
CONGRESS
BROCHURE
RE(ACT) CONGRESS
IRDiRC CONFERENCE
INTERNATIONAL CONGRESS OF RESEARCH ON
RARE AND ORPHAN DISEASES
5TH–7TH MARCH 2025, BRUSSELS

STAND UP FOR SCIENTIFIC RESEARCH

#RAREVOLUTION
#REACTCONGRESS
#IRDiRC
#ERDERA

TABLE OF CONTENTS

WELCOME

Dear RAREvolutionaries,

Welcome to the RE(ACT) Congress and IRDiRC Conference 2025! We are thrilled to host you again in person here in Brussels, a vibrant setting fostering knowledge exchange and lasting connections. This year marks the third joint event of these two influential series, bringing together the 8th edition of the RE(ACT) Congress and the 6th edition of the IRDiRC Conference.

Over the next few days, you can look forward to a dynamic program featuring global leaders in rare disease research, cutting-edge presentations, and ample opportunities to network. Whether you are a scientist, clinician, patient advocate, policymaker, or industry representative, your engagement will be invaluable in shaping the future of rare disease diagnostics, therapies, and care. Our shared goal is to speed the development and delivery of breakthroughs that bring hope to individuals living with rare conditions worldwide.

Initiated in 2012 by the BLACKSWAN Foundation, the RE(ACT) Congress has always provided a collaborative forum for scientists and other key stakeholders committed to advancing research on rare and orphan diseases. IRDiRC -launched in 2011 as a joint initiative of the European Commission and the U.S. National Institutes of Health- continues to empower international partnerships by uniting researchers, funders, and patient advocacy groups under a shared vision. Moreover, with the support of the European Rare Diseases Research Alliance (ERDERA), which aims to leave no one behind, over 180 organizations championed by the European Union and 36 countries are working hand in hand to make Europe a world leader in rare diseases research and innovation. ERDERA takes over EJPRD to deliver concrete health benefits to rare disease patients in the next decade by advancing prevention, diagnosis, and treatment research.

We thank you for joining us and for your active participation in the sessions and discussions that lie ahead. On behalf of the organizers, we hope you find this joint congress inspiring and productive. We hope you will enjoy your time in Brussels.

On behalf of the RE(ACT) Congress and IRDiRC Conference Organizing Committees

Dr. Olivier Menzel
Chairman and founder
BLACKSWAN Foundation

Dr. Daria Julkowska
Coordinator
ERDERA

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, 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
twitter.com/irdirc
#IRDiRC

THE EUROPEAN RARE DISEASES RESEARCH ALLIANCE (EJP RD)

The European Rare Diseases Research Alliance (ERDERA) aims to improve the health and well-being of the 30 million people living with a rare disease in Europe, by making Europe a world leader in Rare Disease (RD) research and innovation, to support concrete health benefits to rare disease patients, through better prevention, diagnosis and treatment. This Partnership will deliver a RD ecosystem that builds on the successes of previous programmes by supporting robust patient need-led research, developing new diagnostic methods and pathways, spearheading the digital transformational change connecting the dots between care, patient data and research, while ensuring strong alignment of strategies in RD research across countries and regions. Structuring goal-oriented public-private collaborations targeted at interventions all along the R&D value chain will ensure that the journey from knowledge to patient impact is expedited, thereby optimising EU innovation potential in RD. To support its ambition and missions ERDERA has been designed as a comprehensive and integrated ecosystem of which structure can be compared to an institute encompassing three main parts: (i) funding, (ii) internal (in house) Clinical Research Network that implements research activities targeting clinical trial readiness of RDs and accelerating diagnosis and translation of research discovery into improved patient care, and (iii) related supporting services (Data, Expertise, Education and Training) as well as an acceleration hub that serve external and internal RD community, all supported by all-embracing coordination and strategy and foundational (inter)national alignment.

erdera.org
x.com/ERDERA_org
bsky.app/profile/erdera.bsky.social
#ERDERA

BLACKSWAN FOUNDATION

The BLACKSWAN Foundation (BSF) is a Swiss-based, not-for-profit organization established in 2010 to advance research on rare and orphan diseases worldwide. Its core mission is to encourage research and promote information campaigns that enhance public understanding of these conditions.

