RE(ACT) CONGRESS
IRDIRC CONFERENCE
INTERNATIONAL CONGRESS OF RESEARCH
ON RARE AND ORPHAN DISEASES
MARCH 2023

STAND UP FOR SCIENTIFIC RESEARCH

#RAREVOLUTION
#REACTCONGRESS
#IRDiRC
#EJPRD

TABLE OF CONTENTS

WELCOME

Dear RAREvolutionaries,

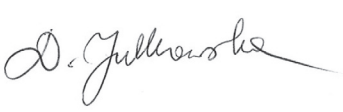
Welcome to the RE(ACT) Congress and IRDiRC Conference 2023; we are excited to host you back in person for the second joint event in the beautiful Berlin city, a superb learning and networking setting.

This joint event will continue the RE(ACT) Congress series (7th edition) and IRDiRC Conference series (5th edition). Over the next few days, a stimulating program awaits with a dedicated, global community of scientists and experts and many opportunities to discuss progress in rare disease research. The overall aim of the joint event is not only to bring together scientific leaders, experts, and young researchers with patients but also to present and promote cutting-edge research on rare and orphan diseases among the general public, industry, and policymakers – all with the ultimate goal of enhancing the rapid delivery of new and promising diagnostics and therapies to patients all around the world.

The RE(ACT) Congress – International Congress of Research on Rare and Orphan Diseases – was initiated in 2012 by the BLACKSWAN Foundation to create a forum for and promote scientific cooperation and research on rare and orphan diseases. IRDiRC – launched in April 2011 as an initiative of the European Commission and the US National Institutes of Health – fosters international collaboration on rare disease research by bringing together researchers, funders, and patient advocacy organizations that work collaboratively within a multinational consortium. The European Joint Programme on Rare Diseases, co-financed by the European Commission and participating countries, aims at structuring and strengthening the rare diseases research ecosystem by providing the necessary funding, tools, and support by building the capacity of rare diseases stakeholders and empowering people living with rare diseases.

Thank you in advance for your active participation in the discussions and events over the coming days, and on behalf of the organizers, we hope you will enjoy your time in Berlin.

Dr. Olivier Menzel
Chairman and founder
BLACKSWAN Foundation



Dr. Daria Julkowska
Coordinator
EJP RD

Pr. David Pearce
Consortium Assembly Chair
IRDiRC

THE INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDIRC)

With the challenging vision to enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention, the International Rare Diseases Research Consortium (IRDiRC) unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical, biotech, and MedTech enterprises), umbrella patient advocacy organizations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide. IRDiRC's reach is global, with stakeholders from Africa, Asia, Australia, North America, Latin America, and Europe. IRDiRC has three Constituent Committees (Funders, Companies, and Patient Advocates) composed of one representative per each of its 60+ Member Organizations and four Scientific Committees (Diagnostics, Therapies, Regulatory, and Interdisciplinary) composed of approximately 15 members in each Committee, with balanced expertise and geographical representation. All Committees collaborate to identify common roadblocks, gaps and priorities, and propose actionable projects specific to their constituency space and scientific areas that will advance rare disease research and bring IRDiRC closer to its goals. Through dedicated Task Forces and Working Groups, IRDiRC has addressed specific topics within rare diseases research and proposed solutions through policy recommendations and technical applications.

irdirc.org
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#IRDiRC

THE EUROPEAN JOINT PROGRAMME ON RARE DISEASES (EJP RD)

The European Joint Programme on Rare Diseases (EJP RD), launched in January 2019, brings together the resources in rare diseases (RD) research at the national and European level. It assembles funders, universities, research organisations and infrastructures, hospitals, and patient organisations, including the 24 European Reference Networks, representing over 130 institutions across 35 countries. Jointly funded by the European Commission (EC) and Member States over five years, its purpose is to create a comprehensive and sustainable ecosystem for RD research. The two main objectives of EJP RD are to improve the integration, efficacy, production, and social impact of research on RDs, and secondly to implement an efficient model of financial support for all types of RDs research.

The EJP RD financed (1) 64 multinational projects for € 83,5 million, including € 10 millions from EC through four Joint Transnational Calls focusing on acceleration of diagnosis, disease progression, RD mechanisms , effective therapies, social sciences and humanities; (2) three RD Research Challenges projects focusing on public-private collaboration to develop therapeutic solutions; (3) 45 networking events supporting knowledge sharing; (4) 3 demonstration and 2 innovation projects for RD clinical trials innovative methodologies; (5) 91 fellowships for young clinicians and 28 transversal workshops for ERNs .

The new functionalities Virtual Platform (VP) (e.g., search through rare diseases hierarchies, search by genes) are being deployed for the release of VP version-1 within the next couple of months. RD resources and tools continue to be optimized and developed to serve RD research. Some resources have already been connected to the Virtual Platform Network through EJP RD set of solution; the onboarding for other resources continues. 110 RD biological pathways are created and exploited through bioinformatic networks with multiomics data to accelerate RD diagnosis. The relating multi-omics analysis workflows are being made ready to be provided through the VP for reuse and reproducibility (e.g., analysis workflow for the Congenital Anomalies of the Kidney and Urinary Tract).

Thirty-seven training activities and two MOOC were delivered to nearly 2800 stakeholders including EU 13 countries.

Multinational RD clinical trials and innovation management support services were implemented through European research infrastructures, supporting 21 clinical trials requests, 49 research projects for translational mentoring. The Innovation Management Toolbox empowers researchers to conduct rigorous translational research has been released.

EJP RD is working on the sustainability of its activities and the generated results including the roadmap towards the future Rare Diseases Partnership.

ejprarediseases.org
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#EJPRD

BLACKSWAN FOUNDATION

The BLACKSWAN Foundation (BSF) is a not-for-profit organization based in Switzerland and created in 2010 to contribute to the development of research on rare and orphan diseases worldwide. Its principal mission is to encourage therapeutic research and to promote information campaigns for a better public understanding of rare conditions.
The Foundation supports rare diseases as a whole to leverage impact, considers the complexity and hurdles of rare disease research, and helps find new solutions that can assist a large variety of projects. Innovation and digital communication are fundamental for BSF and represent a way to improve the effectiveness of its work and empower community participation in existing best practices.
BSF has directly supported research projects on rare diseases through donations to public research institutes. In 2012, the Board of the Foundation also had the idea to promote more sustainable use of financial resources and started focusing its activities on developing tools that support the scientific community's work.
BSF launched the RE(ACT) Initiative in this optic, a project to increase international scientific cooperation and knowledge sharing. As part of this initiative, the RE(ACT) Congress, an international scientific conference with a vast potential to connect researchers working in the field of rare diseases that allows researchers to learn about recent advances in the area, share knowledge and promote their projects, foster new collaborations and inspire new ideas.
Cooperation with partner organizations and stakeholders is of utmost importance for the Foundation, which collaborates with national and international patient organizations, academic institutions, research consortia, and centers of expertise.
The BLACKSWAN Foundation is represented by its multi-talented Board of Trustees and advised by its Scientific Advisory Board (SAB). The Board includes experts from various disciplines, including drug development, marketing, cooperation, and the health sciences. The SAB comprises world-leading researchers from Switzerland, Australia, Belgium, France, Italy, and the US.
The Foundation is officially inscribed in the Swiss commercial register and recognized as a public utility foundation; the competent authority (Swiss Federal Department of Home Affairs - FDHA) supervises it.

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NOTES

KEY FACTS

Scientific advisory board:
Scientific Advisory Board of the BLACKSWAN Foundation
European Joint Programme on Rare Diseases (EJP RD)
The International Rare Diseases Research Consortium (IRDiRC)

Organizing committee (alphabetical order):
Thomas Amiconi, Amiconi Consulting SA, CH
Daria Julkowska, EJP RD, FR
Olivier Menzel, BLACKSWAN Foundation, CH
David Pearce, IRDiRC, USA

Venue
The Meliá Berlin is located in the heart of the German capital, at the corner Friedrichstrasse and Am Weidendamm, next to river Spree. Just a few minutes walk from a choice of monuments and tourist attractions: Brandenburg Gate, Museums Island, the Nikolai Quarter and Alexanderplatz, as well as the government district. Near the subway and train station Friedrichstrasse and only 8 and 23 km from the Berlin airports.

Congress Initiator
BLACKSWAN Foundation
Chemin de la Riaz 11
CH-1418 Vuarrens
blackswanfoundation.ch

Congress Organizers
BLACKSWAN Foundation
IRDiRC, International Rare Diseases Research Consortium
EJP RD, European Joint Program Rare Diseases

Congress partners
RDI – Rare Diseases International (global alliance of people living with a rare disease).

Professional Congress organizer
Amiconi Consulting is an internationally recognized Company, which, thanks to its experience, professionalism and dynamism, is equipped to find efficient and innovative solutions for the organization of Conventions, Meetings, Incentive Travel Programs, Tours, Seminars, Meetings, Product Launches and Events. The Company performs at the regional, national and international level, provides a wide range of services from general advice to highly focused solutions.

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Important information for speakers
We kindly ask the speakers to submit their presentation to the people in charge of the technic at least two hours before their talk.
Speakers presenting in the morning session of the day should submit their presentations the evening before so as to avoid the "mad-rush" in the early morning.
Only presentation saved on a data medium such as a USB stick will be approved. Please note that is not possible to use your own laptop.
Presentation should be created in Microsoft PowerPoint, Keynote or PDF. Furthermore, please use standard fonts of Windows. To facilitate allocation, please create a respective folder on your storage medium including your presentation (e.g. RE(ACT) 2023_Speaker's name_Session).
To avoid missing links to video files, we kindly ask the presenters either to use the "pack for CD" function in PowerPoint or provide all clips used in the presentation in an additional folder on the CD or on the flash drive.

Important information for abstract presenters
We kindly ask all poster presenters to meet the following guidelines:
The size of your poster should not exceed DIN Format A0 Portrait - 841 mm wide and 1189 mm height. Bonding material is provided in the poster area.
– Posters may be set up on 15th March from 12h30.
– Posters should be removed on 18th March.
– Poster which have not been removed after this time will be discarded. Please note that the posters and others material will not be sent to you after the conference.

Posters
Please be present in front of your poster during the poster sessions dedicated to your topic.

Disclaimer:
Biographies and abstracts are printed as received by the authors

TIME TABLE

WEDNESDAY, MARCH 15th

Registration desk opens at 12h30

Session A, 13:30 to 17:00 **"Diagnostic, WGS, artificial intelligence, new technologies"**

Coffee break: 15:30 to 16

POSTER SESSION A, 17 to 18

Opening Ceremony 18 to 19h30

THURSDAY, MARCH 16th

Session B, 9 to 12, **"Therapeutic Development, innovative clinical trials, precision medicine"**

Coffee break: 10:30 to 11

LUNCH & POSTER SESSION B & C 12 to 13:30

Session C, 13:30 to 17, **"Regulatory science"**

Coffee break: 15 to 15h30

FRIDAY, MARCH 17th

Session D, 9 to 12, **"Clinical research"**

Coffee break: 10:30 to 11

LUNCH & POSTER SESSION D, E & F 12 to 13

Session E, 13 to 17, **"Gene and cell therapy"**

Coffee break: 15 to 15h30

SATURDAY, MARCH 18th

Session F, 9 to 12h30, **"Systems thinking towards access"**

Coffee break: 10:30 to 11

FULL PROGRAM

WEDNESDAY, MARCH 15th

Registration desk opens at 12:00

Session A, 13:30 to 17:00 **"Diagnostic, WGS, artificial intelligence, new technologies"**

- Martina Cornel, NL "Sequencing for early diagnosis in neonatal screening and health care"
- Julia Foreman, UK "DECIPHER – Enabling the sharing of rare disease phenotype-linked variant data for diagnosis and research"
- Clara van Karnebeek, NL "A 'negative' exome – what's next?"
- Pierre-Emmanuel Gleizes, FR "A European network to identify and diagnose ribosomopathies"
- Tudor Groza, UK "Rare disease patient stratification in primary care: Challenges and opportunities"
- Kym Boycott, CAN "Strategic approaches to reduce the diagnostic odyssey"
- Elena Rojano, ES (Abstract A010) "PhenoClinWare: a webserver to explore human pathological phenotypes and expand patient clinical characterization"
- Klary Niezen-Koning, NL (Abstract A003) "A Case database for inherited metabolic diseases as a global, shared educational resource"

POSTER SESSION A 17 to 18

Opening Ceremony 18 to 19h30

Welcome messages
- Daria Julkowska (EJP RD)
- David Pierce (IRDiRC)
- Olivier Menzel (BLACKSWAN Foundation)

Keynote presentation
- Ruxandra Draghia-Akli, USA
- Gareth Baynam, AU "The Rare Care Centre"

Session B, 9 to 12, **"Therapeutic Development, innovative clinical trials, precision medicine"**

- Marc Dooms, BE & Anneliene Jonker, NL « Devise – ways forward for medical devices for rare diseases »
- Tim Buckinx, BE « The Potential of Wearable EEG & Real-Time AI to Externalize Brain States in Rare and Orphan Diseases: A Disruptive Vision to Improving Lives using Technologies of Today »
- Lucia Pannese, IT « Why Me? Tackling the Challenge of Rare Diseases through Gamification and Enabling Technologies »
- Jose-Alain Sahel, USA « Developing Gene-Independent Approaches for Retinal Dystrophies »
- Paulien Klap, NL « Developing an arm exoskeleton with the Duchenne Muscular Dystrophy community »

LUNCH & POSTER SESSION B & C 12 to 13:30

Session C, 13:30 to 17, "**Regulatory science"**

- Daniel O'Connor, UK « Evolving regulatory science for rare diseases »
- Anne Pariser, USA "Regulatory opportunities: Facilitating an environment of innovation"
- Kerry Jo Lee, USA « FDA's Center for Drug Evaluation and Research (CDER): Considerations in Rare Disease Drug Development and How CDER is Accelerating Rare Disease Treatments »
- Violeta Stoyanova-Beninska, NL « Innovation in Rare Disease Drug Development – early dialogue with the EU regulators »
- Julienne Vaillancourt, USA « FDA's Center for Biologics Evaluation and Research: Advancing Development of Novel Biologics for Rare Diseases »
- Terence Beghyn, FR (Abstract B008) "Zellweger Spectrum Disorder : individualized research delivered new hopes for patients with PEX deficiency"
- Yustina Puspitasari, CH (Abstract B006) "Arterial thrombosis in Hutchinson Gilford Progeria Syndrome"
- Marjon Pasmooij, NL (Abstract C001) "Centralized and up-to-date data on orphan drugs: the European Medicines Regulatory Database"

FRIDAY, MARCH 17th

Session D, 9 to 12, **"Clinical researc"**

- Marta Alarcón-Riquelme, ES « Heterogeneity of autoimmunity, clinical implications »
- Isabella Batsu, USA « Innovative clinical trial designs for rare diseases »
- PJ Brooks, USA « Beyond "One disease at a time": Focusing on common molecular etiologies to accelerate rare clinical trial access »
- Andrea Gropman, USA « From biomarker to study to basket clinical trials. Advancing science from the bedside or bench to trials: two models in academia »
- Sunil Rodger, DE (Abstract D001) "The Care and Trial Site Registry: FAIRification of an online database of clinical sites and their facilities"

LUNCH & POSTER SESSION D, E & F 12 to 13:30

Session E, 13:30 to 17, **"Gene and cell therapy"**

- Guillaume Canaud, FR « Targeted therapy for patients with PIK3CA-related overgrowth spectrum »
- Arjan Lankester, NL « Lentiviral gene therapy in RAG1 severe combined immunodeficiency: experience from the multicenter RECOMB trial »
- Fernardo Larcher, ES « Advances in cell and gene therapy for genodermatoses. A focus in Epidermolysis Bullosa. »
- Carl Morris, USA « AAV-mediated gene therapy in Duchenne Muscular Dystrophy – Efficacy and immune responses »
- Julia Vitarello, USA From Mila to Millions: Opportunities for Individualized Medicines »
- Federica Tiberio, IT (Abstract E001) "In vitro development of a customized noninvasive nanoparticle-mediated gene knockdown approach for Crouzon syndrome"

SATURDAY, MARCH 18th

Session F, 9 to 12:30, **selected oral presentations and "Systems thinking towards access"**

- Mary Wang, IT « Operational Description of Rare Diseases – A reference to improve the recognition and visibility of rare diseases »
- Samuel Agyei Wiafe, Ghana « Addressing the Unmet needs of persons living with Undiagnosed and Rare Diseases in Ghana »
- Yarlalu Thomas, AU « Lyfe Languages »
- Stefano Benvenuti, IT « Ensuring access to life-saving gene therapy for an ultra-rare disease: a not-for-profit model »
- Rachel Yang, CN
- Anne Parkinson, AUS "(Abstract F003) Delayed diagnosis in three rare diseases: a qualitative study of the experiences of people with myositis, sarcoidosis, and primary immune deficiency in Australia"

SPEAKERS' BIOGRAPHIES

AGYEI WIAFE SAMUEL

Founder/Executive Director, Rare Disease Ghana Initiative
Samuel Agyei Wiafe is a Clinical Psychologist; Founder/Executive Director of Rare Disease Ghana Initiative. After running into a family with an undiagnosed syndrome, he immediately had clear what the impact of these diseases can be on the people affected and those close to them, as well as the incredible challenge they pose for the entire health care system. And so, in a country – such as Ghana – where it is difficult to access specialized multidisciplinary health services and access to treatment, where living with an undiagnosed and rare disease can be challenging; Samuel Wiafe established the Rare Diseases Ghana Initiative (RDGI) as
the National Non-Governmental Advocacy Organization serving as the voice and coordinating care for undiagnosed, genetic and rare diseases in Ghana. Samuel is a change maker who believes in equity and inclusion of all in all aspect of the society. He has received training in MPS Disorders, Fabry & Gaucher and other Metabolic Disorders from FYMCA Medicals LTD and serves as an Advisor on the African Taskforce for Rare Diseases. Samuel is a selective participant in the 4th International Summit in Human Genetics and Genomics held at the National Institute of Health by the National Human Genome Research Institute (NHGRI). He is a member and Co-chair of the Developing Nations Committee of the Undiagnosed Disease Network International (UDNI) and a member of the Panel of Experts from the WHO Collaborative Global Network for Rare Diseases. Samuel a member and the Vice-chair of the Patient Advocacy Constituent Committee (PACC) of the International Rare Disease Research Consortium (IRDiRC).

ALARCÓN RIQUELME MARTA

My background in Medicine, Immunology, and Genetics make a unique combination and provide me with the tools I need to carry out this project successfully. For over 20 years of my research career, I have focused on the identification of the genetic basis of SLE as a first building block toward understanding how such genes lead to cellular abnormalities that eventually lead to clinical disease. In this context, animal models provide possibilities where human studies have limitations. The main goal of my research is to understand the mechanisms behind disease pathogenesis, identify new biomarkers for disease, find new therapeutic targets, understand the mechanisms of response and non-response to therapies, and define the heterogeneity of SLE. I am totally committed to the work for lupus and other autoimmune diseases, and I believe that only through careful longitudinal analysis of the patients, and proper molecular analyses, will we be able to understand this disease. I am focusing importantly on systems biology approaches, -omics data integration and clustering, scRNASeq, and other omics methods and bioinformatics approaches to the understanding of SLE.
With the advent of genome-wide association arrays and the creation of the SLEGEN consortium, new possibilities opened for the study of the genetics of lupus and the identification of genes for the disease. As a founder member of SLEGEN, I participated in the GWAS that identified several new genes, but also had an independent study that allowed my identification of BANK1, and participated in the identification of ITGAM. These papers were all published in the same issue of Nat Genet. In collaboration with Tim Vyse and John Rioux we embarked on a larger GWAS in Europeans that resulted in a top publication in

Nat Genet and we have done the same by publishing the first GWAS in the Hispanic admixed population focusing on the Native American ancestry. More recently our transancestral immunochip study was published. Recently, I focused on rare variants: through exome sequencing of families with multiple cases of lupus, and using very stringent imputation approaches and aggregate analyses to identify candidate genes.
From here, my work has derived from the use of genomics methods for the reclassification of systemic autoimmune diseases and systems biology approaches with the idea that autoimmune diseases are a clinical constellation of the same or nearly similar disease processes. Our most recent publications point towards those approaches by creating software and performing analyses of gene expression data to identify drug targets and learning systems medicine methods for clustering patients. Our first work focuses on lupus, but is planned to extend to other related autoimmune diseases. As PI of the PRECISESADS project, a high degree of coordination has been necessary. In this role, I have acquired enormous experience in the organization of large projects and recruitment of patients, most recent ethical rules. I have also acquired learning on the subject of machine learning bioinformatic methods, clustering and classification of autoimmune diseases, and QTL analyses across autoimmune diseases.
A second path relates to the use of animal models for testing potential new drug targets, new genes, and specific hypotheses. We have now obtained extensive experience in such models and are defining those that may be more effective in testing given systems. We have focused on TLR7 due to the importance of this pathway in autoimmunity and in the genes we have studied, such as BANK1. We have also used biochemistry to understand the function of BANK1.

