allows to mobilize the relevant range of skills.

Building-up a primary prevention plan for congenital anomalies is a transdisciplinary enterprise, an ideal field to implement a OH approach. Some examples LAST BUT LEAST UNCERTAINTY.

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

Domenica Taruscio, Former Director National Centre for Rare Diseases, Istituto Superiore di Sanità; ICORD Past-Presiden; President of Study Centre KOS-Science, Art, Society

Newborn screening (NBS), also called neonatal screening, is an important public health action of secondary prevention. NBS identifies shortly after birth pre-symptomatic conditions that can affect a child's long-term health or survival. Thus, early detection, diagnosis, and intervention can prevent death, disability or ameliorate the clinical manifestations of diseases, enabling children to reach their potential for health and well-being.
In Italy during years 2016-2017 a combined legislative framework established a nationwide NBS for more the 45 disorders. Accordingly, the NBS is funded and supported by the Italian National Health System, and

it included within the essential levels of assistance provided by the State. The framework defines the requirements in order to favor the maximum uniformity at national level of the regional implementation of NBS. Under this respect it establishes at the Istituto Superiore di Sanità (ISS) the NBS Coordination Center, coordinated by the director of the ISS, which includes experts and representatives from central and regional institutions as well as three representatives of patient associations. The screening program at regional level is a system articulated into four main functional structures, namely: screening laboratory, laboratory for confirmatory diagnosis, clinical centers, and regional coordination/supervision centre. 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 (wg) coordinated by Ministry of Health, in collaboration with other government agencies and organizations. This working group has also the mission to elaborate an operational protocol including procedures for the management of positive NBS, positive diagnosis and accessing therapies.
In conclusion, the NBS in Italy is an organized and structured program for secondary prevention, funded by the National Health System.

SVI. Rare Diseases in Bulgaria.

Rumen Stefanov

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 that includes patients, families, and medical professionals. Importantly, these services are provided free of charge, ensuring broad accessibility. The center facilitates personalized responses to inquiries with the support of a dedicated team of volunteers and medical consultants. These consultants specialize in a range of disciplines, including genetics, pediatrics, internal diseases, 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. 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 a strong demand for the center's resources.
A milestone in the center's history 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 center’s website has undergone three major updates between 2004 and 2018, reflecting its commitment to evolving and improving its digital resources.
Legislation plays a crucial role in Bulgaria's strategy for managing rare diseases. At national level, the 2009-2013 National Plan for Rare Diseases and Ordinance No. 16 (2014) establish the regulatory framework for the registration of rare diseases and the creation of expert centers and reference networks. At the European Union level, Recommendation 2009/C 151/02 and Directive 2011/24/EU are pivotal. These EU directives focus 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. This commission, situated within the Ministry of Health, includes four representatives from the ministry, seven medical professionals, and two patient representatives. Its functions are comprehensive and multifaceted. The commission is tasked with defining a list of rare diseases, recommending the official designation of centers of expertise, evaluating the activities of the national registry and the designated centers of expertise, 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. It aids in the designation of centers of expertise, management of the national registry for rare diseases, and planning of medical services. The list supports European and international collaboration and is essential for developing tailored rare disease training programs and establishing expert clinical trial sites.
Bulgaria’s comprehensive approach to managing rare diseases underscores the importance of a coordinated effort involving legislation, collaboration, and dedicated support services. The Information

Centre for Rare Diseases and Orphan Drugs at the Institute for rare diseases stands 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.

SVI. Indian Organization for Rare Diseases - Initiatives in India.

Ramaiah Muthyala, Ph.D.President & CEO Indian Organization for Rare Diseases
Professor, University of Minnesota

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 7000 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 equal opportunities to those with common diseases. Its mission is to raise awareness, advocate 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**;** 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 (APIs) are manufactured in India (~450). Historical facts of patient organizations will be highlighted.

SVI. The model for assisting rare diseases developed at Catalunya.
Mireia del Toro

SVI. Initiatives for Rare Diseases in Colombia
Luis Alejandro Barrera MSc.Ph.D

Colombia was the first country in Latin America to issue a law in favor of patients with orphan/rare diseases (HD/RD) and their caregivers, Law 1392 of 2010. It recognizes these diseases as being of special health interest, it states. the creation of a system of negotiation of medicines, of incentives for research, determines the creation of reference centers for diagnosis, treatment and pharmacy, mechanisms of social integration, international cooperation, determines the creation 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 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, currently there are 2,046 which 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 good protection; in fact, the law provides that no benefits can 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, 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 called a disease with a prevalence of less than 1 in 5000. 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 WHA 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 achieve changes in 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.

SVII. Potential therapeutic use of bacterial flavin monooxygenase to trimethylaminuria.
Tatiana Guendulain

SVII. Synthesis and supramolecular study of an amphiphilic compound for the delivery of idebenone
Mario Contin. Argentina.
Idebenone (IDE) is a synthetic compound analogous to coenzyme Q10 (CoQ10), 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 focused on synthesizing a low molecular weight amphiphilic molecule capable of self-aggregating into supramolecular structures that internalize IDE, increasing its apparent solubility.
Electron microscopy and DLS studies were performed, which allowed verifying the existence of two types of suprastructures when the amphiphilic compound is dissolved in water. Molecular dynamics studies were performed 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.