BSF supports the entire rare disease community, recognizing the complexities and hurdles involved in rare disease research. The Foundation maximizes its impact across various projects by developing innovative and broadly applicable tools. Embracing digital communication is fundamental to BSF's strategy, as it increases the effectiveness of its work and fosters community engagement with best practices.

While BSF has directly supported research through donations to public institutes, in 2012, the Board of the Foundation expanded its focus to include building sustainable resources for the scientific community. A key initiative stemming from this decision is the RE(ACT) Initiative, designed to boost international scientific collaboration and knowledge sharing. Central to this initiative is the RE(ACT) Congress, an international scientific conference that connects researchers, showcases the latest advances, and inspires new ideas and partnerships in the field of rare diseases.

Collaboration is paramount to the Foundation's success. BSF partners with patient organizations, academic institutions, research consortia, and centers of expertise at both national and international levels. A multi-talented Board of Trustees, comprising professionals from drug development, marketing, cooperation, and health sciences, steers the Foundation. Additionally, a Scientific Advisory Board (SAB)—made up of leading researchers from Switzerland, Australia, Belgium, France, Italy, and the United States—guides BSF's scientific endeavors.

BSF aims to transform the outlook for individuals living with rare and orphan diseases worldwide through its commitment to research, collaboration, and innovation.

The BLACKSWAN Foundation is officially registered in the Swiss commercial register and is recognized as a public utility foundation supervised by the Swiss Federal Department of Home Affairs (FDHA).

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NOTES

KEY FACTS

Scientific advisory board:
Scientific Advisory Board of the BLACKSWAN Foundation
European Rare Diseases Research Alliance (ERDERA)
The International Rare Diseases Research Consortium (IRDiRC)

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

Venue
Nestled in the vibrant heart of Brussels, the Pullman Brussels Centre Midi is more than just a hotel—it's a premier destination for business and events. Strategically located adjacent to the Brussels South train station (Gare du Midi), this modern and sophisticated venue offers unparalleled convenience for international and local attendees.
Designed with contemporary elegance, the Pullman Brussels Centre Midi blends cutting-edge amenities with a warm and welcoming atmosphere. Whether you're here for a conference, seminar, or corporate event, you'll find that every detail has been carefully considered to ensure a seamless experience.

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

Congress Organizers
BLACKSWAN Foundation
IRDiRC, International Rare Diseases Research Consortium
ERDERA, European Rare Diseases Research Alliance

Professional Congress Organizer (PCO)
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) 2025_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 USB key or 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 March 5, morning.
– Posters should be removed on March 7, evening.
– 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 5th

Registration desk 8h30 to 10

Opening speech 10 to 10h30

Session A, 10h30 to 13h30, **"Diagnosing rare diseases: from NBS to machine learning"**

Coffee break: 11h30 to 12

LUNCH & POSTER SESSION A & B 13h30 to 14h30

Session B, 14h30 to 17h30, **"Empowering data"**

Coffee break: 16 to 16h30

THURSDAY, MARCH 6th

Session C, 9 to 12h30**, "ATMPs: challenges and opportunities of today"**

Coffee break: 10h30 to 11

LUNCH & POSTER SESSION C & D 12h30 to 14

Session D, 14 to 17h30, **"Impacts of rare diseases on patients, families, and society"**

Coffee break: 15h30 to 16

FRIDAY, MARCH 7th

Session E, 9 to 12, **"Funding models"**

Coffee break: 10h30 to 11

LUNCH & POSTER SESSION E & F 12 to 13h30

Session F, 13h30 to 17h30, **"Drug repurposing in rare diseases"**

Coffee break: 15h30 to 16h

FULL PROGRAM

WEDNESDAY, MARCH 5th

Registration desk 8h30 to 10

Opening speech 10 to 10h30

Session A, 10h30 to 13h30, **"Diagnosing rare diseases: from NBS to machine learning"**
Chairs: Helen Malherbe (ZA) and Alexander Hoischen (NL)