BATSU ISABELA

Isabela is the Global Project Head for the clinical development of the GM2 Gangliosidoses and Gaucher Disease programs at Sanofi devoted to chasing the miracles of science to improve people's lives. As a dynamic and passionate leader in rare diseases, Isabela is responsible in building cross-functional teams to optimize development, execution and maximize efficiencies for clinical trials to ultimately provide disease modifying care to patients with rare diseases.
Isabela received her medical degree from the Carol Davila University of Medicine and Pharmacy in Bucharest, Romania. After spending several years in occupational health, she joined Sanofi and has been providing transformative therapeutic options to individuals with various cancers, cardiovascular diseases, and rare diseases for over two decades. She has co-authored several publications and has been an invited participant on several Think Tank meetings with the Food and Drug Association, National Institute of Health, and several academic institutions.

BAYNAM GARETH

Gareth Baynam is a the Medical Director of the Rare Care Centre at Perth Children's Hospital in WA, a clinical geneticist, intrapraneur and clinician scientist. Gareth equitably translates innovations focussed to unmet rare diseases (RD) need, including through public and public- private partnerships, locally and internationally. He has led the clinical implementation of

genomic and phenomic technologies (including 3D facial analysis and Ai enabled electronic health record tools). CI Baynam led the creation of the Rare and Undiagnosed Diseases Diagnostic Service at Genetic Services of Western Australia, he founded and Directs the Undiagnosed Diseases Program WA and was a founding member of the International Board of Directors of the Undiagnosed Diseases Network International and is a co-Lead of the Undiagnosed Diseases Network Australia. CI Baynam led the creation of the Rare and Undiagnosed Diseases Diagnostic Service at Genetic Services of Western Australia, he founded and Directs the Undiagnosed Diseases Program WA and was a founding member of the International Board of Directors of the Undiagnosed Diseases Network International and is a co-Lead of the Undiagnosed Diseases Network Australia. CI Baynam is the Chair of the Interdisciplinary Scientific Committee of the International Rare Diseases Research Consortium and previous Chair of the Diagnostics Scientific Committee. Gareth founded and leads a 3D facial analysis translational research group, focussed to RD, that has implemented tools in state-wide care; and leads the Lyfe Languages project to globally improve diagnosis and care for Indigenous people with RD. He is the Head of the Western Australian Register of Developmental Anomalies (Birth Defects and Cerebral Palsy Registers) and is a Member of the WA Ministerial Council for Precision Health and Co-Chaired the Standards of Practice for the Global Commission to End the Diagnostic Odyssey for Children with RD.

BENVENUTI STEFANO

Stefano Benvenuti is Head of Public Affairs at Fondazione Telethon (Italy) since 2021. He represents Fondazione Telethon in the International Consortium for Personalized Medicine (ICPerMed) and in the International Rare Diseases Research Consortium (IRDiRC). He co-chairs the ICPerMed Working Group on Health Economic Value of Personalised Medicine Approaches and represents Fondazione Telethon in the Executive Committee of the European Joint Programme on Rare Disease (EJP-RD https://www.ejprarediseases.org/). He is also member of the Italian National Committee on Rare Disease.

After graduating in International Cooperation for Development at the University of Bologna in 2007 he started as a consultant project manager of EU funded projects. In 2010 he joined the healthcare department of Regione Veneto working as EU project specialist where he contributed to re-design the regional system of participation in EU funded programs. During this period he also completed a master degree in Health Technology Assessment at Università Cattolica in Rome.

Being an experienced manager of EU funded project and an expert of EU research policy, he joined Fondazione Telethon in 2016 to set-up the EU affairs office and coordinate the participation of Fondazione Telethon in European and International initiatives. In 2018 he took the role of Global Partnership Manager.

At Fondazione Telethon he currently coordinates the project "Sequencing of newborn genome: feasibility and clinical, ethical, psychological and economic implications" co-funded by the Lombardy Region.

BOYCOTT KYM

Kym Boycott is a Professor of Pediatrics at the University of Ottawa in Canada, where she is a Clinical Geneticist at the Children's Hospital of Eastern Ontario (CHEO), Chair of the

Department of Genetics, and a Senior Scientist at the CHEO Research Institute. Dr. Boycott is a Tier 1 Canada Research Chair in Rare Disease Precision Health whose research program bridges clinical genomics to basic research and is focused on understanding the molecular pathogenesis of rare diseases to improve patient care and family well-being. She leads the national Care4Rare Canada Consortium integrating genomic and other –omic technologies to improve our understanding of rare disease, with a particular focus on solving the unsolved and most difficult rare diseases. To leverage these discoveries, she co-leads the Canadian Rare Diseases: Models & Mechanisms Network, established to catalyze connections between newly discovered rare disease genes and basic scientists who can rapidly study them in model systems. Globally, she moves the rare disease agenda forward as part of the Global Commission to End the Diagnostic Odyssey for Children.

BROOKS PHILIP JOHN (P.J.)

Philip J. (P.J.) Brooks is the acting director of NCATS' Division of Rare Diseases Research Innovation. Brooks represents NCATS in the NIH-wide Gene Therapy Working Group, the Regenerative Medicine Innovation Project and the International Rare Diseases Research Consortium (IRDiRC). He also is the working group co-coordinator for the NIH Common Fund program on Somatic Cell Genome Editing, one of the leaders of the Platform Vector Gene Therapy (PaVe-GT) pilot project and the co-chair of the Bespoke Gene Therapy Consortium.

In May 2022, Brooks was selected as the recipient of the 2022 Sonia Skarlatos Public Service Award by the American Society of Gene & Cell Therapy for consistently fostering and enhancing the field of gene and cell therapy.

Brooks received his doctorate in neurobiology from The University of North Carolina at Chapel Hill. After completing a postdoctoral fellowship at The Rockefeller University, he became an investigator in the NIH intramural program, where he developed an internationally recognized research program focused on two distinct areas: the molecular basis of alcohol-related cancer, and rare neurologic diseases resulting from defective DNA repair, including xeroderma pigmentosum, Cockayne syndrome and Fanconi anemia.

BUCKINX TIM

Tim Buckinx is the founder and CEO of epihunter. Tim has a professional background in global digital strategy leadership and is the father of a son with ring chromosome 20 syndrome, a type of rare refractory epilepsy. In 2015, his son, at that moment 10 years old, asked Tim « Papa, you work in digital, can't you create a light that turns on when my brain switches off? » This pain became a vision, and this vision became the pioneering digital therapeutics company epihunter. Their solutions apply real-time AI to third-party wearable EEG for real-time digital interventions reducing the conditions' daily life impact while generating real-world data for better diagnosis, treatment, and new therapies. The company has already created, clinically validated, and is commercializing a beachhead for absence epilepsy in Europe & Australasia and is now setting up co-development collaborations for a future product pipeline of 15 products in epilepsy and 4 other major brain disorders.

CANAUD GUILLAUME

Guillaume Canaud is a MD, PhD working at hôpital Necker Enfants Malades (Paris). He did his medical school in Montpellier and moved to Paris in 2002 to perform his Residency in Nephrology (2002 to 2007). He became Senior Resident in the Renal Division of Necker (Prof. Legendre) from 2007 to 2012. Concurrently, he spent four years from to 2008 to 2012 in the laboratory of Dr. Fabiola Terzi (INSERM U1151, Necker Hospital) to achieve his PhD degree in molecular and cellular biology. Then, he joined the Joseph Bonventre's Laboratory (Harvard Medical School, Boston, USA) from 2012 to 2014 to achieve a postdoc. He came back to Christophe Legendre's team with a Faculty position (Associate Professor) and built his own group of research dedicated to translational medicine. He obtained an European Research Council starting grant (2015) for his kidney research project, an ERC Proof of Concept Grant for his translational research (2016) and an ERC Consolidator (2020) dedicated to the understanding of PIK3CA related disorders. Guillaume is now full professor at the Université Paris Cité /Hôpital Necker Enfants Malades and is working specifically on rare disorders involving the RAS/PIK3CA/AKT/mTOR pathways.
Very recently, Guillaume and his group, identified and reported in Nature a very promising therapeutic for patients with a rare genetic disorder called PIK3CA-Related Overgrowth Syndrome (PROS). Guillaume and his group pushed the clinical development of this drug for patient with PROS. Three clinical trials were launched since 2019 and led to the US FDA accelerated approval on April 6th 2022 of alpelisib for patients with PROS aged of at least 2 years old.
He published as a first or last author in top leading medical and scientific journals such as Nature, The New England Journal of Medicine, Nature Medicine, Science Translational Medicine or Proceedings of the National Academy of Sciences USA. He received several awards including the 2018 Prize Jean Lecocq of the French Academy of Sciences, the 2019 Prize Eloi Collery of the French Academy of Medicine, the 2019 Ville de Paris Jean Hamburger Prize, the 2021 Unsolicited International Triennial Gagna A. & Ch. Van Heck Prize for Incurable Diseases and the 2022 Robert Schobinger Award from the International Society for the Study of Vascular Anomalies..

CORNEL C. MARTINA

Martina Cornel, M.D, Ph.D. (1959) is professor of Community Genetics and Public Health Genomics at the Amsterdam University Medical Center. She is a physician and epidemiologist. Since 2000, she has mainly been working on the responsible implementation of genetic testing & screening.
She is the former chair of the Public and Professional Policy Committee (PPPC), of the European Society of Human Genetics (ESHG), which developed, amongst others, recommendations on whole genome sequencing in health care (Van El et al., 2013), responsible implementation of expanded carrier screening(Henneman et al., 2017) and postmortem genetic testing after sudden cardiac death (Fellmann et al., 2019).
She is a member of the Netherlands Health Council and of its standing Committee on Population Screening and its Council Group. She is chair of the Netherlands Program Committee Neonatal Heelprick Screening.

CAULFIELD MARK

Mark Caulfield graduated in Medicine in 1984 from the London Hospital Medical College and trained in Clinical Pharmacology at St Bartholomew's Hospital where he developed a research programme in molecular genetics of hypertension, which has discovered over 1000 gene loci for blood pressure. He served on the NICE Guideline Group for hypertension and was President of the British Hypertension Society (2009-2011).
He was appointed Director of the William Harvey Research Institute in 2002 and was elected a Fellow of the Academy of Medical Sciences in 2008. He led on fundraising towards the £25m William Harvey Heart Centre which created a translational clinical research centre. Since 2008 he directs the National Institute for Health Research Cardiovascular Biomedical Research Unit and Centre at Barts. Between 2010 and 2015 he co-led the merger of three hospitals in North London to create the new £400 million Barts Heart Centre which provides 80,000 cardiovascular patient episodes.
He has won the Lily Prize of the British Pharmacology Society, the Bjorn Folkow Award of the European Society of Hypertension 2016 and the Franz Volhard Award of the International Society of Hypertension in 2018.
In 2013 he became an NIHR Senior Investigator and was appointed as the Chief Scientist for Genomics England (100,000 Genomes Project). He was appointed Interim Chief Executive Officer for Genomics England from January to September 2019. Sir Mark was awarded a Knighthood in the June 2019 Queen's Birthday Honours List for services to the 100,000 Genomes Project.

DOOMS MARC

Mr. Dooms (Pharm D) is Senior Orphan Drug Pharmacist at the University Hospitals Leuven. He is compounding/dispensing pharmacist in First in Men Randomized Clinical Trials. He has been a member of the Belgian Order of Pharmaceutical Sciences and the Flemish Society of Hospital Pharmacists (VZA) since 1975 and the Belgian representative to the European Union of Experts in Rare Diseases with frequent collaboration with Orphanet, the European Society of Clinical Pharmacy, and the American Society of Health Care Pharmacists, among others, since 2000.
Marc Dooms received his pharmacist diploma at the Catholic University of Leuven, where he graduated in 1973. In 1974, he was pharmacy teaching studies certificated at the Catholic University of Leuven, and in 1975 pursued an internship in Clinical Pharmacy at St John's University and Columbia University, New York, with a special interest in orphan drugs, compounding of topical therapy and First in Men randomized clinical trials.
Mr. Dooms is founding member of the Belgian National Board on Orphan Drugs within the King Baudouin Foundation and is a graduate-level teacher in dermatological compounding, drug adherence, and orphan drugs, since 2010. He is also teaching pharmaceutical technicians at Leuven Syntra School. He has co-authored a number of publications on orphan drugs.

DRAGHIA-AKLI RUXANDRA

Ruxandra Draghia-Akli, is Global Head, Johnson & Johnson Global Public Health R&D, where her and her team advance global public health into the next era of innovation through discovery, development, and technology capabilities. She accelerates GPH's end-to-end strategy by collaborating with teams across Johnson & Johnson on assets with application in global public health settings. Under her leadership, GPH R&D adds value and generates new external innovation opportunities through our J&J Centers for Global Health Discovery and other external partnerships.

Ruxandra is a cross-sector leader with experience in industry, government, and academia. She led Medical and Scientific Affairs for vaccines at Merck, and she worked for the European Commission, first as Director and later as Deputy Director General, overseeing research and innovation programmatic initiatives, leading public-private partnerships, global programs and consortia, and development of novel research financial instruments, while contributing to the Commission's strategy for improving public health. Ruxandra has a track record of unlocking innovation in biotechnology as both a founder and head of research at ADViSYS, Inc. and VGX Pharmaceuticals (now Inovio Pharmaceuticals).

Ruxandra holds a M.D. from Carol Davila University, Romania, and a Ph.D. in human genetics from the Romanian Academy of Medical Sciences. She undertook doctoral training at University Rene Descartes in Paris, France and a postdoctoral training at Baylor College of Medicine, Houston, Texas, with a focus on rare diseases, molecular biology, gene therapy and novel vaccines. Ruxandra has authored and co- authored more than 100 papers and holds over 100 patents.

FOREMAN JULIA

Julia is Project Manager for DECIPHER, an international web-based platform that shares anonymised genetic and phenotypic data from rare disease patients and provides variant interpretation interfaces. DECIPHER helps clinical and research teams to assess the pathogenicity of variants and to share patient data, which is key to discovery and diagnosis. The platform is under continual development and enables the transition of new datasets and tools developed by the research community into clinic. Julia has been DECIPHER Project Manager for six years, using her molecular biology and genetics expertise to grow and develop the platform.

Julia's undergraduate degree was in Molecular Biology and Genetics, before she studied for a PhD in the genetic and molecular analysis of root hair growth in the model plant Arabidopsis thaliana at the John Innes Centre, Norwich. After several years in academic research at the University of Edinburgh she began coordinating a multi-disciplinary multi centred systems biology project investigating the impact of temperature on the signalling properties of a defined network. Julia transitioned to Human Genetics in 2015, joining the Wellcome Sanger Institute to coordinate projects involved with exploring patterns of mutations that arise in human cells to understand how DNA damage and repair processes contribute towards aging and cancer, before taking up her current role on DECIPHER in 2016.

GLEIZES PIERRE-EMMANUEL

Pierre-Emmanuel Gleizes is professor of cell biology at the University of Toulouse, France, and group leader at the Center for Integrative Biology (CBI; cbi-toulouse.fr/eng/). His work focuses on the mechanisms of ribosome biogenesis in human cells and the cellular disorders associated with defects in ribosome synthesis. This includes the characterization of new molecular and cellular mechanisms involved in the multiple steps required for pre-ribosomal RNA processing, ribosomal subunit assembly and their intracellular transport. He pioneered the field of ribosomopathies by studying the defects in ribosome synthesis associated with Diamond-Blackfan anemia, a rare congenital bone marrow failure associated with variants in ribosomal protein genes. His group has performed the functional characterization of a large proportion of the ribosomal protein genes associated with this disease through various collaborations in Europe and the USA. He was part of the EuraNet EuroDBA2 project and is currently coordinating the EJPRD 2019 RiboEurope consortium, which aims to identify genes involved in ribosomopathies, in particular rare inherited bone marrow disorders, and to improve the diagnosis of these diseases.

GROPMAN ANDREA

Andrea Gropman, MD, FAAP, FACMG, FANA, is Division Chief, Neurodevelopmental Disabilities and Neurogenetics at the Children's National Medical Center and Professor (tenured) of Pediatrics, Neurology, and Genomics and Personalized Medicine at the George Washington University of the Health Sciences.
She received her undergraduate degree from Brandeis University, and her Medical education from the University of Massachusetts, both in the Boston area in the USA. She subsequently trained in pediatrics (Johns Hopkins Hospital), Neurology/Child neurology (George Washington University and the Children's National Hospital), and clinical and biochemical genetics (National Institutes of Health).
She is board certified in neurology/child neurology, clinical and biochemical genetics, and developmental disabilities. She is the division chief of Neurogenetics and Neurodevelopmental Disabilities at Children's National Medical Center and a tenured professor at the George Washington University School of Medicine. She is the principal investigator of the Urea Cycle Disorders Consortium, the Director of the clinical translational core of the DC-IDDRC, and site PI for the North American Mitochondrial Disease Consortium.
Her research interest focuses on establishing biomarkers of neurological injury in patients with inborn errors of metabolism using specialized neuroimaging modalities. She hopes to use these biomarkers to better characterize and understand the underpinnings of neurological injury in these conditions and also to follow neurotherapeutics..

GROZA TUDOR

Tudor Groza is an experienced computer scientist with a background in knowledge representation, ontologies, natural language processing, and artificial intelligence in precision medicine. His work spans across various dimensions of the research – clinical care continuum, from devising algorithms to support clinical decision-making in the rare disorders field to standardization of clinical terminology and integration with national public and

private health systems. Over the course of the last ten years, Tudor focused on contributing to the clinical phenotyping community, both as an academic as well as an entrepreneur, by building deep phenotyping tools to aid the decision-making process in clinical genomics and primary care.
In an effort to enable harmonized phenotype acquisition, Tudor has contributed to various terminology standardization initiatives, including: co-leading the Phenotype Representation group (GA4GH Clinical Data and Phenotype work stream) or co-leading the Data Sharing group within the Undiagnosed Diseases Network International. Currently, he is a member of the Primary Care and Integrating New Technologies for the Diagnosis of Rare Diseases task forces of the International Rare Diseases Research Consortium. From an industry perspective, as former CTO of Genome. One, Tudor led the Personal Health Applications business unit through a clinical accreditation process and the development of the first patient self-phenotyping platform for large-scale precision medicine in collaboration with the largest rural healthcare provider in the US. In 2018, he co-founded Pryzm Health with the goal to reduce the diagnostic odyssey of patients susceptible of rare disorders by introducing phenotype-driven patient stratification methods in primary care.
Currently, he leads the Phenomics team at the European Bioinformatics Institute where he aims to contribute to the acceleration of translational and clinical applications of genomic technologies by creating comprehensive disease models using cross-species phenotype data.

JONKER ANNELIENE

Anneliene Jonker, PhD, is the Programme Lead of Personalized Medicine of the TechMed Centre, at the University of Twente, in Enschede, The Netherlands and a senior Funding and Strategy officer at the same institute. In this position, she is responsible for setting up projects with different researchers in the personalized medicine-, medtech, and rare diseases domain, working with academic and industrial researchers, and she assists in the constitution of new collaborations with different stakeholders, to create new research and implementation projects. Next to this, she is the Vice Chair of the Therapies Scientific Committee of the International Rare Diseases Research Consortium (IRDiRC), where she leads and participates in different Task Forces and Working Groups, such as the MedTech for Rare Diseases Working Group and the Drug Repurposing Guidebook. She is also an assistant Editor for Orphanet Journal of Rare Diseases.
Anneliene has previously worked at the IRDiRC Scientific Secretariat, as Project and Communication Manager, and in this role has assisted many different Task Forces, and been involved with many of the different tasks of the consortium. Anneliene Jonker has had a long interest in rare diseases, was trained as a biomedical scientist, obtaining her PhD in genetics and metabolism of Ewing' sarcoma, a rare childhood cancer, at Institut Curie, Paris, France. She obtained her master's degree in translational sciences in gastrointestinal stromal tumour, a rare intestinal cancer, from the University of Leiden, for which she performed her research at Brigham's and Women's Hospital, Harvard Medical School, Boston, United States. In addition, she has a master's degree in the history of medicine, dedicated to rare bone diseases, from the Free University of Amsterdam, Amsterdam, The Netherlands.

KLAP PAULIEN

Paulien Klap is an industrial designer with focus on assistive devices developed with the users. She joined the Yumen Bionics team in 2017. Her strength lies in combining interdisciplinary approaches and her work contributed significantly to improving the design of the exoskeleton so that it is tailored to home use without professional supervision. Paulien's first-hand experience on Duchenne Muscular Dystrophy, due to her friendship with a man with Duchenne, combined with her professional focus on user needs assurances that the user centricity is never loss out of sight. For assistive devices to be of any help they should fit the lives of the users. Paulien believes that both stigma of assistive devices and inclusion of people living with a physical challenge in society are of major importance to boost the integration of assistive devices in the lives of the users.