SVII. Current perspectives in the molecular genetic analysis of dystrophinopathies: study of a cohort of 471 patients in Argentina.
Micaela Carcione.

SVII. Familial hyperchylomicronemia syndrome: report of cases in Argentina and importance of the Clinical Biochemistry laboratory for its diagnosis.
Magali Barchuk.

SVII. X-chromosome Inactivation, its impact in female hemophilia expression.
Pamela Radik. Argentina.
X-chromosome inactivation (XCI) represents one of the paradigms of epigenetics, involving typically heritable clonal changes that do not correspond to DNA sequence differences and are inheritable at all levels. XCI leads to massive silencing of one of the two X-chromosomes, balancing dosages 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 XIST (X-inactivation specific transcript), 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 significantly 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 respectively with Hemophilia A (HA) or Hemophilia B (HB). The clinical severity of the condition correlates with the levels of factor activity (FVIII, FIX), categorized as severe hemophilia (FVIII or FIX <1%), moderate (1-5%), or mild (5% to 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 reported increased bleeding tendency in hemophilia carriers (HC). 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 HC may have normal 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 HC 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, while studies in females investigate genetic and epigenetic causes of phenotype expression in affected women.

SVIII. Patient's presentations.

SIX. Education for Rare Diseases in Argentina.

Cesar Crespi. HIEAyC San Juan de Dios de La Plata, CERyD (Centro de Referencia en Enfermedades Raras y de Dificultoso Diagnóstico

Rare Diseases (EPF) are a growing Public Health problem in Argentina. Part of the difficulty around this area is the lack of knowledge of all the disciplines involved in caring for people's health. One of the crucial moments to incorporate EPF detection and management tools is undergraduate university education. The experience of the EPF Chair of the UNLP Faculty of Medicine is shared.

SIX. RIBERSER program for Latin America.

Prof. Dr. Manuel Posada. Full Research Professor. Ex-director of the Rare Diseases Research Institute.

The Spanish Agency for International Development Cooperation (AECID) opened the call for proposals NTERCONECTA 2023 in June 2023. The State Foundation, Health, Childhood and Social Welfare, F.S.P. (CSAI), (Spain) (Inicio - FCSAI), 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 the ccess 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 "RIBERSER Program (Ibero-American Network of Health Experts in Rare Diseases (RIBERSER)") report_Conv23_Resolucion_aprob_program.pdf (aecid.es) was approved in the month of 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 of this year and the second in 2025. The other four activities and they 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 be aimed at the genetic diagnosis of complex cases. The format of this meeting will be as hackathon of undiagnosed rare diseases cases.
• Finally, the programming will close with a final congress to present the results that will be 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 be achieved is to optimize socio-health resources and harmonize policies for the promotion of innovative methods in the area of 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 ALIBER Network, which represents many of the associations and federations of rare diseases in LATAM and the Caribbean; the collaboration of ICORD, an international society with activity in the countries of the project's work area, 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 the majority 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

SX. DUCHENNE MUSCULAR DYSTROPHY: MOLECULAR CONFIRMATION AND ITS IMPACT ON PRECISION MEDICINE.

Florencia Giliberto, Laboratorio de Distrofinopatías, Cátedra de Genética, Facultad de Farmacia y Bioquímica, UBA; Instituto de Inmunología, Genética y Metabolismo (INIGEM, UBACONICET-Hospital de Clínicas ¨José de san Martín¨)

Muscular dystrophies (MDs) comprise a heterogeneous group of over 60 genetic and hereditary diseases that cause progressive muscle degeneration, presenting 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 muscular dystrophy 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 on the study of 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, identifying 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 for providing genetic counseling and determining eligibility for specific treatments within the framework of precision medicine. To achieve molecular diagnosis, we implement a diagnostic algorithm utilizing MLPA, NGS (in silico panels), PCR-Sanger, mRNA studies, and bioinformatics tools. The aim of this work is to present the molecular algorithm used for diagnosing muscular dystrophies 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.

SX. Development of a novel therapeutic strategy for CoQ10 deficient newborns
Cristian Garcia Becerra.

SX. Role of the SLC35A3 transporter in congenital disorders of glycosylation
Luis Bredeston (University of Buenos Aires-CONICET)
Congenital disorders of glycosylation (CDG) comprise a group of inherited human diseases related to 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 the use of massive sequencing and mass spectrometry techniques. 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 SLC35A3 transporter in congenital disorders of glycosylation. 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.

SXI.Rare Diseases in Ecuador: A public health perspective.
Enrique Teran

SXI. Extended newborn screening for rare diseases: the Italian system.
Domenica Taruscio

SXI. Brucella infection affects functionality of decidua stromal cells and trophoblast.
Lucía Zavattieri

SXI. Molecular diagnosis of Thyroid Hormone Resistance Syndrome.
Carina Rivolta