- Jim Bonham, UK "What can we learn from 60 years of newborn screening and the challenge of genomics?"
- Steven Laurie, ES "From Data to Diagnosis: The Solve-RD Story"
- Vicente Yepez, DE "When the outlier is the signal: RNA-seq based diagnostics of rare disorders"
- Lisenka Vissers, NL "Long read sequencing as first-tier diagnostic test for rare diseases"
- Chris Hendriksz, UK "Diagnosing rare diseases: from NBS to machine learning"

LUNCH & POSTER SESSION A & B 13h30 to 14h30

Session B, 14h30 to 17h30, **"Empowering data"**
Chairs: Lindsey Murray (US) and Ronald Cornet (NL)

- Nicole Vasilevsky, US "Accelerating Rare Disease Treatment: The Role of Data Sharing in the RDCA-DAP"
- Sabine Österle, CH "The Swiss Personalized Health Network- from clinical routine data to FAIR research data"
- Thomas Hellebrand, BE
- Marieke Bak, NL "Responsible Data Use in Rare Disease Research: An Ethical, Legal, and Social (ELSI) Perspective"
- Patricia Da Silva-Buttkus (Abstract A002) "CHAnging Rare disorders of LysInE metabolism (CHARLIE) – mouse phenotyping in a multidisciplinary endeavor"
- Jernej Kovac (Abstract A004) "Rapid whole genome sequencing in a paediatric intensive care and neonatal unit"
- Simon Lande (Abstract B005) "Applying genetic database analysis to estimate the prevalence of late-onset Fabry Disease"

Session C, 9 to 12h30, **"ATMPs: challenges and opportunities of today"**
Chairs: Jacqui Beckmann (CH) and Eleni Papanikolou (DE)

- Nick Sireau, UK "Challenges and opportunities for mRNA therapy for rare genetic diseases"
- Tiziana Cremona, CH "Cell specific gene editing as treatment of Alfa 1 Antitrypsin Deficiency"
- Johan Flygare, SE "Developing Novel Therapies for Diamond-Blackfan Anemia (DBA)"
- Despina Eleftheriou, UK "Developing gene and cell therapy for rare inflammatory disorders"
- Rimas Orentas, US "ATMPs: Essential Tools or Essential Medicines?"
- Hanlan Liu (Abstract C001) "Development of precision gene engineered B cells as a treatment for hemophilia B"
- Fei Cao (Abstract C003) "GNT0004, Genethon's AAV8 vector-delivered microdystrophin gene therapy for Duchenne muscular dystrophy: dose escalation and preliminary long-term follow-up data of GNT-016-MDYF all-in-one clinical trial in ambulant boys"

LUNCH & POSTER SESSION C & D 12h30 to 14

Session D, 14 to 17h30, **"Impacts of rare diseases on patients, families, and society"**
Chairs: Virginie Hivert (FR) and Gareth Baynam (AU)

- Sue Baker, AU "Impact of a Cross-Sector (Inter-Agency) Care Coordination Program for Children and Families Living with Rare and Undiagnosed Diseases (RUDs)"
- Gina Cioffi, US "Can Highlighting the Societal Value of Rare Disease Treatments Lead to Improved Health?"
- Kirsten Johnson, UK "Mental health and rare conditions: an integrated approach to care and research"
- Sofie Skoubo, DK "School absence legislation governing in Norway, Sweden, and Denmark for children with chronic illness in compulsory education—A comparative study"

Session E, 9 to 12, **"Funding models"**
Chairs: Daria Julkowska (FR) and Magda Chlebus (BE)

- Nivedita Valentine, UK
- Irene Norstedt, EU
- Samatha Parker, FR "Orphan Drugs R&D Productivity and Probability of Success"
- Carmen Fotino, IT "Challenges in aligning funding initiatives in rare disease: Fondazione Telethon experience"

LUNCH & POSTER SESSION E & F 12 to 13h30

Session F, 13h30 to 17h30h, **"Drug repurposing in rare diseases"**
Chairs: Samantha Parker (FR) and Donald Lo (NL)

- Philip Gribbon, DE "Drug repurposing in Rare and Infectious Diseases - lessons learnt from EU projects on how to identify and progress small molecule based therapies to the clinic"
- Catriona Crombie, UK "Challenges and Opportunities for Drug Repurposing in Rare Diseases"
- Lindsay Randal, UK "SLC6A1: A drug repurposing journey"
- Emek Akyurek (Abstract F002) "A Novel Therapeutic Approach for Brody myopathy: A Translational Perspective in Rare Disease Research"