LANKESTER ARJAN C.

After obtaining his M.D. from the University of Leiden and a PhD on B cell receptor signaling from the University of Amsterdam, he was trained as pediatrician-immunologist at Leiden University Medical Center (LUMC). Since 2009 he is clinical director of the JACIE-accredited Pediatric Stem Cell Transplantation program which serves as the national center for stem cell therapy in patients with inherited immune disorders. In 2016 he was appointed as professor of Pediatrics and Stem Cell Transplantation at the University of Leiden. He is heading the LUMC expert center on inherited immune disorders and stem cell transplantation (SCT) which is full member of ERN-RITA. His primary research interest is to improve efficacy and safety of stem cell therapy with particular focus on optimizing conditioning regimens and immune reconstitution after SCT. He has conducted and coordinated many single and multicenter studies including investigator-initiated adoptive cellular therapy trials. He is PI of the ongoing RECOMB trial on lentiviral stem cell gene therapy in RAG1 severe combined immunodeficiency. He is co-founder of the AGORA (Access to Gene therapies fOr RAre disease) consortium, and the past chair of Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and European Society for Immune Deficiencies.

LARCHER FERNANDO

Dr Fernando Larcher is an expert in the field of skin regenerative medicine with a strong background in experimental skin carcinogenesis, tissue engineering, genodermatoses modeling and cell and gene therapies. For more than 20 years, Dr Larcher's laboratory at the CIEMAT's Biomedical Innovation Unit in Madrid has been devoted to translational research in the field of rare skin disorders covering various aspects that include mechanisms of disease and advanced gene therapy protocols at pre-clinical and clinical stages for Epidermolysis Bullosa and other genodermatoses. He is author of more than 100 PubMed-indexed scientific publications with an h factor of 37.

LEE KERRY JO

Dr. Kerry Jo Lee is the Associate Director for Rare Diseases in the Division of Rare Diseases and Medical Genetics, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER). In this role she leads the Rare Diseases Team, a multidisciplinary rare disease programming and policy team that works to promote their mission to facilitate, support, and accelerate the development of drugs and therapeutic biologics for rare diseases and serves as the program management office for CDER's Accelerating Rare diseases Cures (ARC) Program. Dr. Lee joined the FDA as a medical officer in 2014 with the former Division of Gastroenterology and Inborn Errors Products, OND, CDER. Dr. Lee then moved to a position as a clinical advisor for the Office of New Drug Policy, CDER, where she served as a lead in the areas of benefit-risk assessment, modernization efforts (including the integrated review for marketing applications), and real-world data/evidence programming before serving in her current position.
Dr. Lee is a pediatric gastroenterologist/hepatologist and a graduate of Princeton University and the New York University School of Medicine with an honors degree conferred in microbiology. She completed her residency in pediatrics at the Children's Hospital of Los Angeles followed by a post-doctoral clinical fellowship in Pediatric Gastroenterology, Hepatology, and Nutrition at Columbia University College of Physicians and Surgeons in New York. Dr. Lee maintains a steadfast interest in international policy and bioethics and worked for several years at the former National Bioethics Advisory Commission on reports advising the executive branch on ethical and policy issues in both international and domestic clinical trials.

MORRIS CARL

Dr. Carl Morris is the Chief Scientific Officer for Solid Biosciences, joining the company in September 2015. Dr. Morris is a member of the Senior Management team at Solid Biosciences and is responsible for overseeing the company's drug discovery and preclinical development efforts. Prior to joining Solid, Dr. Morris was a Senior Director for Pfizer's Rare Disease Research Unit, leading its biologics and neuromuscular disease area programs. Before moving to industry, he served as an Assistant Professor at the Boston University School of Medicine in the Muscle and Aging Research Unit. Dr. Morris holds a Bachelor of Arts degree in Biology from Franklin Pierce College (NH) and a Ph.D. in Physiology from UCLA.

PANNESE LUCIA

Lucia Pannese is a passionate entrepreneur who established one of Europe's leading and pioneering serious games companies, Milan-based imaginary, in 2004. With her background in mathematics and a very creative, multicultural mind, she acts as both CEO and Research Director and has published numerous international articles and papers.
Her company, Imaginary, is recognized internationally for its pioneering and innovative work, playing a key role in European Research. Since its foundation, imaginary has won and delivered a remarkable >30 European-funded research projects and has received 14 awards for their work.

PARISER ANNE R.

Anne Pariser is the VP of Medical and Regulatory Affairs at Alltrna, the world's first tRNA platform company seeking to develop tRNA as a therapy that could be used in thousands of genetic diseases. Prior to joining Alltrna, Dr. Pariser was the Director of the Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH). During her tenure at ORDR, Dr. Pariser oversaw several research and development programs focused on advancing translational and clinical research into rare diseases. Some of these programs included the Rare Diseases Clinical Research Network (RDCRN), a network of research consortia focused on more than 200 different rare diseases, the Diagnostic Odyssey grants program intended to speed rare disease diagnosis, and the PaVe-GT gene therapy program, which seeks to develop gene therapies for several ultra-rare diseases at the same time using a platform approach, among other programs. Prior to ORDR, Dr. Pariser worked for more than 15 years at the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), where she predominantly focused on rare diseases drug review and most notably founded the Rare Diseases Program, which focused on developing regulatory science, policy, and processes intended to facilitate rare disease drug development and review. Dr. Pariser received her medical degree from Georgetown University School of Medicine and completed her Internal Medicine Internship and Residency at Georgetown University Medical Center. She continues to see patients at the Arlington Free Clinic in Arlington, Virginia USA.

SAHEL JOSÉ-ALAIN

José-Alain Sahel is Professor of Ophthalmology at Pierre and Marie Curie University Medical School, Paris, France and Cumberlege Professor of Biomedical Sciences at the Institute of Ophthalmology, University College London, UK. He chairs a Department of Ophthalmology at the Quinze-Vingts National Ophthalmology Hospital and at the Rothschild Ophthalmology Foundation. He coordinates the Ophthalmology Clinical Investigation Centre and the National Reference Centre for Retinal Dystrophies. Dr Sahel is Director of the Vision Institute that comprises more than 17 research teams and more than 250 members focused on understanding the mechanisms associated with eye diseases and developing novel therapeutic strategies for currently untreatable retinal diseases. A key focus of his research is extending the functional life of cone photoreceptors in retinal degenerations.
Dr Sahel published over 250 peer-reviewed articles in specialty and general audience peer-reviewed journals and co-authored more than 20 patents. He has been the recipient of several awards, including Foundation Fighting Blindness Trustee Award, Alcon Research Institute Award, CNRS Medal of Innovation… He is a Member of the Academy of Sciences, Institut de France. He sits on several editorial boards, including the Journal of Clinical Investigation, Science Translational Medicine, Progress in Retinal and Eye research and Archives of Ophthalmology.

STOYANOVA VIOLETA

Dr. Violeta Stoyanova-Beninska is the Chair of the Committee for Orphan Medicinal Products at the European Medicines Agency (EMA) since 2018. Before that she has been member of the COMP representing The Netherlands, Chair of the National Scientific and Regulatory Advice at the Medicines Evaluation Board, member of CNS working party and Scientific advice working party at EMA. Violeta is vice chair of the Regulatory Scientific Committee of IRDiRC. She is also member of scientific and advisory boards of international projects related to rare diseases, personalized medicine and orphan drug development. Beside her work as a regulator, Violeta is academic supervisor of PhD and master students, guest faculty at several universities, member of editorial board/reviewer panel in scientific peer reviewed journals.

SIREAU NICK

Yarlalu Thomas is an Aboriginal Australian from the Nyangumarta Pitjikarli group. He is, originally from a small Aboriginal community called Warralong, in the Pilbara desert region of North West Australia. The first in his community to complete a high-school certificate, he enrolled in a Bachelor of Medical Science and Doctor of Medicine (MD) currently in his final year at the University of Western Australia.
Between his bachelor's degree and MD, Yarlalu was awarded the inaugural Roy Hill Community Foundation Fellowship. His fellowship has enabled him opportunities to experience working at WA Register of Developmental Anomalies, Genetic Services WA and Cliniface, to transform genetic health care services for remote Indigenous people.
Yarlalu also works with Pilbara Faces, which aims to understand 3D facial variation of ATSI peoples to provide more accessible, quicker and non-invasive diagnosis for children with rare and genetic diseases.
Yarlalu also launched the UNESCO-endorsed Lyfe Languages project to translate medical terminology into ATSI languages, and Indigenous languages internationally. He combines the newest scientific and medical knowledge with old and ancient wisdom.

VAILLANCOURT JULIENNE

Julienne (Julie) Vaillancourt is a pharmacist and a captain in the United States Public Health Service Commissioned Corps (US PHS CC). Since mid-2015, she has served as a policy advisor in the Office of the Director at the US Food and Drug Administration's Center for Biologics Evaluation and Research (FDA/CBER) and serves as the Center's Rare Disease Liaison. In this role she coordinates CBER's Rare Disease Program, facilitates collaboration across CBER, with rare disease partners at FDA, and with external stakeholders including patient advocacy organizations on multiple rare disease-related efforts and issues, and contributes to relevant policy development at FDA. She is a graduate of Massachusetts College of Pharmacy (Boston) and Boston University School of Public Health. She worked as a pharmacist in New England for several years, before starting her career as a US PHS CC officer in 1995, in FDA/CBER's Office of Vaccines Research and Review (OVRR), first as a Regulatory Project Manager (RPM) and later as an RPM Team Leader. There she served on several review teams for biologics license applications (BLAs) and Investigational New Drug Applications (INDs)

for vaccines and related products. As a US PHS CC officer, she also served as an Emergency Health Consultant at the US Agency for International Development from 1999-2001, having returned to FDA/CBER afterward.

VAN KARNEBEEK CLARA

Professor Clara VAN KARNEBEEK is Director of the Emma Personalized Medicine Center and principal investigator at the Amsterdam University Medical Centres, The Netherlands and affiliated with the University of British Columbia in Vancouver Canada.
Clara's work as a pediatrician and biochemical geneticist focuses on early diagnosis and innovative treatment of neurometabolic diseases in a P4-medicine model. Her international team integrates genomic and metabolomics technologies to unravel the cause of degenerative brain conditions in children and adults, discovering novel genetic conditions and treatment targets. She implements this knowledge in the management of her patients, via experimental therapies and clinical trials with personalized outcomes.
Translating new knowledge into expanded newborn screening, as well as useful information and action for the patient and family, using digital applications, are the ultimate goals of her multi-disciplinary team's effort.
She is the Director of United for Metabolic Diseases, a Dutch consortium uniting all 6 academic metabolic expertise centers and the patient organizations to optimize research and care. Clara has founded the Jeroen Pit Huis as an innovative model of transmural care for children with medical complexities in Amsterdam NL.
She published over 230 peer-reviewed journal articles, multiple clinical guidelines and chapters in textbooks. She is a dedicated teacher and mentor for clinical and research trainees at different stages. For her contributions to research and clinical care and commitment to translational science she received the Canadian Organization for Rare Diseases Scientist Award, the Huibregtsenprijs nomination 2022 and was recently knighted as Ridder in de Orde van Oranje Nassau for her outstanding contributions to society in the Netherlands.

VITARELLO JULIA

In December 2016, Julia founded Mila's Miracle Foundation (MMF) upon learning that her seemingly healthy six-year-old daughter, Mila had Batten disease, a fatal genetic condition with no cure. In an unprecedented race against time to save her daughter, Julia's collaboration with Dr. Timothy Yu from Boston Children's Hospital (BCH) led to the first ever drug tailored to just one person, affectionately named milasen. After showing great promise in the first year of treatment, Mila's disease slowly continued to progress. In February 2021, Mila's big spirit left her little body. Driven by a sense of hope and responsibility, Julia is on a mission to turn the groundbreaking work that went into an impactful solution to the global health crisis of rare disease in children.
In her quest to open up the field of individualized medicines which Mila pioneered, Julia has engaged academics, biotechs, government and foundations in this space and created a global following of Mila's story. On top of her work running MMF, Julia co-founded the N=1 Collaborative which serves as the global scientific hub for medicines like milasen, as well as a biotech aiming to prove a viable business model to make individualized medicines sustainable. Julia regularly presents at scientific meetings and conferences across the coun-

try. In collaboration with fellow rare disease foundations, she initiated the work toward an ongoing novel gene replacement therapy trial targeting Mila's variant of Batten (CLN7) and a Neurodegenerative Disease Clinic at Children's Hospital Colorado. Through MMF, Julia co-runs the first-ever single cell atlas of pediatric disease with BCH, funds basic science research in the US and Europe, and hosts meetings with industry experts, families and change-makers. Julia is focused on moving "From Mila to Millions", making individualized medicines routine worldwide.

YANG RACHEL

Physician scientist by training, Rachel's career spanned basic research (UVA, IMCB), clinical research (PPD), and information technology (Oracle, developing software application for clinical trials). She was a Product Strategy Director at Oracle Health Sciences Global Business Unit. From 2016-2018, Rachel worked in two startup companies, Gendi Health and Phoebus Medical, where she was the General Manger.

Rachel has been working on a volunteer base in RD Patient Advocacy since 2015. She was responsible for international affairs for Chinese Organization for Rare Disorders (CORD) from 2015-2019, and later for Chinese Alliance for Rare Diseases (CHARD) since 2019. Rachel has been a RDI Council Member since 2018, and is currently RDI's Secretary of the Board.

Rachel received her M.D. from Fudan University, Shanghai Medical School in China and Ph.D. from the University of Virginia in US. Rachel is based in Zurich, Switzerland.

SPEAKERS' ABSTRACTS

NOTES

THE RARE CARE CENTRE – INTEGRATED, HOLISTIC AND SUSTAINABLE CARE FOR CHILDREN AND FAMILIES LIVING WITH RARE DISEASES

OPENING CEREMONY

Gareth Baynam, Rare Care AUS

The Rare Care Centre is the first centre in the Southern Hemisphere created to respond to the need to connect and provide a range of innovative and sustainable cross-sector rare disease care services to address challenges for children and families living with rare and undiagnosed diseases.

Alongside implementing its state-wide clinical service in the world's geographically largest publih health jurisdiction as of 2022, the RCC has commenced streams of activity covering: education and workforce capacity building; digital technologies and devices; partnership and systems advocacy; and connection to global expertise, research, and clinical trials.

Increasing primary care provider capacity and confidence in rare disease care is a key focus for the RCC. This includes General Practitioner (GP) training and Aboriginal Health Worker (AHW) positions, GP and AHW training resources and workshops; as well as co-creating online communities of practice linking primary and specialist care. Collectively, RCC activities are also helping to inform and help lay pathways for adult care.

The RCC is a partnership between Child and Adolescent Health Service in Western Australia and multiple philanthropic foundations. The RCC model of care and other streams of activity will be described.

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SEQUENCING FOR EARLY DIAGNOSIS IN NEONATAL SCREENING AND HEALTH CARE

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Martina Cornel, Amsterdam University Medical Center

Next generation sequencing (NGS) of an individual's exome or genome can provide information on many variants that are potentially disease causing. Increasingly, authors plea to integrate sequencing technologies in neonatal screening programmes. Traditionally neonatal screening aimed to identify conditions for which an early diagnosis would avoid irreparable health damage in the child. The screening is offered to all newborns a few days after birth. Tests used in neonatal screening have to be highly specific, sensitive and relatively cheap. A diet or medication in early diagnosed infants contributes to health gain.
How would NGS fit into such a programme? Sequencing can in theory be used as first tier test or after initial testing with other methods. Should tandem mass spectrometry indicate that a metabolic condition is likely, sequencing could identify the gene variants involved. Should a low number of T cell receptor excision circles (TRECs) be identified, then sequencing could help to identify the cause of the primary immune deficiency. The UK Newborn Genomes Program aims to sequence and analyze the genomes of >100.000 neonates as first tier. Treatable conditions that are not easily recognized with existing methods perhaps can be diagnosed earlier, but many challenges can be expected. Some variants in genes may be hard to interpret: variants of uncertain significance. More infants may turn out to have two variants in a gene associated with an autosomal recessive disorder, perhaps indicating very mild phenotypes. Finally gene variants may be encountered that lead to problems later in life.
Sequencing in acutely ill infants may be genomic medicine's critical application. This appears to be clinically useful, but the value of this diagnostic test should be rigorously demonstrated before it is accepted as a standard of care. Examples of treatable conditions have been published, but also of lethal conditions where the care in the last phase of life of these infants could be adapted in accordance with family's wishes.
In the next few years the evaluation of sequencing in these different health care setting will provide interesting insights.

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DECIPHER – ENABLING THE SHARING OF RARE DISEASE PHENOTYPE-LINKED VARIANT DATA FOR DIAGNOSIS AND RESEARCH

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Julia Foreman1,2, Daniel Perrett1,2, Yusra Haider1,2, Blessing Ashimi1,2, A Paul Bevan1, Sarah E. Hunt2, Matthew E Hurles1 Fiona Cunningham2, and Helen V Firth1,3

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DECIPHER is a global platform enabling the sharing of anonymized rare disease phenotype-linked variant data for diagnosis and discovery. It currently hosts >43,500 searchable open-access records containing >56,500 variants and >179,000 phenotypes. The platform supports the sharing and interpretation of many types of genetic variation, including sequence variants, copy-number variants, aneuploidy, uniparental disomy, short tandem repeats, inversions and large insertions. DECIPHER presents genomic data in GRCh38, enabling the most recent genome build and transcript information to be utilized for accurate variant interpretation. The platform supports the deposition and sharing of patient phenotypes, including the sharing of aggregate quantitative data such as developmental milestone and anthropometric measurements.

DECIPHER provides variant interpretation interfaces which summarize and contextualize genotypic and phenotypic data. These include a protein browser, which allows users to visualize their patient's variant on a 2D protein view and on an experimental or AlphaFold predicted 3D protein structure. Variant annotation is also available such as Ensembl Variant Effect Predictor, functional annotations from the neXtProt knowledgebase and case/cohort data. A dynamic patient/variant matching interface allows users to identify similar patients. Information about the gene is provided including gene/disease associations, predictive scores and management resources, such those highlighting possible therapies.

The platform supports the interpretation of variants according to international standards. The ACMG/AMP pathogenicity evidence interface for sequence variant includes the ClinGen SVI Bayesian framework for ACMG variant classification and also displays criteria specific ClinGen expert panel recommendations. The interface also presents predictions for the activation of specific criteria based on ACMG/AMP guidelines. A pathogenicity interface supporting the interpretation of copy-number variants using ACMG/ACGS standards is also available.

DECIPHER is a pioneering partner in GA4GH and of the Matchmaker Exchange, which enables the federated discovery of similar entries in connected databases. Since its inception DECIPHER has facilitated over 3,000 publications in peer-reviewed scientific literature; a testament to the importance of match-making in rare disease.

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A 'NEGATIVE' EXOME – WHAT'S NEXT?

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Prof Clara van Karnebeek, Emma Center for Personalized Medicine, Depts of Pediatrics and Human Genetics, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Exome sequencing (ES) in the clinical setting of inborn metabolic disorders (IMDs) has created tremendous improvement in achieving an accurate and timely molecular diagnosis for a greater number of patients, but it still leaves the majority of patients without a diagnosis. In parallel, (personalized) treatment strategies are increasingly available, but this requires the availability of a molecular diagnosis. IMDs comprise an expanding field with the ongoing identification of novel disease genes and the recognition of multiple inheritance patterns, mosaicism, variable penetrance, and expressivity for known disease genes. The analysis of trio ES is preferred over singleton ES as information on the allelic origin (paternal, maternal, "de novo") reduces the number of variants that require interpretation. All ES data and interpretation strategies should be exploited including CNV and mitochondrial DNA analysis. The constant advancements in available techniques and knowledge necessitate the close exchange of clinicians and molecular geneticists about genotypes and phenotypes, as well as knowledge of the challenges and pitfalls of ES to initiate proper further diagnostic steps. Functional analyses (transcriptomics, proteomics, and metabolomics) can be applied to characterize and validate the impact of identified variants, or to guide the genomic search for a diagnosis in unsolved cases. Future diagnostic techniques (genome sequencing, optical genome mapping, long-read sequencing, and epigenetic profiling) will further enhance the diagnostic yield. During this presentation an overview of the challenges and limitations inherent to ES followed by an outline of solutions and case vignettes as well as a clinical checklist, focused on establishing a diagnosis to eventually achieve (personalized) treatment

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RARE DISEASE PATIENT STRATIFICATION IN PRIMARY CARE: CHALLENGES AND OPPORTUNITIES

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Tudor Groza, European Bioinformatics Institute, UK

Precision medicine, as an initiative, has provided a novel and disrupting view on performing prevention and treatment of diseases, by placing an emphasis on the individual and hence putting the individual in the centre of the model, rather than aligned to a "mean". More concretely, it recognises the uniqueness in every patient by taking into account inherent variables such as the personal and family medical history, the environment or lifestyle. Gaining a better understanding of these differences is critical to advancing the medical field and in particular to providing better care and an improved experience for the patients. The increasing adoption of electronic health records, health-oriented wearables and mobile applications, corroborated with a much more open view on genetic tests targeted directly at consumers, has enabled a paradigm shift that led to more and more patients being engaged with the management of their health-related decision-making process. The data produced by these patients together with the recent advances in data science - via various Machine Learning and AI approaches - lays the perfect foundation for developing the next generation methods to prevent and treat disease.