SPEAKERS' BIOGRAPHIES

BAK MARIEKE

Marieke Bak is an Assistant Professor in the Department of Ethics, Law, and Humanities at Amsterdam UMC and a Senior Research Associate at the Institute for the History and Ethics of Medicine at the Technical University of Munich (TUM). She earned her PhD in Medical Ethics from the University of Amsterdam, focusing on the ethics of big data in cardiac arrest research. Her research interests include the ethical implications of medical research and innovation, with a particular focus on data-driven healthcare and AI-technology. Dr. Bak leads the Ethical, Legal, and Social Implications (ELSI) work packages in several interdisciplinary national and EU projects and serves as a board member of the Amsterdam Public Health Institute's Personalized Medicine program and the Dutch Society of Bioethics.

BAKER SUE

Sue Baker is currently the Program Director of the Rare Care Centre at Perth Children's Hospital in Western Australia and co-founder of the Global Nursing Network for Rare Diseases. With over 40 years of experience in children's healthcare in the UK and Western Australia, Sue has established her place at the forefront of innovative service design and translational health system research evaluation, particularly for vulnerable cohorts of children and families. Sue has held a variety of director and executive positions and has extensive experience leading complex projects. Sue is known for challenging the status quo and is passionate about driving system change that delivers tangible, effective outcomes that benefit children and families. Sue's commitment to health care has been recognized through multiple Health Awards, including the prestigious honor of being a WA Nurse and Midwife of the Year.

BONHAM JIM

Prof Bonham is currently the President of the International Society of Neonatal Screening and national laboratory adviser for newborn screening in the UK on behalf of NHS-England and adviser to the National Screening Committee on behalf of Department of Health and Social Care.
He has a long standing interest in the diagnosis of inherited metabolic disorders in childhood and travels extensively, taking part in meetings related to the organisation, conduct and development of newborn screening.
He has an interest in the potential for the use of genomics in newborn screening alongside biochemical assays.
He also Chairs an International group in partnership with the International Federation of Clinical Chemistry seeking to develop and extend newborn screening in low and middle income countries.

CIOFFI GINA

An experienced advocate for people living with rare diseases, Gina served 7 years working as a legislative staffer in the US Congress before joining Cooley's Anemia (Thalassemia)

Foundation as National Executive Director where she drove initiatives to raise disease awareness, drive science and expand partnerships with stakeholders for more than 16 years. Gina then moved to industry as Head of Patient Advocacy and Communications for ApoPharma, and now serves as US Public Affairs Lead for Global Rare Diseases at Chiesi Group. She holds a bachelor's degree in the Great Books from Saint Mary's College of California and a J.D. from The Catholic University of America, Columbus School of Law and is a retired member of the New Jersey Bar.

CREMONA TIZIANA

Dr.Cremona Tiziana Patrizia holds a strong academic and research background in cellular and molecular biology. She studied cellular and molecular biology at University of Rome Tor Vergata, she continued her education and received a master on Biology applied at Biomedical Research at University of Rome La Sapienza. Her academicjourney continued obtaining a PhD in Biomedical Science at the University of Bern focusing on development of emphysema caused by cigarette smoke exposure.
In 2017, Dr Cremona was awarded a fellowship at Harvard University to further her studies on lung remodeling and asthma models.
She is currently a senior Post-doc at the University of Bern, Department for Biomedical Research working in the Lung Precision Medicine program focusing on a rare lung disease: Alpha 1 antitrypsin deficiency.
Her current project "Cell specific gene editing as treatment of Alpha 1 antitrypsin deficiency" aims to aims to develop a novel model for targeted gene editing to prevent disease progression. This research goes beyond correlation studies, seeking to definitively address critical questions surrounding disease mechanisms and therapeutic interventions.

CROMBIE CATRIONA

Dr Catriona Crombie is an expert in translational medicine, specifically moving research out of universities and into the commercial environment. She has worked for over 15 years in research funding in the state and charity sectors.
Catriona is Head of the LifeArc Rare Disease Translational Challenge. She has responsibility for LifeArc's rare disease research portfolio, which includes grant funding for academics to progress their research towards patient impact as well as the awards made in partnership with others e.g. Innovation Hubs for Gene Therapy funded in partnership with the MRC.

ELEFTHERIOU DESPINA

Professor Despina Eleftheriou is a distinguished expert in paediatric and adolescent rheumatology, specializing in systemic vasculitis and autoinflammation. Since 2006, she has been an integral part of Great Ormond Street Hospital (GOSH), where she leads clinics dedicated to rare inflammatory disorders.
In addition to her clinical roles, Professor Eleftheriou holds a professorship at the UCL Great Ormond Street Institute of Child Health. Her research is primarily centered on discovering novel genetic causes of autoinflammation and developing novel cell and gene therapies for

rare inflammatory disorders. The ultimate goal of her work is to enhance diagnostic methods and treatments, thereby improving survival rates and reducing morbidity associated with these conditions. Professor Eleftheriou is also dedicated to education, having successfully supervised multiple PhD, MD, MSc, and BSc students at UCL. She has co-authored several textbooks and frequently delivers lectures at national and international conferences. Her contributions to the field have been recognized through numerous publications and her active involvement in advancing the understanding and treatment of paediatric rheumatological conditions.

FLYGARE JOHAN

Research focus:
Develop therapies for Diamond-Blackfan Anemia.

Current positions:
Director of the Swedish national research school in advanced therapies.
Deputy head of Department of Laboratory Medicine, Lund University.

Education:
2007: MD and PhD from Lund University, Sweden
2007 -11: Postdoctoral education at Whithead Institute, MIT, USA

FOTINO CARMEN

Carmen graduated in Biological Sciences at the University of Pisa, Italy in 2002. In 2008 she obtained a Ph.D. in Endocrinology and Metabolic Sciences from the University of Pisa, Italy working on the genetics of Type 2 Diabetes and Obesity. In 2009 she joined the Diabetes Research Institute at the University of Miami where she was fully immersed in islet cell biology and immunology related to Type 1 Diabetes (T1D) and Transplantation. In 2015, Carmen joined a research program at the University of Grenoble, France to work on an islet transplant bioengineering program project funded by the European Commission. She then returned to the US at City of Hope (Duarte, LA) as a Scientist focusing her research on the identification of T cells relevant to the progression of T1D determining the phenotypic signature of these cells. In 2018 Carmen joined JDRF (Juvenile Diabetes Research Foundation) as a Scientist in the Immunotherapies program where she managed a large grant portfolio and helped develop new funding initiatives (clinical and translational research). In 2020 Carmen joined Fondazione Telethon (Italy) as a Research Program Manager leading the Spring Seed Grant funding initiative in collaboration with Patient Associations and is now managing all the calls released by Fondazione Telethon.

GRIBBON PHILIP

Philip is Head of Discovery Research at the Fraunhofer ITMP and is involved in several national and European consortia working on targeted protein degradation, target validation, and compound repurposing especially in the rare disease setting. He also

serves as Director General of the European Infrastructure for Chemical Biology, EU-OPEN-SCREEN, and as President of the Society of Laboratory Automation and Screening (SLAS). Previously, Philip was Chief Scientific Officer of the European ScreeningPort GmbH Hamburg, Germany, and has experience working in Pharma in drug discovery roles. https://orcid.org/0000-0001-7655-2459

HELLEBRAND THOMAS

Thomas works for the Dutch Ministry of Health Welfare and Sport as a senior policy officer on the European Health Data Space. I that capacity he has been involved in the formation of national positions and the political negotiations on the EHDS. Currently, he is preparing the national implementation of the EHDS with a focus on secondary use, including the coordination of the Health Data Access Body-NL programme. This brings together the legislative and practical perspectives form the Netherlands. Previously, he has worked on the broader scala of EU data law in the context of digital industries.