A key factor in the successful development of novel analytical methods is (and will be) the 'language' used by both clinicians and patients to communicate about their health care. Ontologies can, in this instance, bridge the terminological gap and provide the appropriate level of consistency and uniformity.

In this talk, Tudor will discuss the intermediary outcomes of a study aimed at acquiring and using structured and standardised longitudinal data (covering the medical and family history) to identify rare disease patient candidates in the Australian Primary Care setting. The study uses a conceptual framework developed to embed the screening process into the standard clinical care, with both the inputs and the outcomes being informed by the appropriate clinical stakeholders – in this case, the domain experts and the primary care physicians.

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STRATEGIC APPROACHES TO REDUCE THE DIAGNOSTIC ODYSSEY

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Kym M Boycott, MD, PhD, FRCPC, FCCMG
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Accurate diagnosis is the cornerstone of medicine. Progress toward the discovery of the genetic basis of every rare disease (RD) has been substantial over the past decade secondary to the introduction of exome sequencing into both research and clinical environments. However, families with a RD often spend more than five years on a diagnostic odyssey of specialist visits and invasive testing that is lengthy, costly, and often futile. Many patients remain undiagnosed because they are not recognized as having a RD; new approaches using machine learning and electronic health records bring the opportunity to address this particular challenge. For those patients who do enter the appropriate care pathway, the current diagnostic paradigm for RDs is not designed for those who remain undiagnosed after initial investigations because of several challenges, including interpretation of test results and limitations inherent to the paradigm. An expansion of approaches in the clinic is required for undiagnosed RD patients including some level of data sharing. Leveraging opportunities to participate in research programs that promote international sharing of deeper levels of data and utilizing new technologies to understand RDs is an important path forward. Given recent advancements in such technologies and international initiatives, the prospect of identifying a molecular diagnosis for all patients with RDs has never been so attainable, but achieving this goal will require global cooperation at an unprecedented scale. This presentation will highlight new approaches to RDs that will hopefully enable diagnoses for all such patients in the coming decade.

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DEVISE – WAYS FORWARD FOR MEDICAL DEVICES FOR RARE DISEASES

THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Anneliene Jonker, University of Twente, NL
Marc Dooms, University Hospitals Leuven, BE

Traditionally, rare diseases research and development has primarily focused on medicinal products which are assessed through regulatory frameworks, while the development of medical technologies for rare diseases, orphan devices, have been underserved. However, the current COVID-19 crisis and the subsequent additional challenge for rare disease patients to access the healthcare professionals, has favored the flourishing of digital remote monitoring and other medical technologies, and shed a new light on the traditional way of looking at the medical device field.
Medical technologies constitutes a very diverse group of products. Medical technologies or medical devices are instruments, apparatus, appliance, software, implant, material or other articles for the diagnosis, prediction, treatment or alleviation of a disease. These devices range from diagnostic products, surgical products to medical aids. Many medical technologies are essential for patients living with rare diseases, and their carers. Nevertheless, very few medical devices are developed specifically for rare diseases, while many patients and carers have expressed that there is a strong unmet need for new medical devices. Device needs for rare diseases are for example noninvasive markers for monitoring disease activity, tests that allow home monitoring by patients of disease and treatment side effects or imaging enhanced functional scans. As such, there are high needs to connect patients, carers and their families to technology that can address these needs.
In this talk, we will go in detail of the first results of the IRDiRC Working Group MedTech for Rare Diseases. We set out the framework of the regulatory incentives, and the recommendations that potentially can improve interest in the field. We show examples of medical technology development, and the challenges these encounters. We will also go into detail about the ways to involve and interact with patients in the process.

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THE POTENTIAL OF WEARABLE EEG & REAL-TIME AI TO EXTERNALIZE BRAIN STATES IN RARE AND ORPHAN DISEASES: A DISRUPTIVE VISION TO IMPROVING LIVES USING TECHNOLOGIES OF TODAY

THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Tim Buckinx, epihunter nv, Belgium

For many brain disorders, including epilepsies, the diagnostic odyssey for patients is long, and the journey to precision medicine is mostly unchartered. The use of wearable EEG and real-time AI technology provides a solution to externalize brain state, generating new research insights, helping a faster accurate diagnosis and optimizing treatment outcomes. Yet foremost, this approach enables the delivery of real-time digital interventions that reduce the impact of a brain disorder in everyday life.

By collecting real-world data, researchers and physicians can gain deeper insights into the underlying mechanisms of these conditions. Rather than solely focusing on identifying patterns in EEG recordings to classify for classical outcome features, this approach allows for a deeper understanding of the building blocks contributing to the full impact of the condition.

Yet, it is crucial that the development of health tech prioritises the needs and experiences of individuals with brain disorders and their caregivers. Technology should not be designed to primarily benefit medical professionals, pharmaceutical companies, or researchers, but rather it should focus on improving the lives of those who live with these conditions.

For example, a clinically validated and certified beachhead product for absence seizures is available and has been used by over 500 individuals, providing a digital intervention for the classroom to make teachers aware of absence seizures in real-time so content can be repeated later, reducing their impact on school performance.

We invite individuals and organizations who work on brain disorders causing sudden changes in brain state with documented EEG biomarkers to consider the potential of wearable EEG and real-time AI technology. By simply training an algorithm on the biomarker and creating appropriate digital interventions on our platform, we can make a significant impact on daily life for those affected by these conditions. We believe this provides an unprecedented opportunity for people with rare or orphan brain disorders.

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WHY ME? TACKLING THE CHALLENGE OF RARE DISEASES THROUGH GAMIFICATION AND ENABLING TECHNOLOGIES

THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Lucia Pannese, Imaginary s.r.l., Italy

Rare diseases are distressing for both sufferers and their family. They not only affect physical health but also mental well-being as patients try to come to terms with the apparent injustice of their condition. The presentation will showcase some recent research results and current work in the area of serious games applied to rare diseases. Specifically, a game for children with cystic fibrosis and a game-based tele-rehabilitation system under validation for Pompe disease will be described and discussed in terms of the benefits to both physical and mental wellbeing.

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DEVELOPING GENE-INDEPENDENT APPROACHES FOR RETINAL DYSTROPHIES

THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Inherited retinal dystrophies (IRDs) display remarkable genetic heterogeneity, with over 300 retinal disease genes mapped and/or identified. Profound vision loss and blindness, often from birth, is a common occurrence in these clinically heterogeneous disease conditions. The therapeutic options for IRDs are currently very limited but recent advancements in understanding mechanisms of retinal degeneration and technological progress paved the way towards development of novel therapies. Much progress has been made in moving from gene discovery to gene therapy. However, the genetic heterogeneity of IRDs represents a significant challenge for development of gene therapy.

Many studies from our group have demonstrated that the survival of cones (responsible for diurnal and high resolution vision) depends on the presence of rods (responsible for vision at low light levels) that secrete a diffusible trophic factor identified as rod-derived cone viability factor (RdCVF). The discovery of RdCVF, of its receptor and mechanism of action, and the demonstration of its mutation-independent therapeutic potential in several animal models of IRDs paved the way to the development (with the start-up company Sparing Vision) of RdCVF neuroprotective gene therapy that will enter in clinical trial in 2022.

IRDs destroy photoreceptors but leave intact and functional a significant number of inner retinal cells. Using viral vectors, light-sensitive microbial opsins can be expressed in these remaining cells, making possible their conversion into "artificial photoreceptors". Our group in Paris, together with Botond Roska (IOB, Basel) and the biotech company GenSight, demonstrated that this technology, named optogenetics, can restore vision in secondary retinal neurons which can survive years after the degeneration of photoreceptors. Our groups established the foundation for the first-in-man clinical trial (NCT03326336) with the photoactivatable optogene ChrimsonR (developed by Ed Boyen at MIT) delivered in the eye via adeno-associated viral vectors and electronic goggles to intensify the light and provide adaptation. We demonstrated (Nat Med 2021) that optogenetics is a remarkably effective way to restore partial vision and provide useful vision restoration in blind people. Gene-independent approaches such as neuroprotection and optogenetics would allow for treatment of a broad spectrum of retinal dystrophies, even at advanced stages of disease, giving hope for vision rescue and vision restoration to approximately 2 million people with IRDs worldwide.

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DEVELOPING AN ARM EXOSKELETON WITH THE DUCHENNE MUSCULAR DYSTROPHY COMMUNITY

THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Paulien Llap Yumen Bionics, The Netherlands

What did Yumen Bionics encounter during the development of assistive technology for people living with Duchenne Muscular Dystrophy(DMD)?
DMD is, just like all neuro muscular diseases, a rare disease that affects approximately 1 in every 7000 live births. Due to the low prevalence, there is not much technology developed for this specific target population. The question 'What could new innovative technologies that I see around mean for me?' (male with DMD) initiated a big research project to answer this question. This project resulted in an arm exoskeleton concept that enables children with DMD to keep using their arms in a natural way. Yumen Bionics founded, by the Dutch Duchenne Parent Project foundation is on its way to bring this technology to the market. The road is obviously not without any hurdles, but the opportunity to develop the technology together with the Duchenne community made it possible to keep moving.

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EVOLVING REGULATORY SCIENCE FOR RARE DISEASES

REGULATORY SCIENCE

Dan O'Connor, Medicines and Healthcare products Regulatory Agency, UK

Regulatory authorities have an important role to play in supporting the rare disease community, from engaging patients in their decisions to expedited pathways to access for innovative products. This presentation will cover some of the growth areas of interest from a UK perspective and the Medicines and Healthcare products Regulatory Authority (MHRA).

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REGULATORY OPPORTUNITIES: FACILITATING AN ENVIRONMENT OF INNOVATION

REGULATORY SCIENCE

Anne Pariser, MD, Alltrna, Cambridge Massachusetts, USA

There has been considerable progress in the conception and development of novel treatment approaches for rare genetic diseases in recent years, including a number of first-in-class and first-in- disease innovations that hold promise for the creation of highly efficacious precision medicines for patients in a broad array of rare diseases. Given the novelty of these approaches and products, early and iterative engagement with regulators can be of substantial benefit. These engagements can allow for scientific exchange, protocol assistance, discussion surrounding endpoint selection and clinical trial design, and the opportunity to explore flexibility and methods to expedite therapeutics development for ultra-rare diseases with unmet medical needs and no regulatory precedent. EMA, FDA, MHRA and other international authorities have put in place programs to assist sponsors developing novel therapeutics for rare diseases, many of which encourage early interactions, in some cases at early preclinical stages of development, and at times even before specific products or disease areas have been selected. In this presentation, recent early engagement experience with regulatory authorities will be shared, including preparation for meetings, timing, and how these interactions and programs are facilitating forward progress in novel of areas of research and development. Some of these programs include Innovative Licensing and Access Pathway (ILAP) with MHRA, Initial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) with FDA's Center for Biologics Evaluation and Research (CBER), and Critical Path Innovation Meetings (CPIM) with FDA's Center for Drug Evaluation and Research (CDER), as well as longer established programs for Orphan drugs and scientific advice.

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REGULATORY OPPORTUNITIES: FACILITATING AN ENVIRONMENT OF INNOVATION

REGULATORY SCIENCE

Kerry Jo Lee, MD, Division of Rare Diseases and Medical Genetics; Office of Rare Diseases, Pediatrics, Urological and Reproductive Medicine; Office of New Drugs, CDER, FDA, USA

FDA's Center for Drug Evaluation and Research (CDER) is committed to advancing development of novel drugs and biologics for rare diseases. In CDER, the percentage of novel approvals with orphan designation doubled between 2010 and 2020 and this growth continues as the majority of novel approvals in 2022 (54%) were for orphan products. Despite the growth of rare disease drug development, there is still significant need, as fewer than 10% of rare disorders have FDA-approved treatments. Rare disease drug development can be complex due to limitations in our understanding of disease natural history, limitations or lack of trial endpoints that are fit-for-purpose, and challenges in trial design and interpretation. This presentation is an overview of how CDER is addressing these challenges through innovative and collaborative programs, such as the Rare Disease Endpoint Advancement (RDEA) pilot program and CDER's Accelerating Rare disease Cures (ARC) program.

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INNOVATION IN RARE DISEASE DRUG DEVELOPMENT – EARLY DIALOGUE WITH THE EU REGULATORS

REGULATORY SCIENCE

Stoyanova-Beninska, MD, PhD, MPH; Chair of Committee for Orphan Medicinal Products at EMA; Policy, Regulatory and International Affairs at MEB, NL

Stimulating development of innovative methodologies seems to be on the top of many agendas and stakeholders are joining efforts to encourage development, save resources and increase efficiency. The EU ecosystem is facing very dynamic times with the pharmaceutical legislation as well as these for orphan and pediatric diseases being under revision. While the final outcome is still to be discussed and defined, the common goal remains to be creating a robust regulatory framework that will drive innovation and improve access to transformative treatments for patients with a rare disease. The discussions about innovative approaches of stimulating research and bringing efficacious and safe medicines sooner to these patients is still a top priority. The lecture will provide a brief introduction of the EU regulatory system and then focus on the different possibilities of stakeholders involved in research and development of medicines for rare diseases to involve in early dialogue with EU regulators. The aim of such interactions would be to avoid unnecessary efforts in development and agree on the most relevant and efficient steps to be taken. More specifically the presentation will include an introduction of the European Medicines Agency specific procedures for support of innovative drug development in EU. This will include the procedure for Orphan designation at the Committee for Orphan Medicinal Products, the Small and Medium Enterprise (SME) office, the Innovation Task Force (ITF) program, Priority Medicines (PRIME), protocol assistance and qualification procedure for novel technologies at the Scientific Advice Working Party (SAWP). In addition the role of patient engagement will be described in general and with some concrete examples of patient involvement in the regulatory decision making process. Finally the possibilities for an early and continuous dialogue, as well as the existing international collaboration of EU regulators with their colleagues from regulatory authorities in other parts of the World will be highlighted.

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FDA'S CENTER FOR BIOLOGICS EVALUATION AND RESEARCH: ADVANCING DEVELOPMENT OF NOVEL BIOLOGICS FOR RARE DISEASES

REGULATORY SCIENCE

Julienne Vaillancourt, MPH; Center for Biologics Evaluation and Research, FDA, USA

FDA's Center for Biologics Evaluation and Research (CBER) is committed to advancing development of novel biologics for rare diseases. Historically, most CBER-regulated biologics for use in rare diseases were plasma-derived products; however, that has been changing. In recent years CBER has experienced unprecedented growth in the number of investigational new drug application (IND) submissions for cell and gene therapy development programs, the majority of which are for rare diseases. While such novel biologics hold promise for many devastating rare diseases that currently have no treatment, development of these products is faced with challenges. An overview of how CBER is addressing these challenges and needs through innovative outreach programs, such as the RegenMedEd workshop and webinar series, collaborative efforts such as the Bespoke Gene Therapy Consortium, and implementation of recent legislation such as the ACT for ALS Act, and more will be presented.

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HETEROGENEITY OF AUTOIMMUNITY, CLINICAL IMPLICATIONS

CLINICAL RESEARCH

Marta Alarcon Riquelme, GENyO Spain

Systemic lupus erythematosus and other systemic rheumatic autoimmune diseases suffer of great delays in their diagnoses and a high rate of non-response to therapy. One of the main reasons for this is their heterogeneity. In my group we have worked to dissect such heterogeneity with the use of clustering and stratification, based on machine learning approaches. The work I shall present will show how these diseases may share pathogenic pathways and hence may share therapies. I also show some examples of prediction of flares and remission, as well as how the stratification may help predict therapeutic responses to various drugs.

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INNOVATIVE CLINICAL TRIAL DESIGNS FOR RARE DISEASES

CLINICAL RESEARCH

Isabela Batsu, sanofi, USA

Aberrant glycosphingolipid metabolism is the cornerstone of rare lysosomal storage disorders including Late Onset Tay-Sachs and Late Onset Sandhoff diseases as well as other ultra-rare GM2-related disorders. Due to similar underlying pathology, these disorders are strong candidates for basket trial designs when evaluating new therapeutic options. This methodology was the foundation for the design of the AMETHIST trial to evaluate the safety, tolerability, and efficacy of venglustat, a novel, small molecule glucosylceramide synthase inhibitor, in adults with LOTS and LOS. A strong understanding of the patients' journey led to the inclusion of patient-reported outcomes and novel functional assessments in this trial. During this session, the learner will receive additional insight into the evolution of this trial and how it can pave the way for future research in rare diseases.

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BEYOND "ONE DISEASE AT A TIME": FOCUSING ON COMMON MOLECULAR ETIOLOGIES TO ACCELERATE RARE CLINICAL TRIAL ACCESS

CLINICAL RESEARCH

PJ Brooks, Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, USA

Based on the most recent estimates,bthere are over 10,000 known human diseases, and more are being discovered each day. However, the number of underlying disease etiologies is far smaller, and many of these molecular etiologies are shared across multiple diseases. The most common etiologies include premature stop codons, protein misfolding, abnormal RNA splicing, and gain of function mutations. In addition, defects in molecular signaling pathways (signalopathies) underlie multiple rare diseases. Importantly, all of these shared molecular etiologies are in principle therapeutically actionable, in some cases by the same small molecule drug (e.g. rapamycin for mTORopathies). Despite this fact, the current strategy is to carry out clinical trials of these drugs in one disease at a time, and typically in the most common rare diseases. This approach leaves patients with very rare diseases, who could potentially benefit from such trials, unable to enroll in them. A solution to this problem is to adapt the basket trial design from oncology, and apply it to drugs targeting shared molecular etiologies across multiple are diseases. I will discuss the activities of the IRDiRC task force on ShAred Molecular Etiologies (SaME) which was formed to focus on this issue. Gene-targeted therapies, such as gene therapy, gene editing, and oligonucleotides are therapeutic platforms that are broadly applicable to a large fraction of monogenic diseases. Directly adapting the basket trial approach from oncology is not possible, as it requires the use of a single drug, whereas gene targeted therapies are sequence specific. However, these technologies can be developed as therapeutic platforms to treat monogenic disease. I will also discuss examples of this approach for gene therapy (https://pave-gt.ncats.nih.gov/, https://fnih.org/our-programs/AMP/BGTC) and gene editing (https://commonfund.nih.gov/editing).

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FROM BIOMARKER TO STUDY TO BASKET CLINICAL TRIALS. ADVANCING SCIENCE FROM THE BEDSIDE OR BENCH TO TRIALS: TWO MODELS IN ACADEMIA

CLINICAL RESEARCH

Andrea Gropman, M.D., FAAP, FACMG, FANA
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Rare diseases were once considered medical curiosities with little public-health impact. But though such diseases are individually rare, collectively an estimated 25 to 30 million Americans are affected. To date, approval of drugs for rare disorders are based on endpoints that are considered "surrogate". In the urea cycle disorders several drugs have been approved based on hyperammonemia as a surrogate marker: Glycerol phenlybutarate: ammonia; N carbamylglutamate: ureagenesis and ammonia. Biomarkers offer a way to accelerate biomedical research by uncovering the pathophysiological mechanisms of disease. Biomarkers can also be novel tools for monitoring disease progression, prognosis, and response to drugs, especially in clinical trials, where they can be used to assess the efficacy, efficiency, and side effects of novel drugs or therapies.
In ultrarare disorders biomarkers may lead to personalized medicine, a rapidly developing field that is of particular interest in these rare diseases (RDs), i.e. those with a prevalence of less than 5/10,000, which are often genetic in origin. Although rare genetic diseases may be lessappealing targets for pharmaceutical companies, they are nevertheless in urgent need to evaluate ways for rapid diagnosis, treatment, and establish care guidelines. Without early diagnosis and effective treatment strategies, it is impossible to improve the quality of life and/or life expectancy of such patients. Due to the small numbers of patients with a particular rare disease, standard methods of clinical trials may not be appropriate. In addition, the trials of drug development in an academic environment will be contrasted to that supported by industry as well as consideration of novel trial design in two groups of rare disorders, urea cycle disorders, and two mitochondrial conditions that have differing clinical manifestations but are related through defects in complex 1 of the electron transport chain. These two conditions provide a basis for exploration of basket clinical trial design in rare disease.