HENDRIKSZ CHRIS

Chris Hendriksz qualified as a medical doctor in South Africa in 1985 from the University of Pretoria. He completed his Master's degree in Sports Medicine at the same university. Following a rare disease diagnosis of his own child, he moved to the United Kingdom, where he continued his studies, becoming an expert in inborn errors of metabolism across all ages. He obtained his MRCP and FRCPCH with subspecialty registration after training at the world renowned Willink Unit in Manchester, UK.

He spent 22 years in the UK National Health Service in various roles leading both pediatric Birmingham Children's Hospital and adult Salford Royal NHS foundation trusts rare disease centres with patient populations in excess of 1500 at each unit. Currently, he is an Extraordinary Professor of Human Metabolomics at North-West University, Potchefstroom, South Africa, and an Extraordinary Professor of Paediatrics and Child Health at the Steve Biko Academic Unit, University of Pretoria. He was employed by Nestlé Health Science as the Global Clinical Development Lead for Rare Diseases, IEM, and Innovative Pharmaceuticals until his retirement at the end of March 2024. Post-retirement, he will continue his lifelong passion for medical education and supporting rare disease service developments in low- and middle-income countries.

He is currently the Chief Community Impact Officer for A Rare Cause, a non-profit organization based in England that educates clinicians on rare disease management in more than 50 countries, with the list growing yearly. Building diagnostic networks and AI associated tools to support their work. This creates "hope for those with the least chance of being recognized," in his own words. He also provides expert knowledge as a consultant for FYMCA Medical Ltd, a family-owned company, to patient organizations, foundations, regulators, and payors in his field of expertise.

His publication list includes more than 250 works, with the majority focusing on Lysosomal Storage Disorders. He has numerous publications related to clinical trials, quality of life, clinical guidelines, and review papers, as well as several book chapters in the field of inborn errors of metabolism.

JOHNSON KIRSTEN

Dr Kirsten Johnson is Chair of the Council of Rare Diseases International. She is President and one of the founders of Fragile X International, a global charity representing those with Fragile X Syndrome and Fragile X Premutation Associated Conditions. Kirsten is also on the board of EURORDIS – Rare Diseases Europe; an Advisor to the Screen4Care forum on newborn screening; and sits on the Platform Advisory Group for Rare Disease Research UK. Kirsten is a FMR1 premutation carrier and has two adult daughters who live with Fragile X Syndrome. Her husband lives with a rare cancer, hairy cell leukaemia. Kirsten works as a professional musician and has a doctorate in music.
In her advocacy work, Kirsten was one of the co-authors of the 2022 Cells article which led to the renaming of the FMR1 gene and protein, removing offensive and outdated terminology. She has also co-authored a 2020 article in Frontiers, on Fragile X Premutation Associated Conditions ' and was lead author on a 2024 article in JARID on a holistic approach to Fragile X Syndrome. Her most recent article is The joys of fragile X: Understanding the strengths of fragile X and delivering a diagnosis in a helpful, holistic way.

LAURIE STEVEN

Dr Steven Laurie is a Senior Genomics Data Analyst at the Centro Nacional de Análisis Genómico (CNAG) in Barcelona, specialising in genomic data analysis and interpretation for rare diseases. Originally from Scotland, Dr. Laurie began his research career in molecular genetics before transitioning to human genetics and bioinformatics. He earned his PhD in Biomedicine from Universitat Pompeu Fabra, Barcelona in 2013, and has been affiliated with CNAG since.
In collaboration with his mentor at CNAG, Dr. Sergi Beltran, Dr. Laurie was instrumental in the development of the RD-Connect Genome-Phenome Analysis Platform (GPAP) as part of the EU RD-Connect Project. Over the past six years, he has focused primarily on the EU H2020 Solve-RD initiative, which leveraged the RD-Connect GPAP to analyze over 25,000 whole-genome and exome sequencing datasets.
Currently, Dr. Laurie is engaged in the European Rare Disease Research Alliance (ERDERA) project, which aims to provide diagnoses for thousands of undiagnosed individuals with rare diseases. The RD-Connect GPAP will continues to serve a key role in this endeavour, supporting data-driven advancements in rare disease research and diagnostics.

NORSTEDT IRENE

Irene Norstedt works at the European Commission where she is the Director responsible for the People: Health and Society Directorate within the DG for Research and Innovation. The People Directorate works towards the development of a healthy, safe, more equal, free, open and fair society, where the voice of the citizen and different communities are better heard.
Irene has been at the European Commission since 1996, and has worked on various aspects of research in life sciences and particular health research throughout her career in the Commission. Areas of particular interest have been the set up of the public private

partnership the Innovative Medicines Initiative (IMI) and the International Rare Diseases Research Consortium (IRDiRC),
Prior to joining the European Commission, she worked for the Swedish life science company Biacore AB and at the Swedish embassy in London.
Irene studied at the Royal Institute of Technology in Stockholm and University of Sussex, and holds a Master of Science (MsC) in Chemical Engineering.

ORENTAS RIMAS

Rimas J. Orentas, PhD, is Senior Scientific Director, R&D Immunotherapy, in Miltenyi Biotec, Inc. He leads groups focused on CAR-T cells, NK-CARs, gd T-cell and HSC-engineering in Gaithersburg, Maryland, USA and Bergisch-Gladbach, Germany. Dr. Orentas also holds an adjunct professorship in the Johns Hopkins Bloomberg School of Public Health. He is co-founder of Caring Cross, a non-profit implementing low-cost approaches to engineered cell therapies. He has led teams that delivered 6 first-in-human CAR-T products. Previous positions include Professor of Pediatrics, University of Washington School of Medicine, Director of the Ben Towne Center for Childhood Cancer Research (Seattle Children's Research Institute); Scientific Director of Lentigen, a Miltenyi Biotec Company; Associate Scientist, Pediatric Oncology Branch, NCI, NIH, and faculty positions at the Medical College of Wisconsin.

ÖSTERLE SABINE

abine Österle is the Lead of the Semantic Interoperability Strategy & FAIR Data Team at the SIB Swiss Institute of Bioinformatics. She holds a B.Sc. and an M.Sc. in Interdisciplinary Science from ETH Zurich, where she also earned her Ph.D. within the Department of Biosystems Science and Engineering. Sabine has been a driving force in ensuring that the data processed as part of the Swiss Personalized Health Network (SPHN) complies with the FAIR principles — i.e., that it is Findable, Accessible, Interoperable, and Reusable.
With her team, Sabine oversees the technical development of SPHN tools and services, bridging the gap between various data and research areas, medical informatics, IT, and clinical disciplines. She has been actively involved in the SPHN initiative since its inception and has significantly contributed to national and international efforts related to semantics, data standards, and FAIR data.

PARKER SAMANTHA

Samantha Parker is Patient Advocacy Lead at Italfarmaco and Vice Chair of the International Rare Disease Research Consortium. She has over two and a half decades of international rare disease experience in the biopharmaceutical industry. She has a proven track record in patient advocacy, small molecules, gene therapy development, natural history studies, registries, novel patient-centered outcomes, healthcare education and collaborative networks.
At IRDiRC, Samantha is currently involved in task forces set up to better understand the complexity of funding for rare disease research and motivating factors for organisations to invest.

Samantha is an adamant believer that patients should be at the front and center of rare disease research and development. She has been among the thought leaders of patient-industry collaboration from the early 2000s which led her to become involved in policy making for rare diseases and she served on the EU committee of experts in rare diseases. She was involved in determining the policy framework for the establishment of European Reference Networks for Rare Diseases.

RANDALL LINDSAY

Lindsay Randall graduated as a Children's Nurse in 2013, after 10 years in the property market. She worked at the Evelina London tertiary children's hospital across orthopaedics, neurology, cardiology and surgery, before taking on the role of Clinical Educator for Paediatric Surgery. In 2018, Lindsay's first child, age 2, was diagnosed with ultra rare condition SLC6A1 Developmental and Epileptic Encephalopathy. Lindsay founded Arthur's Quest in 2019, a UK registered non-profit, raising awareness and funds to support advancing research and developments for this disease. Lindsay relocated to her local DGH to be closer to home, working in the role of Paediatric Practice Development Nurse at MTW, Kent. She is currently completing a PG Cert in Leading Practice Education.
In 2019, having tested negative for the SLC6A1 mutation, Lindsay and her husband welcomed their second child into the world, but SLC6A1 was not finished with them, and against all odds, their daughter was diagnosed in 2020 following increasing seizure activity. Arthur's Quest, is part of a global network of parent run organisations that work as a consortium of highly motivated CEO's and Trustee's, sharing ideas, progress, research initiatives and resources. They connect patients and families, clinicians, researchers, scientists, drug makers, funders and umbrella organisations with the primary focus of advancing translational science to treat this disease. Last year the organisation officially dual registered to include the name SLC6A1 Connect UK, in line with global partners, with a new web address www.slc6a1connectuk-aq.org.