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TARGETED THERAPY IN PATIENTS WITH PIK3CA-RELATED OVERGROWTH SYNDROME

GENE AND CELL THERAPY

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CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) is a genetic disorder that results from somatic, mosaic gain-of-function mutations of the PIK3CA gene, and belongs to the spectrum of PIK3CA-related overgrowth syndromes (PROS). This rare condition has no specific treatment and a poor survival rate. Here, we describe a postnatal mouse model of PROS/CLOVES that partially recapitulates the human disease, and demonstrate the efficacy of BYL719, an inhibitor of PIK3CA, in preventing and improving organ dysfunction. On the basis of these results, we used BYL719 to treat nineteen patients with PROS. The drug improved the disease symptoms in all patients. Previously intractable vascular tumours became smaller, congestive heart failure was improved, hemihypertrophy was reduced, and scoliosis was attenuated. The treatment was not associated with any substantial side effects. In conclusion, this study provides the first direct evidence supporting PIK3CA inhibition as a promising therapeutic strategy in patients with PROS.

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LENTIVIRAL GENE THERAPY IN RAG1 SEVERE COMBINED IMMUNODEFICIENCY: EXPERIENCE FROM THE MULTI-CENTER RECOMB TRIAL

GENE AND CELL THERAPY

Arjan C. Lankester, MD, PhD; Willem-Alexander Children's Hospital/Dep of Pediatrics; Leiden University Medical Center, NL

Inborn Errors of Immunity (IEI) are a heterogeneous and growing group of over 450 rare genetic disorders affecting either the development or the function of the immune system. One of the most severe IEI is severe combined immunodeficiency (SCID), a life-threatening disorder caused by a severe deficiency of T lymphocytes which may be accompanied by deficiency of B or NK lymphocytes depending on the genetic defect. SCID babies are usually born asymptomatic but develop severe infections during the first months, including pneumonia, meningitis, sepsis, as well as failure to thrive, and without adequate treatment, they generally die within their first year. SCID is estimated to affect around 1:30,000-1:50,000 infants in the EU each year and the diagnosis is increasingly made through national new born screening programmes, improving their chance of survival.

Since more than half a century, allogeneic stem cell transplantation (allo-HSCT) represents the established curative treatment for SCID patients, by which the patients' deficient immune system is corrected by replacing the affected autologous stem cells by those from a healthy donor. While the chance for survival has increased during the last decades, allo-HSCT has the best outcome when performed with a human leukocyte antigen (HLA) matched family or unrelated donor, while the outcomes with a mismatched donor are less successful. One of the major limitations of allo-HSCT remains the intrinsic risk of GVHD, a harmful immune reaction of donor T-cells directed against the recipient's organs and tissues which has an unfavourable impact on clinical outcome and survival. Innovative autologous haematopoietic stem cell-based gene therapy (GT) has the potential to be an effective and safe alternative treatment while avoiding the classical allo-HSCT related complications. GT aims to introduce the therapeutic gene into the target cells using vectors to restore the production and function of wild-type protein. GT been successfully pioneered in two genetic SCID variants, ADA-SCID and X-SCID.

During last decade we have developed lentiviral (LV)-based GT for RAG1 deficient SCID which has resulted in the current RECOMB trial funded by the EU Horizon 2020 program. In contrast to all previous single center academic GT trials, the RECOMB trial has a multicenter design which includes centralized academic manufacturing of the LV-RAG1 product which allows the patient to be treated in its own national expert center. The first patients have been recruited, and the LV-RAG1 product was successfully generated and administered. Data on the clinical and immunological outcome of the study patients will be presented as well as our experiences with clinical trial implementation at multinational level.

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ADVANCES IN CELL AND GENE THERAPY FOR GENODERMATOSES. A FOCUS ON EPIDERMOLYSIS BULLOSA

GENE AND CELL THERAPY

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Regardless of the sophistication of the healthcare environment, access to and the effective Genodermatoses represent a substantial proportion of the nearly 7,000 known rare diseases, most of them monogenic entities. Within the long list of genodermatoses, skin fragility disorders en-compass a large group that includes all four types of Epidermolysis Bullosa (EB) (i.e., Simplex, Junc-tional, Dystrophic, and Kindler Syndrome), all of which sharing widespread blistering and fragility but differing in severity and associated comorbidities. Recessive dystrophic EB (RDEB) is one of the most severe and devastating forms due to the absence or greatly reduced levels of collagen VII (C7), the component of anchoring fibrils, one of the protein structures that adhere the epidermis with the underlying dermal skin compartment. In addition to skin fragility, RDEB presents with scar-ring, severe fibrosis, and a high propensity to develop aggressive squamous cell carcinomas. Exper-imental gene therapy approaches to correct the lack of C7 due to mutations in the COL7A1 gene have been explored for more than 20 years. In recent years, some of these gene addition strategies, after passing Phase III clinical trials, are close to reaching the final stages of becoming ap-proved RDEB drugs. More recently, precise and biosafe approaches involving COL7A1 gene editing have been refined to the point that their efficacy and safety are rapidly making their way to clinical applications. In my talk, I will describe our efforts to achieve ex vivo and in vivo clinically relevant gene editing strategies currently based on CRISPR/Cas technology to correct different mutations in COL7A1 that, combined with skin bioengineering, will provide advanced therapies for a devastating disorder as RDEB.

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AAV-MEDIATED GENE THERAPY IN DUCHENNE MUSCULAR DYSTROPHY – EFFICACY AND IMMUNE RESPONSES

GENE AND CELL THERAPY

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Adeno-associated virus (AAV) is widely used as a gene delivery vehicle partially due to its low immunogenicity. Promising results have been seen in many clinical studies, with several approved products now available for patients. However, a number of the high dose systemic gene therapy clinical trials have observed heightened innate immune responses such as complement activation, decreased platelets and red blood cell counts, elevated liver enzymes, and acute kidney injury. Mechanistic understanding of the immune responses is limited but the apparent benefits of AAV gene therapy are driving large efforts to mitigate safety risks for this approach.

Several clinical trials are testing high dose AAV gene therapy for the potential treatment of Duchenne muscular dystrophy (DMD), a progressive, lethal form of muscular dystrophy caused by the absence of the protein dystrophin. One such study is IGNITE-DMD, a Phase I/II study of SGT-001, an AAV9-mediated microdystrophin gene therapy that is evaluating a unique, rationally designed form of dystrophin that contains critical domains for protein functionality, and that fits within the packaging capacity of an AAV. Functional benefits over 2-plus years have been shown, with stabilization or improvement in multiple assessments determined when compared to both baseline and against expected natural history declines. However, notable immune responses to AAV gene therapy were also observed, with several subjects have experiencing SAEs associated with complement activation within the first weeks following dosing of AAV.

Despite the apparent benefits of high dose AAV gene therapy, an increased understanding of the immune response in the clinical setting, as well as the development of methods to better evaluate the interactions, are critical. We have investigated innate immune activation, including complement activation, stimulated by AAV vectors using several in vitro systems, as well as investigation into the clinical observations. The findings suggest many of the responses are dependent upon the presence of anti-AAV antibodies and occur in a dependent manner for AAV capsid levels. The development of the in vitro systems has provided additional insights to the mechanism of immune system activation. Mitigation strategies to reduce the level of the response must now be considered to increase the opportunity for the safe and efficacious use of AAV-mediated gene therapy.

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FROM MILA TO MILLIONS: OPPORTUNITIES FOR INDIVIDUALIZED MEDICINES

GENE AND CELL THERAPY

Julia Vitarello, Mila's Mom; Mila's Miracle Foundation, USA

My six-year-old daughter Mila was diagnosed with a rare fatal genetic disease with no cure. In a race against time together with Dr. Tim Yu and his team at Boston Children's Hospital, Mila became the first person in the world to receive a drug tailored to just one person, called milasen.

Unfortunately, my fight was not in time for my daughter. However, her story showed what is possible: that a medicine can be made to target the underlying genetic cause of disease, often a single mutation, even if unique to just one person. Instead of one drug for tens of thousands of people, Mila's story lights the way towards a future of tens of thousands of drugs each for one or very few.

Genetic disease is a global health crisis, with hundreds of millions of children alone affected, many of which will die before the age of five. The individualized medicine approach offers a cross-cutting, impactful solution. We can now pinpoint the underlying genetic cause and design a medicine to target it. But this approach doesn't fit within our current system. We have the science and technology, we have millions of dying children who could benefit, but there is no rational framework for making this approach accessible to those who need it.

So, how do we get from Mila to Millions?

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OPERATIONAL DESCRIPTION OF RARE DISEASES - A REFERENCE TO IMPROVE THE RECOGNITION AND VISIBILITY OF RARE DISEASES

SYSTEMS THINKING TOWARDS ACCESS

Mary Wang, Amy Whiting
Rare Diseases International

Improving health and social equity for persons living with a rare disease (PLWRD), and their families, is increasingly recognized as a global policy priority. The adoption of both the Political Declaration on Universal Health Coverage that includes mention of rare diseases and the United Nation General Assembly Resolution on "Addressing the Challenges of Persons Living with a Rare Disease and their Families" are important milestones, recognizing the need of PLWRD and their families.

As public health agencies and governments at regional, national, and international levels develop and implement new policies to support the rare disease community, they need a common reference – an operational description – that describes what diseases are considered rare, how many persons are affected, and why the rare disease community demands their specific attention. Rare Diseases International (RDI), in collaboration with a global panel of rare disease experts and the World Health Organization, has developed an internationally endorsed Operational Description of Rare Diseases. The Operational Description of Rare Diseases is framed in two parts: 1) A core definition of rare diseases, complemented by 2) a descriptive framework of rare diseases.

The adoption of this Operational Description of Rare Diseases as a common reference is an essential step toward improving the recognition of all rare conditions, and their visibility in health systems and allow for a baseline to monitor measurable change at different levels. Beyond its purpose to guide policy decisions, the operational description will serve as a common reference to inform the work of a wide range of stakeholders. It can bring positive impact on prioritisation of research and development activities, and advance new actions and policies to improve health and social care services for PLWRD.

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ADDRESSING THE UNMET NEEDS OF PERSONS LIVING WITH UNDIAGNOSED AND RARE DISEASES IN GHANA

SYSTEMS THINKING TOWARDS ACCESS

Samuel Agyei Wiafe, Rare Disease Ghana Initiative

Persons living with with rare diseases in Ghana face considerable gaps in access to health and social services. This is aggravated by competing public health priority including the high incidence of infectious diseases and other existing socioeconomic issues such as poverty. Also negative sociocultural beliefs and practices compound and worsen the experiences of affected families leading to a squeal of mental health challenges. The Rare Disease Ghana Initiative is a non-profit organization in Ghana dedicated to improving the lives of individuals and families affected by rare diseases. It aims to raise awareness, provide support and advocacy, and improve access to information, treatment, and care for those affected by rare diseases in Ghana. The organization works with various stakeholders, including healthcare providers, patients, government agencies, and international organizations, to achieve its goals. The Rare Disease Ghana Initiative also aims to build a network of healthcare providers, researchers, and patient organizations to advance research and improve treatment options for rare diseases in Ghana. Some common achievements include organizing campaigns and events to raise awareness about rare diseases and the challenges faced by those affected by them through its awareness and educational programs; Offering support to patients and families affected by rare diseases, including emotional and practical support, and connecting them with others in similar situations through its care coordination and support programs; Encouraging and supporting research into rare diseases, including clinical trials and genetic studies, to advance the understanding of these conditions and improve treatments through its Diagnostic and Treatment access programs; Working with government agencies and other stakeholders to advocate for policy changes and increased funding for research and treatment of rare diseases through its advocacy programs and Developing and maintaining a comprehensive resource center to provide information about rare diseases, treatments, and care options.

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LYFE LANGUAGES
SYSTEMS THINKING TOWARDS ACCESS

Yarlalu Thomas, Lyfe Languages AUS

Lyfe Languages – Linguistic and cultural differences, as well as the prevalence of medical jargon, are among the major factors impacting the ability of Indigenous Australians to engage with the health system and receive effective treatment. This is also evident globally for other First Nations groups who speak an Indigenous language as a primary language.
The Lyfe Languages project is aimed at breaking down barriers of communication by translating medical resources and terminology into the languages spoken by Indigenous people globally. Connecting with new technologies enables equitable transformation of health and well-being, and to create connected communities. The end goal, creating a universal medical translator via a mobile application to be used clinically for non-English speaking First Nations people.
The project first translations were created in the Rare and Genetic disease domain through the translation of human phenotype ontology (HPO) terminology. By linking translations with HPO terms with background coding capabilities, translations have the ability to be integrated into new and emerging technology such as artificial intelligence and Pilbara faces - 3D facial technology diagnosis platforms.
Through Language, Lyfe languages will contribute to closing the health gaps for First Nations people all across the globe.

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ENSURING ACCESS TO LIFE-SAVING GENE THERAPY FOR AN ULTRA-RARE DISEASE: A NOT-FOR-PROFIT MODEL

SYSTEMS THINKING TOWARDS ACCESS

Stefano Benvenuti, Fondazione Telethon, Italy

Fondazione Telethon has the mission to advance biomedical research towards the cure of rare genetic diseases. It is a charity funded 30 years ago by a patient organization (Unione Italiana Lotta alla Distrofia Muscolare – UILDM) and since then it has invested million of euro in biomedical research on rare genetic diseases. One of its main achievements was the EMA approval, back in 2016, of Strimvelis®, the first ex-vivo gene therapy approved worldwide. This therapy intends to treat children affected by severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) who lack a matching bone marrow donor. ADA-SCID is an inherited disorder caused by mutations in the ADA gene and results in a seriously compromised immune system. People affected by ADA-SCID almost lack all immune protection from bacteria, viruses and fungi becoming prone to repeated and persistent infections that can be very serious or life-threatening. Most patients are diagnosed in the first 6 months of life and, without treatment, they usually die before 2 years of age. Strimvelis® was developed by the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy who then partner with GlaxoSmithKline to complete the CMC activities of scaleup and validation of vector and transduced cells manufactured at the Italian biotech MolMed (now AGC biologics). In 2018 the marketing authorization was transferred to Orchard Therapeutics LTD (OTL) that is still distributing Strimvelis® but announced, at the end of march 2022, that it will discontinue the programme. As no other alternative therapies are available for those patients, Fondazione Telethon decided to step-in and started a negotiation with OTL to ensure Strimvelis® will remain available to the patients. The parties agreed on a two-step process:

1. a transition period when OTL will keep the ownership of the marketing authorization, but the costs not covered by the reimbursement of the treatment will be covered by Fondazione Telethon. This transition period will allow Fondazione Telethon to re-organize internally in order to become able to take over the marketing authorization.
2. the transfer of the marketing authorization of Strimvelis® to Fondazione Telethon

The first step is almost complete, and soon Fondazione Telethon could become the first and only (at least in Europe) not-for-profit holder of a marketing authorization for an EMA approved gene therapy.

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NOTES

DELEGATES' ABSTRACTS

IN SILICO DRIVEN DRUG REPURPOSING OF LYSOSOMAL STORAGE RARE DISEASES INHIBITORS

ABSTRACT N° A001 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Lysosomal storage rare diseases represent a group of about 50 pathologies, characterized by accumulation of lipid substrates in lysosomes. Among them, our interest focused on Niemann–Pick type C (NPC). NPC is an autosomal recessive disease caused by the mutation of NPC1 and NPC2 genes, coding for two proteins involved in the intracellular trafficking of cholesterol and other lipid, that is characterized by an accumulation of unesterified cholesterol and sphingolipids, finally resulting in severe visceral and neurological symptoms. Glucosylceramide synthase (GCS), the enzyme able to catalyze the key reaction in the biosynthesis of glycosphingolipids, is the target of the only available therapeutic approach in use. Thanks to a state of the art computational approach, we have been able to characterize at an atomistic level this enzyme, by means of Induced Fit Docking, classical Metadynamics, Well-Tempered Metadynamics and Free-Energy Surface analysis on a model system obtained by AlphaFold protein structure database. Specifically, we have elucidated the binding mechanism of the endogenous substrates, the ceramide and the UDP-glucose, as a prerequisite for a better characterization of the binding mode of two different inhibitors: Miglustat and Cambinol. The first one is an already approved drug for treatment of NPC and related lysosomal disorders such as Gaucher disease. Cambinol is a sirtuin inhibitor, that has been demonstrated to inhibit also GCS activity with completely different chemical characteristics with respect to Miglustat. The aim of this study is to identify the structural determinants in the GCS enzyme that may be target of other novel drug compounds using an in silico driven drug repurposing approach.

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MULTI-OMICS MOLECULAR SIGNATURES IN INCLUSION BODY MYOSITIS

ABSTRACT N° A002 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Introduction
Inclusion Body Myositis (IBM) is a rare progressive muscle disease in elderly individuals. Despite extensive research effort, the molecular etiology remains unclear, primarily due to the complexity caused by the co-existence of inflammation and muscle degeneration. The analysis of multi-omics data provides a promising avenue for elucidating the mechanisms causing IBM by providing a comprehensive view of the molecular state of the tissue.
Methods
We have constructed a multiplex multi-omics IBM disease network from prior knowledge and gene correlation data. We used four types of information to represent the edges in this network:

- Protein-protein interactions from STRING.
- miRNA targets from miRTarBase.
- mRNA-mRNA and mRNA-miRNA correlation from IBM expression data.

Gene nodes were given a combined p-value based on differential gene expression and genetic variant burden, while miRNA nodes were given a p-value based only on differential miRNA expression. We applied the active subnetwork identification algorithm, MOGAMUN, on the integrated network in order to detect dense subnetworks with low p-values.
Results
Our analysis resulted in the detection of five subnetworks. We annotated these subnetworks with the most representative GO terms, which were "antigen processing and presentation", "chemokine-mediated signaling", "mRNA splicing", "rRNA processing" and "immune response – signal transduction" respectively.
Interestingly, the antigen processing and presentation subnetwork contained many overexpressed HLA genes, which are consistently found to be an important feature of IBM. In this subnetwork, these genes are connected to the underexpressed miR-16, which is known to inhibit the immune system in mice in combination with miR-15a. We also detected an interesting indirect link between the HLA genes and SQSTM1.
Discussion
The resulting subnetworks show that our approach is able to find changes in one omics, that are linked to changes in the same, or another omics in our network. Biologically, the resulting subnetworks point to hypotheses that could be explored in follow up experiments. In the case of miR-16, this indicates a possible role of this miRNA in the regulation of the HLA genes and the potential of increasing the abundance of this miRNA through miRNA delivery in order to inhibit the immune response in IBM. This, and other hypotheses that result from our experiment, could be starting points for future studies.

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A CASE DATABASE FOR INHERITED METABOLIC DISEASES AS A GLOBAL, SHARED EDUCATIONAL RESOURCE

ABSTRACT N° A003 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Purpose: The early identification of Inherited Metabolic Diseases (IMDs) and initiation of therapy (when available) can help to reduce its morbidity and mortality. Since IMDs are (ultra)rare diseases with often rather aspecific presenting symptoms, medical doctors/ metabolic specialists will not always recognize them. Both from clinical and laboratory perspectives, recognition of an IMD depends on the experience with the specific IMD and the knowledge of its clinical spectrum.
Methods: The case database on inherited metabolic diseases (CDB-IMD) is built with the open-source web platform Drupal. The CDB-IMD is a repository of structured IMD case which are extensively described both on clinical and laboratory aspects. The cases undergo a peer review process before they are visible in the CDB-IMD to guarantee high quality. The CDB-IMD will contain both typical and atypical cases representing > 1400 IMDs as classified in the ICIMD 2020. The General Data Protection Regulation (GDPR) warrants the patient's privacy in the CDB-IMD. Patient's informed consent should accompany every submission of a case.
Results: The CDB-IMD contains > 40 IMD cases from different institutes. The added value of the CDB-IMD lies not only in studying a case but comparing and discussing cases on various aspects. In early 2023, free access will be granted to all professionals who have shown their credentials and are involved in the diagnostics and treatment of IMDs.
Conclusion: The cases in this database are intended to help CDB users to learn from, teach with and share IMD cases. Sharing of knowledge and exchanging experiences with IMDs will enhance the awareness and recognition of an IMD. Future plans are incorporating an e-learning tool into the CDB-IMD as well as patient trajectories.
The initiative was funded by United for Metabolic disease (UMD), the Netherlands with a Catalyst grant (UMD-CG-2019-003), and got donations from the SSIEM as well as Metakids. The authors like to acknowledge Prof. dr. CDM van Karnebeek and Prof. dr. J Häberle for their ongoing support.

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IMPLEMENTING A MULTIDISCIPLINARY PROGRAM FOR UNDIAGNOSED RARE DISEASES IN CHILE

ABSTRACT N° A004 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Exome sequencing (ES) has revolutionized the diagnosis of rare diseases (RDs). Nevertheless, availability is limited in most countries. We aimed to implement a pilot program of ES for undiagnosed RDs in Chile to increase diagnostic yield, discover new disease-causing genes and variants in our understudied population, and produce data that can contribute to public policies for the health system. Patients of any age, with a broad spectrum of phenotypes that suggest a RD of presumptive genetic origin, and in whom clinical services available in Chile have not allowed to reach a causal diagnosis, were invited to participate. Human Phenotype Ontology terms were used to describe clinical manifestations. Clinical ES (CES) was performed in-house, while solo or trio whole ES (WES) were outsourced abroad. Bioinformatics and interpretation were performed locally by an interdisciplinary team of clinicians, laboratory scientists, and bioinformaticians, using Sophia DDM®, and the results were returned to participants. To date, 98 patients have participated (50.1% females), with a median age of 10.88 years, ranging from 0 to 52 years. Most cases were isolated within a family: phenotypic manifestations included major congenital anomalies, growth disorders, neurologic abnormalities, and immune dysregulation, among others. The overall diagnostic rate of ES was 51%. The diagnostic yield, according to the sequencing strategies, was 25% for CES (first 16 participants), 50% for solo WES (25 participants), and 60% for trio WES (57 participants). The majority (61%) of identified disease-causing variants were de novo, while 30% of them were inherited in recessive, dominant or X linked patterns. Remaining variants are awaiting parental studies. These results show the high impact of ES in diagnosis of RDs across heterogeneous clinical manifestations, with trio ES resulting in the highest yield. This hybrid outsourced sequencing and local interpretation model may be a feasible option for genomic diagnosis in countries with limited sequencing capabilities. Ongoing studies by our team are exploring the impact of achieving a diagnosis (or not) in patients' and caregivers' quality of life, health care management and their journeys in the healthcare system. Finally, our program aims to incorporate the voices and experiences of persons living with RDs and their families in the process of generation of new knowledge, necessary to contribute to public policies with a local perspective.

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DIAGNOSIS OF RARE DISEASES IN PRIMARY CARE: THE SINGLE-PRACTICE EXPERIENCE

ABSTRACT N° A005 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Introduction
Despite the low prevalence of each of the rare diseases, the proportion of patients suffering from at least one of them is estimated at 5–8% of the population in developed countries. Israel has a strong public health system with comparable diagnostic support in all its regions. It can be assumed that the number of patients with rare diseases in each primary care division should be close to the estimate.
Material & methods
The study was conducted at Clalit Medical Services' typical outpatient clinic in Israel. The distribution of patients by age corresponded to the structure of the population in the country, with a slight deviation towards the population over 45 years of age.
During 2022 current diagnoses of every patient were checked according to the personal electronic medical record and added with diagnoses from the medical specialists. The persons diagnosed with a rare disease were merged into the first group. The second group consisted of patients with rare clinical syndromes for whom we couldn't establish an accurate diagnosis during the study period.
Additionally, we located a group of patients under the age of 45 who had a concoction of various unrelated illnesses. We suggested that they might be signs of a single, incredibly rare disorder with clinical manifestations in different body systems.
Results
The total number of 1916 patients seen at the clinic throughout the year remained essentially constant. Among them were 1,515 adults and 401 kids under the age of 15.
There were 60 (3.13%) people with a registered rare disease, 18 in the continued medical delay group, and the same number of young patients with a combination of several isolated disorders.
In total, there were 96 patients in three groups which is 5.01% of all patients observed in our clinic.
Conclusion
In the typical Israel outpatient practice, there are fewer patients with rare diseases with diagnoses than predicted proportion. Simultaneously, adding people with rare clinical syndromes and the youngest part of patients with multiple isolated diagnoses allows us to get close to an estimate.

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CRITICAL STEPS TOWARDS LARGE-SCALE IMPLEMENTATION OF THE FAIR DATA PRINCIPLES

ABSTRACT N° A006 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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The process of making data Findable, Accessible, Interoperable and Reusable (FAIR - FAIRification) varies across projects, depending on their objectives and domain needs. However, such variation can complicate identifying the best workflow for an efficient large-scale national implementation. It is therefore necessary to align the different FAIRification processes and workflows. With this aim in mind, we mapped a set of FAIRification workflows to understand the divergence among them and identify critical common FAIRification and domain-specific steps. This work was executed in the context of the Dutch Health-RI and the European Joint Programme on Rare Diseases (EJP RD), which both rely on the FAIR principles to enable sustainable data reuse in the healthcare domain. First, we gathered a group of FAIR experts amongst the collaborators in the two initiatives. Next, we identified a set of relevant workflows used within the rare disease domain and the Dutch health research infrastructure context. A total of seven workflows were selected, including the EJP RD FAIRopoly, given its compilation of the De Novo and Generic workflows. Through several hands-on meetings, we discussed the interpretation and best mapping of the workflows' steps. Finally, we considered any steps that were mapped in more than four workflows (>50%) as critical. Preliminary results show three critical steps: a) identification of FAIRification objectives and expertise, b) (meta)data assessment, definition and semantic modelling, and c) defining data licensing (or consent), access and use conditions. The first can impact the success of the FAIRification of projects, whereas (meta)data assessment and modelling are intrinsically related to the core of the FAIR principles: semantic interoperability and machine actionability of (meta)data. Finally, licensing (consenting), accessing and reusing conditions are equally crucial for healthcare data reuse as they protect sensitive information.

Future work includes identifying and analysing domain-specific steps and detailing each critical step into recommended resources, checklists and needed expertise. Any training needs regarding the FAIR expertise capacity can then be identified from such descriptions. We expect that embedding critical steps in the national research infrastructure can improve FAIR data availability.

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THE IMPACT OF DEDICATED FAIRIFICATION STEWARDSHIP GUIDING EUROPEAN REFERENCE NETWORKS TOWARDS MAKING RARE DISEASE RESOURCES FAIR

ABSTRACT N° A007 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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The EJP RD stewards' team was established in July 2020 to support European Reference Networks (ERNs) in creating Findable, Accessible, Interoperable and Reusable (FAIR) patient registries. To track the evolving registry FAIR implementations, the steward's team collected the ERNs' reported updates in an implementation status inventory. We here analyze the progress registered to understand the impact of the team's approach on supporting ERNs. The team conducted two rounds of online interviews in 2020 and 2021 to collect the ERNs implementation status. Prior to the interview, they sent ERNs an inventory structured into five phases: a) modelling; b) building the registry and collecting data; c) registering the registry; d) making data accessible for querying, e) querying data; and instructed ERNs to fill it using the terminology "Implemented", "Implementing assisted by expert", "Plans to Implement", "Needs Expert help" and "Not applicable". From a total of 24 ERNs, 20 completed the inventory. The results indicate an increase in the number of FAIR tools implemented from 2020 (32.6%) to 2021 (56.0%). Additionally, the percentage of tools that shifted from "Plans to implement" or "Needs expert help" to "Implemented" in 2021 were, respectively, 35.8% and 18.8%. In both years, the most significant increases in implemented tools are related to the modelling phase - 17.3% in 2020 and 29.2% in 2021 - and "making data accessible for querying" - 5.2% in 2020 to 13.2% in 2021. Out of all five stages, the tools more frequently marked as "Plans to Implement" in 2020 concerned the modelling phase (9.8%), which in 2021 decreased to 4.6%. Changes in staff and different people completing the inventory are limitations of this analysis, as they could result in different interpretations of categorizing the tools and, occasionally, the loss of reported evolution. Regardless, the joint approach between ERNs and Stewards appears to have resulted in more implemented tools, mainly in the modelling stage. It also allows prioritizing future efforts on accessibility and discoverability for querying, and data reuse. We expect the number of implemented tools to plateau and the tools planned for implementation or needing expert help to decrease as a result of the ERNs learning more about the options for FAIR data. "

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THE IRDIRC TELEHEALTH TASK FORCE: ENABLING AND ENHANCING TELEHEALTH FOR RARE DISEASES ACROSS THE GLOBE

ABSTRACT N° A008 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Purpose: The IRDiRC Telehealth Task Force was formed in October 2021 to explore the use of telehealth (TH) to improve access to diagnosis, care, and research experiences for rare disease (RD) patients worldwide, to identify existing models of TH, and to develop "best practices" for introducing TH services into RD communities.
Methods: Composed of 22 members, the group has met monthly since February 2022 to establish a definition of TH, then subdivide into working groups to focus on three topics: (1) diagnosis, treatment, and prevention; (2) research and evaluation; and (3) continuing education of healthcare providers. The group has conducted a systematic review of literature on the topic, and is now interviewing ~25 key opinion leaders (KOL) about existing models of TH.
Results: The group modified a definition of TH from the World Health Organization (2010) specifically for RD: "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of RD , research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals with RD and their communities." For the literature search, the team first identified 440 articles in PubMed from the intersection of TH and RD keywords, then reduced that to 256. Publications were assigned to Topic 1 (180), Topic 2 (136), and Topic 3 (40). Many papers identified patients and families as the main beneficiaries of TH. Papers were most often published by European (159) and North American (78) authors. A peak of publications occurred in 2021 at the time of the COVID-19 pandemic.
Conclusion: While the analyses of the literature and the KOL interviews are ongoing, there are some emerging conclusions. The use of TH for those with pre-existing medical conditions or wishing to avoid COVID exposures at hospitals and clinics has led to increased utilization by those with RD. Different regions with varying resources and technology platforms may require different approaches to TH for RD patients. Finally, TH affords the opportunity to conduct research and train a specialized workforce to build an interconnected RD community. In spite of regulatory, legal, and privacy challenges, TH will likely grow in use, at least for RD patients with limited access to personalized therapies.

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ADVANCES IN RARE HEREDITARY RED BLOOD CELL-RELATED DISEASES

ABSTRACT N° A009 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Red blood cell (RBC)-related diseases represent a highly heterogeneous group of disorders that are rare to ultra-rare. They can be divided in hemoglobinopathies, membranopathies or enzymopathies. Recent discoveries of the molecular basis of hydration defects is a major advance in the field. This resulted in the identification of causative genes in distinct types of hereditary stomatocytosis which improved diagnostic workup. As a result, the reported incidence of hereditary xerocytosis (HX), previously calculated to be ca. 1:50,000 births, is now estimated 1:8,000 adults. It is widely accepted that other unknown genes are involved in these disorders. Most of the reported pathogenic variants reside in the PIEZO1, KCNN4, SLC4A1, RHAG and SLC2A1 genes which code for large multispanning transmembrane proteins and the mutations determine unregulated cation movement across the membrane. Most of the HX-associated PIEZO1 gain-of-function mutations decrease the kinetics of channel inactivation. They may, however, also affect the response to osmotic stress and membrane trafficking, thus contributing to phenotypic heterogeneity. The large number of causative variants, the very high number of VUS, the interactions with other transporters or proteins and finally the coinheritance of other gene variants further determine the hematological and phenotypic heterogeneity. In this study we present the recent progress and the open challenges in diagnosis and pathophysiology of these disorders. In particular:

- How PIEZO1 mutations impair channel function and alter RBC physiology;
- Cell-type-specific roles of PIEZO1 depending on lipid composition and interacting protein complexes;
- How to develop functional test to assess novel variant pathogeny.

Different studies have demonstrated the usefulness of t-NGS panels to classify rare anemias, that are, however, insufficient to identify the molecular causes in all patients. A conspicuous percentage of patients remain undiagnosed after t-NGS analysis. Among 122 hemolytic patients with a clear indication for hemolytic anemia, the final diagnosis was confirmed in 74% of the patients; the rate of diagnosis falls to ca. 35% in hemolytic patients with no diagnostic orientation. Establishing the correct differential diagnosis is highly important for proper treatment, whereas splenectomy for example can be beneficial in some of the hereditary RBC disorders, it is strongly contraindicated in others, such as dehydrated stomatocytosis.

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PHENOCLINWARE: A WEBSERVER TO EXPLORE HUMAN PATHOLOGICAL PHENOTYPES AND EXPAND PATIENT CLINICAL CHARACTERIZATION

ABSTRACT N° A010 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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In the era of precision medicine, it is crucial to have a system for the complete phenotypic characterization of patients to ensure accurate diagnosis. For this purpose, we developed PhenoClinWare (https://clinsysbiolab.es), a webserver for the deep phenotyping of patients using terms for human anomalies from the Human Phenotype Ontology (HPO).
PhenoClinWare has an account system that allows the user to create patient records to store HPO phenotypic data, quantified external features and descriptive data, such as patient age and sex and test results. Groups can be created, to share patient data with other researchers. It includes a phenotypic term search engine to help the user select ontology terms when characterizing the patient, avoiding redundancy of information and terminology errors. It includes a visualization system for the HPO structure that shows when there are more specific terms available within the ontology, helping the user to perform accurate and deep characterization. It also offers phenotype suggestions based on co-occurrence across hundreds of OMIM and Orphanet diseases via the Mondo Disease Ontology. Finally, PhenoClinWare implements Phenogrid from the Monarch Initiative to suggest related human diseases and genes from animal models, helping to infer what potential disease the patient has and what genes may be involved.
We used PhenoClinWare to analyse patients in the Undiagnosed Diseases (ENoD) Program from the CIBERER initiative, a Spanish research network for rare disease, to improve their phenotypic characterization and suggest genes and related diseases. We selected four patients whose primary clinical feature was syndromic retinitis pigmentosa. The patient profiles were expanded with the phenotype suggestions based on the comorbid data and confirmed based on professional expertise. Phenogrid results returned retinitis pigmentosa among the top three disease suggestions for three of the patients, among other conditions. We conclude that PhenoClinWare can be used to expand patient phenotyping, providing information to suggest subsequent analyses to determine the possible molecular consequences of the disease, and improves the quality and accuracy of diagnosis.
This work is supported by the Spanish Ministry of Science (PID2019-105010RB-I00, PID2019-108096RB-C21), the Andalusian Government, FEDER, Universidad de Málaga and IBIMA-BIONAND grants (UMA18-FEDERJA-102, UMA18-FEDERJA-220, PY20 00257, PY20 00372, RH-0079-2021).

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ESTABLISHING ADVISORY COMMITTEES FOR THERAPEUTICS (ACT) IN RARE DISEASES

ABSTRACT N° B001 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Within the European Joint Programme for Rare Diseases (EJP RD), we have developed a toolkit to replicate the TREAT-NMD Advisory Committee for Therapeutics (TACT) model. This model has been successful in the neuromuscular field for over 13 years and has reviewed over 70 applications, from both academia and industry, for advice on the translational and development pathway of therapeutic programs in neuromuscular diseases. The Advisory Committee for therapeutics (ACT) toolkit provides procedural advice on how to set-up a committee of drug development experts, including patient representatives, to provide independent and objective advice on drug development programmes in rare diseases. The ACT toolkit is now freely available within the EJPRD Innovation Management Toolbox, accessible via the EJP RD website.

Aim

An aim of EJP RD is to identify good practices and support adoption in other communities. A degree of strategic oversight is needed to expand the ACT model into other rare disease communities and the thematic groupings of European Reference Networks (ERNs) provide a logical framework to set-up an ACT in other rare diseases. To support the facilitation of the toolkit, we applied for and were successful in receiving funding to hold an EJP RD ERN workshop designed to communicate the benefits of the model and to discuss the feasibility of adopting the ACT model with ERN representatives. This introductory workshop was attended by representatives, including ePAGs, from 11 different ERNs. After the conclusion of the workshop, we identified three ERNs who are looking to explore the feasibility of setting up their own ACT within a specific disease area. Our aim is to support them in applying the learnings from the ACT toolkit and the Neuromuscular TACT model to set-up their own ACT.

Conclusion and next steps

The EJP RD ERN workshop introduced the concept of the ACT model, presented lessons learned from the neuromuscular field and facilitated discussions about the feasibility of adopting the model within participant's ERNs. We now plan to hold a more focused workshop to allow these ERNs to explore the feasibility of adopting an ACT along with key stakeholders in their field.

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DISSECTING THE PATHOGENETIC ROLE OF NON-MYOGENIC MESENCHYMAL CELLS IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY PATIENTS: SEARCHING FOR NOVEL THERAPEUTIC TARGETS

ABSTRACT N° B002 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Facioscapulohumeral muscular dystrophy (FSHD) is a rare muscular disease characterized by a highly variable pattern of muscle involvement. It is due to an epigenetic modification involving the inappropriate expression of DUX4 gene, a transcription factor normally silenced in adult human tissues. The pathogenetic mechanisms underlying the progressive muscle weakness in FSHD patients have not been fully clarified and there is no efficient treatment available to date. In the skeletal muscle different cell types cooperate to maintain tissue homeostasis, and non-myogenic mesenchymal cells play key roles in orchestrating tissue homeostasis. They promote myogenesis upon a damage, but in a degenerative environment they accumulate and cause the aberrant deposition of fibrous and adipose tissue promoting muscle wasting. We have recently demonstrated that non-myogenic mesenchymal cells contribute to FSHD pathogenesis showing a direct association between an altered accumulation and differentiation of these cells and muscle degeneration in FSHD affected muscles. The purpose of our study is to better define in which way non-myogenic mesenchymal cells sustain muscle degeneration in patients, focusing on their crosstalk with myoblasts, to identify novel therapeutic targets.
Non-myogenic mesenchymal cells and myoblasts were isolated from muscle specimens of FSHD patients and controls. To assess the effects of non-myogenic mesenchymal cells on the proliferaton and differentiation properties of FSHD myoblasts, we conducted co-culture experiments using transwell systems. We also performed direct in contact co-cultures to investigate the molecular effects of the cell contact. We then evaluated the expression of DUX4 signalling by digital droplet PCR (ddPCR) in non-myogenic mesenchymal cells isolated from FSHD muscles.
Our results showed that the presence of non-myogenic mesenchymal cells promote myoblast proliferation. In contrast, smallest effects were exerted on myogenic differentiation. Regarding the activation of DUX4, our data suggested that MBD3L2 expression levels were increased in cells isolated from FSHD muscles compared with control cells.
The role of non-myogenic mesenchymal cells in tissue damage and regeneration is an emerging topic in current research on muscular dystrophies, so elucidating their role in FSHD could help to clarify disease pathogenesis and to identify specific pathways eligible as novel therapeutic targets in patients.

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RARE DISEASES CLINICAL TRIALS TOOLBOX: PUBLIC RESOURCES AND MAJOR CONSIDERATIONS TO SET UP A CLINICAL TRIAL ON MEDICINAL PRODUCTS FOR HUMAN USE IN EUROPE

ABSTRACT N° B003 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Background: Drug development programmes in rare diseases have many challenges, some of which differ from those facing researchers working on common diseases, like the scarcity of patients.
Over the past years, research and regulatory initiatives and resources have been introduced to expedite drug development for rare diseases. Nevertheless, these tools have been developed in the frame of different projects and with different aims and therefore they have not been yet framed as a whole for the conduct of clinical trials. To address this issue, the EJP RD (European Joint Program for Rare Diseases) has developed the Rare Diseases Clinical Trial Toolbox.
Purpose: The toolbox collects the accumulated knowledge, experience, and resources (collectively termed as 'tools') generated by previous projects and/or research infrastructures and other organizations into an organized, practical and guided instrument to help clinical trialists and trial managers understand the regulations and requirements for conducting trials, with special focus on investigator-initiated trials for rare diseases.
Methods: The toolbox is structured into five domains: research question, plan, execute, analyse, and end of trial. Each domain describes one or several activities to be considered and at what stage of the trial pathway these activities should take place, regardless of the therapeutic area. Each domain/activity is further hyperlinked to resources that are relevant for those specific activities. Associated resources are public documents, deliverables, templates, and other outcomes of previous projects and/or developments of relevant clinical research stakeholders. Selected tools must be of fundamental importance to clinical trials and with special focus on the rare diseases clinical research.
Results: The current version of the toolbox, which has been labelled "IRDiRC recognized resource" (https://irdirc.org/resources-2/irdirc-recognized-resources/) includes 96 resources tagged as relevant for any of the 18 activities within the clinical trial outline. Overall, 75 % of all resources are relevant to any clinical trial while 25 % are tagged as "rare disease/paediatric-specific".
Conclusion: Access to public resources relevant for the development of clinical trials for rare diseases is sometime challenged by limited awareness and/or absence of an adequate frame that make them findable. This Toolbox aims at building a frame for the optimal use of existing tools.

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THE IRDIRC DRUG REPURPOSING GUIDEBOOK – CREATING AN EFFICIENT AND VISIBLE PATHWAY FOR RARE DISEASES

ABSTRACT N° B004 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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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 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.

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ACCELERATING DRUG REPURPOSING FOR RARE NEUROLOGICAL, NEUROMETABOLIC AND NEUROMUSCULAR DISORDERS BY EXPLOITING SIMILARITIES IN CLINICAL AND MOLECULAR PATHOLOGY

ABSTRACT N° B005 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Background: Drug repurposing can fill an important gap for rare disease patient groups with large unmet medical needs. In comparison to traditional drug development, drug repurposing reduces the time and costs for drug development, regulatory approval, and market authorization. Yet, we need to increase the efficiency of the drug repurposing pathway to provide broader access to new therapeutic modalities for larger groups of patients.
Purpose: To unite multidisciplinary expertise to develop a novel approach of accelerating drug repurposing for rare neurological, neurometabolic and neuromuscular disorders.
Results: We have assembled the SIMPATHIC consortium comprising representatives for patients & families, pharma companies, basic, translational and clinical scientists, bio-informaticians, ethicists and methodologists. The project has been selected for funding in tn the Horizon Europe program. Our main accelerating innovation is the simultaneous drug development for groups of patients with different genetic diagnoses but overlapping neurological symptoms and molecular pathomechanisms. SIMPATHIC's key outputs accelerating the drug repurposing pathway include: Standard operating procedures for culturing stem cell-derived neuronal cell models with proven relevance for clinical symptoms and amenable to high-throughput drug screens; new drug repurposing candidates with proven efficacy in advanced brain-on-a-chip and 3D brain organoid models, as demonstrated by reversal of molecular biomarker signatures and cellular readouts associated with clinical symptoms; designs of innovative basket clinical trials to which patients with different disorders are recruited, utilizing and aggregating personalized clinical endpoints; a training module for patients and patient organizations to empower them as drivers of the drug repurposing pathway; blueprints for intellectual property strategies, business models, regulatory dossiers and patient access strategies, developed in co-creation between all relevant stakeholders.
Discussion: SIMPATHIC's proof-of-concept for the simultaneous development of repurposed drugs for multiple indications will show the path forward to development of personalized treatment opportunities for groups of rare disease patients in a cost- and time-efficient manner.

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ARTERIAL THROMBOSIS IN HUTCHINSON GILFORD PROGERIA SYNDROME

ABSTRACT N° B006 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Introduction: Hutchinson-Gilford Progeria Syndrome (HGPS) is a genetic disorder characterized by progressive premature aging. It is caused by defects in the nuclear A-type lamin gene, leading to intracellular accumulation of progerin. Children with HGPS have a decreased life expectancy with the most frequent cause of death being myocardial infarction and ischemic stroke – two cardiovascular events that are tightly linked to arterial thrombosis. Declined vascular function and compliance have been reported in HGPS patients. However, the effect of the specific lamin A gene mutation on coagulation and thrombus formation remains uninvestigated.

Methods: 28- to 30-week-old male and female transgenic heterozygous LmnaG609G knock-in (HGPS) mice and corresponding wild-type (WT) littermate controls were exposed to photochemically-induced carotid artery endothelial injury to trigger arterial thrombosis. Coagulation and fibrinolytic factors were measured in these animals using ELISA kits. Ex-vivo platelet activation assay was also performed.

Results: HGPS mice displayed accelerated thrombus formation compared to the WT animals as underlined by a shortened time to occlusion. No significant differences were found in the level of tissue factor, von Willebrand factor as well as factors involved in the fibrinolytic system, as also confirmed by the comparable level of D-dimers in both groups. Interestingly, a higher level of thrombin-antithrombin complex was observed, accompanied by lower level of antithrombin. In addition, HGPS animals displayed enhanced platelet activation markers expression upon collagen- and thrombin-induced activation compared to WT group, demonstrating a higher platelet reactivity in progeria animals.

Conclusions: Our results show an increased arterial thrombotic response in HGPS mice as compared to WT littermates, which, at least in part, is mediated by higher platelet reactivity. This novel observation may provide a mechanistic explanation for the increased incidence of acute cardiovascular events observed in HGPS patients, thus warranting further clinical investigations also in consideration of the available antiplatelet therapies.

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INFRAFRONTIER: VALUABLE IN VIVO RESOURCES FOR MODELLING RARE DISEASES

ABSTRACT N° B007 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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An estimated 30 million people in Europe suffer from one of the 7000 rare diseases (RDs) known, which affect less than 1 in 2000 individuals. The prevalence of these diseases is remarkable, yet the field still experiences a deficit of medical and scientific knowledge. The EU helps mitigate the shortage of information by backing research and cooperative initiatives regarding RDs.
INFRAFRONTIER, the European Research Infrastructure for modelling human diseases, provides services for the systemic phenotyping of genetically modified mice in participating mouse clinics. Furthermore, thanks to the European Mouse Mutant Archive (EMMA), the Research Infrastructure offers the archiving and distribution of mouse-mutant strains, including RD-related ones, for research. Users can access relevant resources on RDs from the INFRAFRONTIER consortium presented in three forms: a) as EMMA strains linked to RDs, b) as EMMA publications related to RDs, and c) as information on INFRAFRONTIER activities at RD conferences, meetings, and projects.
This presentation will highlight INFRAFRONTIER services and resources geared towards RD research. That includes access to over 2200 mouse strains - via EMMA - related to more than 1600 distinct RDs, state-of-the-art rodent model generation with precise genome editing, and systemic phenotyping of these models. The number of mouse strains relevant to the RD community is continually growing due to new mutant strains deposited at EMMA and to the effort of the INFRAFRONTIER data curators responsible for the appropriate annotation.
Through our participation in the European Joint Programme on Rare Diseases (EJP RD), EMMA mouse models relevant to RD research will be easily findable via the EJP RD virtual platform - currently under development -.

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ZELLWEGER SPECTRUM DISORDER : INDIVIDUALIZED RESEARCH DELIVERED NEW HOPES FOR PATIENTS WITH PEX DEFICIENCY

ABSTRACT N° B008 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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APTEEUS is bringing drug discovery tools to patient bedside to identify opportunities of repurposing existing drugs in monogenetic disorders. Since 2019, we are working in close collaboration with patient affiliated to 'La Marche de Noé', a French patient organization affected by peroxisomopathies, with clinicians and international researchers. A first program that lasted 12 months led to the compassionate use of a drug that would have benefit a very unique patient suffering from D-Bifunctional Protein deficiency, an ultra-rare peroxisomopathy. Unfortunately, the child died before we managed to demonstrate any effect of the drug. In 2020, we started a new program on peroxisome biogenesis disorder. We screened all existing drugs directly on patient cells and managed to increase significantly the biogenesis of cell peroxisomes and their function. That time, there is a real opportunity of repurposing a drug for a population of patients affected by the disease. The process of discovery, the pharmacological characterization of candidate drugs and the perspective of treating the animal model will be presented and discussed as a systematic approach to promote drug repurposing in the field of rare disorders.

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ANTISENSE OLIGONUCLEOTIDE EXON-SKIPPING AS A THERAPEUTIC APPROACH FOR A RARE DISEASE

ABSTRACT N° B009 / THERAPEUTIC DEVELOPMENT, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Introduction: Mucolipidosis II (MLII) is a Lysosomal Storage Disorder caused by the deficiency of the enzyme GlcNAc-1-phosphotransferase, which is responsible for the Mannose-6-Phosphate marker addition to lysosomal enzymes. Of all MLII mutations, the c.3503_3504delTC in GNPTAB exon 19 is the most frequent, making it a good target for a personalized therapy. Here, we explored an innovative therapeutic strategy based on the use of antisense oligonucleotides (ASOs) for MLII. Previously, on MLII patients' fibroblasts, ASOs were used to skip exon 19 of the GNPTAB pre-mRNA, successfully resulting in the production of an in-frame mRNA[1]. Now, our aim is to analyze if these results are translated to the enzymatic and cellular phenotype level.

Materials & Methods: The levels of GlcNAc-1-phosphotransferase activity were assessed through a radioactive assay. Briefly, ASOs were transfected into patient cells harboring the c.3503_3504delTC mutation, as well as into healthy control cells. Following transfection, cells were incubated during 24/48 hours and then the presence of skipped transcripts levels was confirmed and the GlcNAc-1-phosphotransferase activity was measured.

Results: GlcNAc-1-phosphotransferaseactivity levels were similar in all cells analyzed (treated and non treated ML II fibroblasts and control fibroblasts) showing that this assay is not appropriate to measure the endogenous levels of this enzyme and can only be used when this enzyme is overexpressed. Therefore, we are now using a human WT GNPTAB cDNA plasmid to generate a mutant construct without the exon 19. This construct will be transfected in Hep3B/HEK293T cells and the levels of GlcNAc-1-phosphotransferase will be measured. To further validate our ASO approach, the levels of lysosomal storage as well as the activity of several lysosomal hydrolases will be assessed after treat ML II fibroblasts carrying the c.3503_3504delTC with ASOs.

Conclusions: The mentioned assays will allow to analyze the feasibility of our approach for the treatment of MLII patients carrying mutations in the GNPTAB exon 19, namely the c.3503_3504delTC which is most frequent one worldwide. The results obtained so far will be presented. References: [1] Matos L, Vilela R, Rocha M, et al. Hum Gene Ther, 2020, 31(13-14):775-783.

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CENTRALIZED AND UP-TO-DATE DATA ON ORPHAN DRUGS: THE EUROPEAN MEDICINES REGULATORY DATABASE

ABSTRACT N° C001 / REGULATORY SCIENCE

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Data about drug regulation are of great value to various stakeholders such as drug developers, regulatory scientists, healthcare professionals, patients, as well as regulators themselves – to aid consistent decision-making. However, in Europe, data about regulated drugs are dispersed over various websites and numerous documents per drug and often highly technical due to the complex legal and regulatory framework. Consequently, these data can be poorly accessed, understood, and used by all stakeholders. We have developed the European Medicines Regulatory Database (EMRD): an up-to-date, website-based dashboard that centralizes and contextualizes data about drugs authorized and orphan designations (ODs) granted by the European Medicines Agency (EMA) since its establishment in 1995. The EMRD combines data that are scraped from the EMA website and the European Commission's Union Register of medicinal products, as well as a broad array of legal and regulatory documents on these websites. These documents include all drug labels, legal decisions, and assessment reports ever published for each drug. Up to 31 December 2022, the EMRD's algorithms accessed over 60,000 documents from which they extracted almost 70 variables (i.e., drug, disease, legal and regulatory characteristics) of 1,648 drugs and 292 ODs. The dashboard provides explanations of these characteristics and their legal and regulatory history, as well as options to download, visualize or analyze selected data, or upload additional user-generated data. For example, information on orphan drugs is real-time available. In the timeframe 2001-2022 (when drugs could receive OD), 1,493 drugs were authorized of which 231 drugs (15%) had at least one OD at time of marketing authorization. By 31 December 2022, these 231 drugs had 292 ODs, of which most drugs had one OD (194, 84%) or two ODs (23, 10%). The highest number of ODs was six for two drugs (Glivec, Ravicti). The most common ATC codes were Antineoplastic and immunomodulating agents (code L) and Alimentary tract and metabolism (code A). Information on the time from designation to authorization can also be displayed with the longest time being 21 years for Xenpozyme (indication acid sphingomyelinase deficiency). We will make the EMRD openly available mid 2023, and are confident that it will enhance accessibility, understanding and (consistent) use of European regulatory data.

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RARE DISEASE MODELLING IN THE GERMAN MOUSE CLINIC

ABSTRACT N° C002 / REGULATORY SCIENCE

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Animal models are crucial to gain new insights into the pathophysiology of rare diseases and to uncover new therapeutic avenues. The German Mouse Clinic (GMC) is partner within the International Mouse Phenotyping Consortium (IMPC) and in the European research infrastructure INFRAFRONTIER for modelling human diseases (www.infrafrontier.eu). The GMC offers the generation of knock-out and humanized mouse mutants to model human disorders and to characterize disease onset and phenotypes by a comprehensive phenotypic analysis. The systemic primary phenotyping covers more than 550 parameters from areas like behavior, neurology, bone and cartilage development, clinical chemistry, allergy, immunology, cardiology, energy metabolism, eye morphology, and pathology. Further characterization of the models includes ageing, rescue and treatment studies. Moreover, specialized pipelines to address specific research questions focus on neuro-behavioural tests, secondary metabolic analysis and imaging technologies like computer-tomography and magnetic resonance imaging. The phenotypic analyses are offered on the basis of a scientific collaboration (www.mouseclinic.de).
In addition, the GMC is partner for generating and phenotyping rare disease models in the European program "Solving the unsolved rare disease (Solve-RD)" and in the CHARLIE consortium (CHAnging Rare disorders of LysInE metabolism) of the "European Joint Programme on Rare Diseases (EJP-RD)". Next to other examples we will present our efforts in CHARLIE as a prominent case for a successful collaboration of rare disease modelling. The German Mouse Clinic has generated and phenotyped the Aldh7a1 KO mouse model for the disorders pyridoxine-dependent epilepsy (PDE). Metabolomics analysis at the Radboudumc Translational Metabolic Laboratory successfully identified both known and new biomarkers in brain, liver and plasma of Aldh7a1 KO mice. Metabolite identification by infrared ion spectroscopy (IRIS) and characterization by mass spectrometry imaging (MSI) at the HFML-FELIX Laboratory are ongoing. We demonstrate that joining forces of mouse modelling scientists, human geneticists and clinicians enable fast translation for new diagnosis and therapies.

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ERN REGISTRIES ADAPTABLE INFORMED CONSENT FORM FOR RESEARCH PURPOSES

ABSTRACT N° C003 / REGULATORY SCIENCE

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Background:
The lack of harmonisation among Ethics Committees (ECs) evaluation in the European Union (EU) lead to inconsistent ethics reviews of the same study across participating research sites. This is also linked to the General Data Protection Regulation (GDPR) being implemented at national level with a certain degree of variance in interpretation.
The European Reference Networks (ERNs) were struggling in setting an Informed Consent Form (ICF) for registries, allowing reuse of data for research purposes. The ICF initially developed for the ERN Clinical Patient Management System, that included the submission of patients' data to the ERN registries, was not accepted by all the ECs for research purposes.
Methods:
A team was established to work on this challenge, within the European Joint Programme on Rare Diseases, through the creation of a registry ICF template allowing easy adaptation to ERNs, country, and site-level specificities. ERNs representatives validated the choice of a GDPR compliant template for research purposes.
The initial ICF, the rejection letters received from the ECs, the amended ICFs that followed and other ones developed by some ERNs, and the EU consent regulatory framework were analysed along with existing ontologies for data access and reuse. The ICF development followed iterative cycles of consultation and review by clinicians, research experts, ethics and regulatory advisors, and patients' representatives.
Results & Conclusions:
One ICF template version for patients and one for parents/legal representatives were released in 26 national languages.
This ICF will foster, according to patients' preferences, the reuse of registries data for research purposes in compliance with the applicable laws and standards.
Paediatric material is being finalised to collect minors' assent. ICF machine-readability is progressing to enhance the data discovery and display its access and re-use conditions.

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THE ORPHAN DRUG APPROVALS IN THE US AND THE EU: A COMPARATIVE ANALYSIS FROM 2011 TO 2020

ABSTRACT N° C004 / REGULATORY SCIENCE

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Background: The US first introduced the landmark Orphan Drug Act in 1983, and the EU launched similar legislation in 2000. By offering incentives, such as market exclusivity, tax credit, and waiver of approval application fees, the number of approvals for orphan indications has increased significantly over time both in the US and the EU.
Methods: We used descriptive statistics to analyse the relevant EU regulatory status of US orphan approvals. The study cohort was the Food and Drug Administration (FDA) drug approvals with orphan designations between 2011 to 2020, and data was collected from the FDA publicly accessible dataset. The European public assessment reports (EPAR) were searched to determine the regulatory status - whether these FDA orphan approvals were designated and approved by the European Medicines Agency (EMA).
Results: Between 2011 to 2020, the FDA granted 571 drug approvals with orphan designations, of which only 25% were approved with orphan designations by the EMA. Nearly half (44%) of the US orphan drug approvals were not approved by the EMA and 31% of them were approved in the EU without orphan designations. A major driver of this difference was in the field of oncology which accounted for over 50% of all orphan drugs. In terms of regulation, the EMA has restricted the use of biomarkers in the definition of orphan conditions compared to the FDA and this is a significant reason for the growing divide. The other major factor shaping the divergence in orphan drug approvals was company behaviour. The majority of large companies did not seek orphan designation for FDA orphan drugs in the EU and instead gained approval without any orphan incentives. Smaller companies sponsored few orphan products in the EU. This was most obvious in the case of small US firms, with ~90% of their US approved orphan drugs not available in the EU.
Conclusions: Our findings suggest a large and growing divergence in orphan drug approvals between the US and EU, with EU patients only having access to significantly fewer drugs for rare diseases than their US counterparts. Furthermore, EU orphan EU legislation is failing to provide sufficient incentives to firms to either market their drugs in the EU or where they do, to use orphan incentives.

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THE CARE AND TRIAL SITE REGISTRY: FAIRIFICATION OF AN ONLINE DATABASE OF CLINICAL SITES AND THEIR FACILITIES

ABSTRACT N° D001 / CLINICAL RESEARCH

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Overview
Fragmented knowledge, expertise, and resources are a major challenge to rare disease (RD) research. Recently, concerted efforts have been made to adopt FAIR data principles (Wilkinson 2016), making resources Findable, Accessible, Interoperable and Reusable (RDs GO FAIR). Technical and governance challenges to FAIRifying resources holding individual-level data, such as patient registries, have been identified and addressed (Groenen & Jacobsen 2020, Vieira 2022). Clinical sites are an important strand of the RD ecosystem, bringing together patients, care and research expertise, facilities, and activities. Site-level data is thus essential to a comprehensive FAIR RD ecosystem (EJP RD). We describe the FAIRification of a resource of such data, enabling privacy-preserving integration of different scales of data within a FAIR ecosystem.
Methods
The Care and Trial Site Registry (CTSR) is an online self-report database of specialised neuromuscular and neurodegenerative sites. It holds site contact details, aggregate totals of patient cohorts (but not individual-level data), and data on clinical care and trial experience, capabilities, and facilities. Its integration into a FAIR ecosystem required identifying data with most value for reuse, defining ontological models to represent data and access conditions unambiguously for humans and machines, and creating a workflow to expose FAIR data at an appropriate level of granularity.
A common CTSR use-case is to identify sites with particular patient cohorts in specific geographies. Initial FAIRification has replicated this, creating ontologised RDF data representing location, contact details, and cohorts (ORPHAcodes). This permits federated filtering on these properties and, within a FAIR ecosystem, the possibility of integrating site- and patient-level data while respecting privacy (e.g. by performing only pre-verified queries). Combining aggregate clinical data from patient registries with CTSR site data permits novel insights into care patterns, with applications such as monitoring health outcomes across European Reference Networks (ERNs) and clinical trial planning.
Summary of results
The FAIRification of the CTSR demonstrates the value of combining different scales of FAIR data for clinical research and trial planning, with broad applicability across the RD field and beyond. The CTSR contributes a dedicated function to the FAIR ecosystem, with new possibilities for computational applications.

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EXPLORING THE ENROLL-HD DATASET USING MACHINE LEARNING FOR PERSONALIZED PREDICTIONS

ABSTRACT N° D002 / CLINICAL RESEARCH

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Huntington's disease (HD) is a devastating disorder that is still lacking an effective treatment or disease modifying therapies that can prevent or slow down the progression of the disease. The Enroll-HD study is an integrated clinical research platform operating in the field of neurology, and is a large effort by the HD community to address the research and clinical needs of HD. Their more recent version PDS5 encompasses more than 20.000 participants in different clinical sites worldwide, including baseline and follow up visits for each patient, both manifest and premanifest. Enroll-HD is collecting longitudinal observational data regarding the clinical aspects of HD, covering motor, cognitive, and behavioral domains.
We analyzed this dataset in a large scale manner using machine learning (ML) algorithms to obtain valuable insights to the manifestations of HD for personalized treatments and prognoses for both manifest and premanifest patients. In particular we applied ML methods for data preprocessing and for making personalized predictions. We explored the utility of ML to predict Age of Onset in comparison to the widely implemented Langbehn formula. In addition, we applied recurrent neural networks to demonstrate how neural networks can learn from temporal data to enrich future predictions and make personalized predictions regarding the quality of life of patients. We demonstrate a use case on the prediction of the driving capability of HD patients. By giving a data-driven assessment on driving capability and a trajectory of the driving capability in the next year, we can assist clinicians in their experience based decision making. The resulting pre-processed Enroll-HD dataset as well as the pre-processing workflow are available to be used for related HD-disease predictions.

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ERN ITHACA: THE EUROPEAN REFERENCE NETWORK ON CONGENITAL MALFORMATIONS AND RARE NEURODEVELOPMENTAL DISABILITIES

ABSTRACT N° D003 / CLINICAL RESEARCH

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ERN ITHACA is the European Reference Network for Intellectual disability, TeleHealth, Autism and Congenital Anomalies. The name also echoes the diagnostic odyssey experienced by so many patients with developmental anomalies. ERN ITHACA is a coordinated network of more than 70 clinical genetics department across academic hospitals established within the European Union, that serves as an example of a clinical research network.
ERN ITHACA brings together experts in rare multiple congenital anomalies and rare neurodevelopmental disorders, the latter field mainly covering intellectual disability and autism spectrum disorder. ERN ITHACA's field of expertise covers the clinical and biological/genetic diagnosis of these developmental anomalies, the coordination of their multidisciplinary treatment, and also their prenatal diagnosis and fetal pathology. A very large number of children and adults are affected by rare developmental anomalies. Many malformations occur together as part of complex 'syndromes' that often show also neurodevelopmental disorders. Over 5 000 rare syndromes have been described.
ERN ITHACA networks patient representatives and medical experts with the aim to develop best practices and coordinate guidelines production, to provide a collaborative support for clinical research and to generally improve early diagnosis, care and cure of patients with rare developmental anomalies. ERN ITHACA has established the patient registry ILIAD dedicated to disorders falling under its scope of expertise. ILIAD is a "meta-registry", that aims to connect all member HCPs, databases, and biobanks across the EU for patients with dysmorphic/MCA syndromes and/or intellectual disability. Through the ERN-ITHACA's expert and patient participation network, ILIAD is able to provide an infrastructure for diagnosis, highly specialised multidisciplinary healthcare, evidence-based management, and collection of secure patient data.
ERN ITHACA also encourages the development of telemedicine and tele-expertise to allow collegial discussion of complex situations between referring doctors and rare disease experts who are scattered in the EU. ERN ITHACA aims to produce advanced training and e-learning tools dedicated to health professionals, lay persons and Patients Advocacy Groups. ERN ITHACA has been funded by the EU4Health Programme, Grant Agreement nr. 101085231
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DEVELOPMENT OF A PATIENT-REPORTED OUTCOME MEASURES (PROMS) REPOSITORY FOR USE IN RARE DISEASES

ABSTRACT N° D004 / CLINICAL RESEARCH

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Introduction: The European Rare Disease Research Coordination and Support Action (ERICA) consortium aims at promoting and disseminating the adoption of standardized PROMs for rare diseases. The Patient-Centred Research group worked at maximizing existing knowledge on RD and optimizing use of existing PROMs to develop a PROMs Repository, which supports the identification of PROMs eligible for use in RD clinical research.
Method: First, among the 4,000 questionnaires described in the Mapi Research Trust PROMs database, PROQOLID™, we have selected PROMs developed and validated for rare diseases and PROMs measuring specific functional impacts (such as mobility, self-care or communication) and ERN concepts of interest. Second, we conducted a survey among European Reference Networks and patient organisations to collect additional PROMs of interest. Third, to extend the identification of eligible PROMs suitable for RD, a Multiple Factorial Analysis (MFA) has been performed to group together RD sharing similar functional impacts in clusters.
Results: 279 PROs developed in RD, 151 extra non-RD PROs measuring functional impacts and 160 measuring concepts of Interest for ERN (e.g. Burden, Self-efficacy, Adherence, Independence) were selected from PROQOLID™. The ERN survey identified 211 additional PROs. The 801 identified PROs are now described in the ERICA PROs Repository, in a user-friendly interface allowing for quick and refined searches for relevant PROMs (https://erica-rd.eu/work-packages/patient-centred-research/proms-repository/). Within PROQOLID™, there is additional PROs information, which can help ERNs decide if the selected PRO is well suited to their needs. The clustering work led to the identification of 57 RD clusters sharing similar functional impacts, of which 21 include 6 to 58 RD. Further clusters analysis will be performed to identify new PROMs and proposing them in the repository.
Conclusion: The ERICA PROMs Repository is the first attempt to identify and centralize PROs of relevance for RD. As next steps, Observer-Reported Outcome measures will be included in the repository, for a use in paediatric population. Moreover, the clustering work will be implemented into the repository to extend the search results to PROMs-related RD with similar functional impacts.

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IN VITRO DEVELOPMENT OF A CUSTOMIZED NONINVASIVE NANOPARTICLE-MEDIATED GENE KNOCKDOWN APPROACH FOR CROUZON SYNDROME

ABSTRACT N° E001 / GENE AND CELL THERAPY

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Crouzon syndrome (CS) is a rare autosomal dominant disorder characterized by craniosynostosis and caused by heterozygous gain-of-function mutations in the Fibroblast Growth Factor Receptor 2 (FGFR2) gene. These leads to constitutive activation of the receptor and of downstream signals. The treatment is based on multiple surgeries to release the skull constraint that impairs brain growth. The aim of this project is to develop a customized noninvasive therapy for CS using allele-specific siRNAs targeting the mutant FGFR2 allele delivered by highly biocompatible nanoparticles to restore FGFR2 signaling. Calvarial mesenchymal stromal cells (CMSCs) were isolated from surgical waste tissue resulting from cranial vault remodelling of FGFR2 mutation-positive CS (Ethical Committee UCSC: prot.N.0023584/22). A set of 27-mer double stranded siRNA specifically targeting the mutant FGFR2-alleles of each patient enrolled was designed and tested in patient cells. Briefly, the guide strand of each siRNA has been designed fully complementary to the mutated FGFR2 mRNA sequence of CS patients and with a single base difference (mismatch) with wild-type mRNA. The mismatch was introduced to obtain a Single Nucleotide Polymorphisms (SNP)-specific siRNA able to distinguish between the mutant and wild-type FGFR2 mRNAs. The efficiency of each siRNA was evaluated through real time PCR and Western blot analyses. Human recombinant ferritin-based nanocarrier (HFt) and PLGA-PEG-based nanoparticles have been produced through PH-dependent HFt dissociation into subunits and re-association method and by nanoprecipitation technique, respectively. NPs have been evaluated for siRNAs delivery in CMSCs by cell viability assay and through fluorescence microscopy and Incucyte Live-cell analysis system. Gene expression analysis allowed identifying specific siRNAs showing the strongest inhibitory effect on the expression of mutant FGFR2 allele without reducing levels of wild-type FGFR2 allele in CMSCs derived from CS patients. Cell viability assay assessed a high biocompatibility of both NPs with our cellular model. Fluorescence microscopy showed an efficient internalization of the tested NPs within CMSCs cytoplasm, thus demonstrating they are suitable delivery systems. Our data suggested that allele-specific FGFR2 knockdown by siRNA represents a desirable strategy to silence FGFR2 mutant allele in CS patients, and delivery through biocompatible NPs would allow using them as a medical treatment.

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THE USE OF IMPC KO MICE AS MODEL ORGANISMS TO STUDY HUMAN RARE DISEASES

ABSTRACT N° E002 / GENE AND CELL THERAPY

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The German Mouse Clinic (GMC), as part of the International Mouse Phenotyping Consortium (IMPC), has long served the research community in generating and characterising mouse mutants to understand human disease biology and develop new interventions. The IMPC, in an international effort, endeavours to annotate all protein-coding genes and provide phenotypic information of knockout (KO) mouse models. Single-gene KO mice are systematically analyzed covering a broad range of tests to identify phenotypes (https://www.mousephenotype.org/). Parameters from homozygotes mutants were statistically compared with those from wild-type controls of the same background strain. As a result, the IMPC renders valuable insight into the genetic basis of rare diseases (RD) and their clinical spectrum.
Rare diseases (RDs) pose a challenge for medicine because of heterogeneous clinical manifestation and scarce prevalence. There is a lack of specific treatments and only a few hundred of the approximately 7.000 described RDs have an approved treatment.
We show KO IMPC mouse models that are not only proprietary genes like proof-of-concept RD targets (Nacc1, Bach2, Klotho alpha), moreover we focus on recognized RD genes with no pre-existing KO mouse models (Kansl1l, Acsf3, Pcdhgb2, Rabgap1, Cox7a2). Additionally, we present yet unknown genes (Zdhhc5) with phenotypic data not presently associated with known human RDs suggestive of causal genes underlying undiagnosed diseases.
We stage an inventory of IMPC genes that, when deleted, cause differences in the mouse organ-wide, providing a mine of accessible valuable data to explore gene-disease associations. In this pursue, we adhere to tools such as GeneMatcher and Modelmatcher to enable a collaborative alliance with geneticists, clinicians and patients worldwide who disclose an interest in the same gene.
Therefore, the standardised phenotypic characterization of RD genes in the GMC augments the efforts of the IMPC KO mouse model data-rich resource in promoting new RD gene targets discovery and potential accelerate mechanistic understanding and development of effective treatments or interventions.

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CLINICAL IMPORTANCE OF SCREENING AND THERAPEUTICALLY ADDRESSING NEUROPSYCHIATRIC SYMPTOMS NEUROPSYCHIATRIC 1 IN ALL INDIVIDUALS WITH CRD.

ABSTRACT N° F001 / SYSTEMS THINKING TOWARDS ACCESS

Sophie Muir

Timothy Syndrome Alliance (TSA)

This registry went live in June 2022 and collects information from CACNA1C individuals and caregivers worldwide to serve as a research platform for real-world data.

Comprehensive multisystemic characteristics and symptomology data, including variant, age at diagnosis, plus full demographics data, are collected upon enrollment and yearly thereafter.

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REMEDI4ALL – A NEW EUROPEAN CONSORTIUM TO DRIVE PATIENT-CENTRIC DRUG REPURPOSING IN RARE DISEASE AND BEYOND

ABSTRACT N° F002 / SYSTEMS THINKING TOWARDS ACCESS

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Drug repurposing (DR) – identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication – represents a great opportunity for rare disease and patients with unmet needs. DR is an innovative and alternative option in drug development and might offer various advantages over developing an entirely new drug for a given indication: fewer risks, lower costs, and shorter timelines.
Although there are notable successes for DR in the rare disease field and policy, funding and research attention in this area is steadily growing, major caveats to ensure efficient and effective patient-centric DR needs to be addressed. These include but are not limited to a fragmented DR R&D environment that lacks a framework for true co-creation with patients and without an easily identifiable value chain, as well as a lack of understanding among many DR researchers of all the steps and substantial patient engagement (PE) needed to advance their specific project into practice.
REMEDi4ALL, an EU-funded multi-year initiative will overcome these issues by creating a vibrant European research and innovation eco-system that facilitates fast and cost-effective patient-centric development and implementation of repurposed medicines. The consortium of 24 leading European organizations will establish and operate a sustainable European Repurposing Platform comprising the complete value chain for cutting edge, patient-centric repurposing by supporting high potential DR projects at any phase of development, upskilling all stakeholder groups through a comprehensive education and training portfolio, and advancing cross-sectoral policy dialogue. The tools and processes will be validated in a portfolio of 4 ambitious demonstrator projects, representing high patient need in a variety of disease areas including rare and ultra-rare diseases.
Working closely with DR researchers and the patient community, REMEDi4ALL will position the patient's voice and experience at its heart and bring patient champions to the center of each project, empowering them as co-creators of the repurposing programs. The project is expected to make a major leap forward in patient-centric DR in areas where there are high unmet medical needs and will act as a role model for structured, effective, meaningful, and ethical PE throughout the entire DR developmental process.

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DELAYED DIAGNOSIS IN THREE RARE DISEASES: A QUALITATIVE STUDY OF THE EXPERIENCES OF PEOPLE WITH MYOSITIS, SARCOIDOSIS, AND PRIMARY IMMUNE DEFICIENCY IN AUSTRALIA

ABSTRACT N° F003 / SYSTEMS THINKING TOWARDS ACCESS

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Introduction: Many rare diseases present with a complex constellation of symptoms that may mirror more common conditions, and therefore present diagnostic dilemmas for first-contact and specialist clinicians. Lengthy delays from symptom onset to diagnosis can be distressing for the person and may lead to the underlying condition deteriorating. We aimed to examine the experiences of people with rare diseases from symptom onset to diagnosis with the aim of identifying factors that contribute to or mitigate diagnostic delay.
Methods: We conducted semi-structured in-depth interviews with 26 adults (10 with sarcoidosis, 8 with myositis, and 8 with primary immune deficiency) living in Australia. We asked participants to reflect on the symptoms that prompted them to seek medical care, and to describe their interactions with clinicians and health services up until the time they received a correct diagnosis. A group thematic analysis was undertaken by the whole research team which includes people with a rare disease.
Findings: We identified four themes: (1) Patients and clinicians normalising or misattributing symptoms; (2) Clinicians having a lack of trust in patients' self-knowledge; (3) Patients having self-belief and persistence; and (4) The "diagnosable moment" when the cluster of symptoms reach a diagnostic threshold for the clinician. Recurrent and persistent illness often accompanied by fatigue was a common experience among most participants with many attempting to normalise their symptoms in the absence of a diagnosis. Clinicians and participants alike often misattributed symptoms to self-limiting illnesses or environmental factors. Some participants reported feeling they were not believed; that clinicians did not listen to them and minimised their symptoms. Some participants requested second or more opinions if they were not satisfied with the diagnosis they had. Participants commonly consulted multiple general practitioners and specialists before receiving a diagnosis. While timing of the diagnosis required the cluster of symptoms to reach a diagnostic threshold for the clinician, some participants reported that this relied on finding the "right clinician at the right time".
Conclusion: Persistence within the therapeutic relationship is often key in seeking and obtaining a diagnosis. Strategies to increase awareness for static, diagnosis-resistant or evolving presentations may improve overall time to diagnosis for people with rare diseases.

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RARE DISEASE PATIENT ORGANISATIONS' ROLES AND RESPONSIBILITIES IN THE APPRAISAL OF ORPHAN MEDICINES

ABSTRACT N° F004 / SYSTEMS THINKING TOWARDS ACCESS

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An increasing number of orphan medicinal products (OMPs) is projected to reach marketing authorisation in the coming years. As pressures on national healthcare systems increase, questions emerge regarding the ability and willingness of national authorities to pay for expensive OMPs. The question of how we (e)valuate OMPs thereby grows in significance and is central to Health Technology Assessment (HTA), pricing, and reimbursement decision-making processes. These processes for orphan medicinal products involve the weighing of the generally limited evidence of their clinical effectiveness against the often hefty price tags attached to them. Rare disease patient organisation (RDPO) involvement in these appraisal processes varies in European countries, but generally revolves around patient experiences with a disease and the (potential) impact of the new OMP. This input is thought to be highly valuable in promoting a more complete review of the clinical and cost effectiveness of products. At the same time, the position of RDPOs in appraisal processes can be hard to navigate. Organisations share multiple and complex relationships with actors like pharmaceutical and biotechnology companies, medical experts, and regulators. Their relationships with industry, through collaboration and/or funding can conflict with their efforts to maintain an image of objectivity and independence in the face of regulators. Patient organisations, through patient registries or other resources, might be involved directly or indirectly in the generation of evidence for the clinical and cost effectiveness of an OMP, which further complicates their position in the appraisal of such a product. In addition, patient organisations might struggle to balance their clear desire for the accessibility of orphan medicines to patients with the wish to promote the financial sustainability of healthcare systems, so that the influence of pricing is a complex issue. In this presentation, I discuss findings from my ongoing PhD research, involving qualitative interviews with representatives of RDPOs and pharmaceutical and biotechnology companies, as well as medical experts and regulators involved in the appraisal of OMPs, regarding the role(s) and responsibilities that patient organisations might take on in these processes. This is an important issue in light of the ongoing issues of inequality of access across European countries as well as concerns over the financial sustainability of healthcare systems.

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EPAGS' (EUROPEAN PATIENT ADVOCACY GROUPS) ROLE IN THE EUROPEAN REFERENCE NETWORK ITHACA ON INTELLECTUAL DISABILITY, TELEHEALTH, AUTISM AND CONGENITAL ANOMALIES: HOW PATIENTS' VOICES IMPROVE CARE

ABSTRACT N° F005 / SYSTEMS THINKING TOWARDS ACCESS

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The importance of patients' voices is essential. ERN ITHACA's challenge, a patient-centred network, which aims to develop closer cooperation with ePAGs and member patient organisations. Our Patient Council is empowered through formal roles in the governance and participate through deep interaction in each or across Work Groups. All activities of ITHACA include patients, their families, and patients' organisations as equal partners. ITHACA covers more than 5000 rare and complex genetic disorders and its name is a reference to the diagnostic Odyssey on which families embark with their children affected by rare developmental diseases. Our approach is based on patient involvement in several projects in collaboration with the EURORDIS network, in particular on the impact of patient engagement on ERNs, to highlight the value of patient clinician partnership (Rare Dis Orphan Drugs J 2021;1:2) .
It is a day to day step Building Method, with fantastic result . One of our last example is a Patients-Clinicians Team-building Sessions . In end of 2022 to Improved patient-clinician shared leadership and collaboration was a cross-cutting need identified by our ERN ITHCA and our Patient Advisory Board (ePAGs). We did organise three patient-clinician teams building sessions supervised by professional coach (co funded Eurodis) . 16 participants, ePAGs and Clinicians. The overall objective was to improve our work perception, develop interactions, and harmonize everyone's working methods. The results of this pilot are very positive and have allowed us to strengthen the clinicians - patients collaboration and to identify areas for improvement. Or we could also mentionned the growing participation in our last december Workshop with clinicians, sharing expertise and expectations who brought together over 70 participants .
The expected results are, to improve the partnership involvement, a common understanding of ePAGs in the daily activities of ERN ITHACA. The UN has formally adopted, on 16 December 2021 with the consensus of all 193 UN Member States, the Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families. This recognition of the voices of patients with rare diseases is increasingly understood at the EU level and by patient organisations across ERNs.
References:Rare Dis Orphan Drugs J 2021;1:2 / Grants: ERN-ITHACA [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516]

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PARTICIPATION IN PATIENT SUPPORT GROUP AND TIMELY TREATMENT CONTRIBUTES TO IMPROVED OUTCOMES OF PRADER-WILLI SYNDROME

ABSTRACT N° F006 / SYSTEMS THINKING TOWARDS ACCESS

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Introduction: Prader-Willi syndrome (PWS) is a rare genetic disease involving multiple systems: neurodevelopment, short stature, and hyperphagia leading to serious outcomes such as obesity, early onset diabetes, cardiovascular diseases, and respiratory system disruption. Early diagnosis of PWS and treatment with growth hormone (GH) could provide cognitive benefits, and improves body composition. Active parental participation in caregivers support groups could indirectly improve health status and including control hyperphagia for patients with PWS.
Methods: Retrospective data of 26 patients with genetically confirmed PWS diagnosis in Lithuania were analyzed. The body mass index (BMI) by the standard deviation (SD) at age 3 years (yrs.) and 5 yrs. was compared between 2 groups of patients (group 1 – early diagnosed PWS (n=5) and group 2 – delayed (n=21)). Patients from 1st group received GH as soon as possible after a confirmed diagnosis. Four families from 1st group and two from 2nd were involved actively in a caregivers support group of PWS. Statistical analysis was performed with SPSS 28.0.
Results: The early diagnosis of PWS (group 1) was confirmed at age 1 (0.25–2) mo. versus 6 (2.5–14) yrs. for patients from the 2nd group. BMI was 0.6 (0.2–1.7) and 2.2 (0.5–3.7) SD at the age of 3 yrs. (p=0.027); 0.9 (0.5–1.5) and 2.8 (0.2–3.7)SD at the age of 5 yrs. (p=0.022), respectively. Parents from the patient of 1st group did not participate in the caregiver support group what resulted higher BMI (1.7 SD) at age 3 yrs. and demonstrated the poorest social adaptation among peers. Two patients from 2nd group had normal BMI (0.5 and 1.2; 0.2 and 1.5) at the age 3 and 5 yrs., respectively. parents of both patients actively participate in PWS association activities.
Conclusions: Treatment with GH should be administered in the early stage of development (before 2 yrs.) to obtain lower BMI, better cognitive function, and social adaptation. Active participation in caregivers support groups demonstrated better parental adherence to specific recommendations (strict diet regimen, physical activity, etc.) and helped improve the quality of life of patients with PWS.

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COLLABORATION IS THE KEY TO THERAPIES

ABSTRACT N° F007 / SYSTEMS THINKING TOWARDS ACCESS

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The problems around developing a therapy for a rare disorder are multifaceted. First, those affected have a heavy health, financial, and time burden, and no advocates. Second, researchers that develop therapies might be unaware of the specific needs of those patients. Third, clinicians do not find the means to bring all parties together. All stakeholders struggle to communicate or collaborate – a lot of time and money is (mis-) invested on the way to a therapy.
The ultra-rare enzymatic disorder, "SSADH-deficiency" (ALDH5A1 gene), with various and often severe clinical symptoms, has encountered all the above-mentioned problems. Engaged parent groups teamed up and were able to overcome the hurdles. Today, numerous research groups are involved in investigating several therapy approaches, spanning from seizure control and microbiome altering to enzyme folding correction using chaperones and enzyme replacement therapy. Since June 2022, the favored approach has been adopted by a biotech company to create a commercially available treatment.
How can this success story be transferred to other rare diseases? CureRare emerged as a spin-off from the patient advocacy group and is dedicated to foster collaboration among rare disease stakeholders. The first of its kind workshop was run during the RNTD-R2T conference in Belgrade in 2022. Through questionnaires with 79 inputs and a subsequent webinar, four key clusters of success factors were identified to enhance communication among patients, scientists and clinicians: "access to scientific language," "management of time restraints," "facilitation of collaboration," and "ease of funding access."
During the conference, 50 scientists and patients were distributed among the working groups to provide their diverse experiences and expertise and to elaborate strategies for overcoming the hurdles in an efficient way. It became apparent that the need of one stakeholder group can be matched by the offer and expertise of another group. While some problems can be overcome by implementing dedicated organizational structures, digital approaches are also readily available to ease access and facilitate collaboration. Equally important is a keen, diverse expert pool that is in regular exchange with other stakeholder groups. Some ideas are currently being implemented and have to be proven in practice.

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