SIREAU NICK

Nick Sireau, PhD, is the CEO and Chair of Trustees at the AKU Society, a patient group that helps people with AKU, a rare genetic disease affecting both his children. The AKU Society and Nick are the winners of the 2021 Members Award by EURORDIS (the European Organisation of Rare Diseases) because of their work on successfully developing a new treatment for AKU. He is also co-founder of Sireau Labs, a biotech that is developing mRNA therapy for AKU and other rare genetic diseases. Nick is co-founder and Chair of Beacon, an organization that helps all rare disease patient groups. He is the editor of 'Rare Diseases: Challenges and Opportunities for Social Entrepreneurs' (Greenleaf 2013) and of the 'Patient Group Handbook: A Practical Guide for Research and Drug Development' (Beacon 2016). Nick is co-founder and Chair of Orchard OCD, a medical charity that funds research into obsessive-compulsive disorder (OCD), a common yet debilitating mental health condition. Nick has a PhD in social psychology from City University. He is a fellow of the Ashoka Fellowship of Social Entrepreneurs.

SKOUBO SOFIE

Sofie Skoubo is a PhD student at the Department of Public Health, Aarhus University, and the National Rehabilitation Center for Neuromuscular Diseases. Sofie's research focuses on educational support by using the telepresence robot AV1 for children with neuromuscular disease. Since 2020, Sofie has worked with telepresence robots for children with cancer, neuromuscular diseases, and anxiety. Her PhD project is a collaboration between the Norwegian company No Isolation, which developed the telepresence robot AV1, and the National Rehabilitation Center for Neuromuscular Diseases. She has neuromuscular diseases and is a two-time Paralympian athlete.

VALENTINE NIVEDITA

As Vice President of Global Product Innovation, Nivedita oversees heads Pharmanovia's pipeline strategy, with a primary focus on novel therapeutic options in neurology, cardiology, endocrinology & oncology supportive care, as well as the revitalization of legacy iconic brands. Some of her other associations include:
- IRDiRC (International Rare Diseases Research Consortium) task force for funding models for rare diseases and Drug Repurposing Guidebook, which aims to improve care for people with rare diseases.
- Remedi4all is a funders network led by ZonMw and in collaboration with the Anticancer Fund dedicated to advancing Drug Repurposing initiatives.
- Medicines for Europe's Value-Added Medicines (VAM) Sector Leadership Group, which aims to rethink, reinvent and optimise medicines based on known molecules by bringing untapped innovation to improve care delivery. Additionally, the group provides industry insights into evolving EU pharmaceutical legislation regarding repurposed medicines.

Before Pharmanovia, Nivedita held various senior management positions, responsible for leading portfolio planning and business development covering international markets.
She has a Masters in Biochemistry and a Master's in Business Administration.

VASILEVSKY NICOLE

Nicole Vasilevsky is the Associate Director of Data Science in the Data Collaboration Center (DCC) at the Critical Path Institute in Tucson, Arizona, USA. She earned her PhD in Cell Biology from Oregon Health & Science University. Her interests are in developing and applying semantic technologies in the biomedical domain to facilitate novel knowledge discoveries by structuring disparate data types to adhere to the FAIR data principles (findable, accessible, interoperable, and reproducible). Dr. Vasilevsky joined C-Path in January 2023 to leverage her expertise in ontology development, data standards, and annotation application as she leads a team of data scientists to develop and implement a data curation pipeline utilizing the organization's knowledge graph that is used to accelerate drug development and improve health outcomes.

VISSERS LISENKA

I am a pioneer of the translation of genetic research into clinical diagnostics. I started my scientific career with a PhD project in the optimization of high-throughput technologies for the detection of genetic causes underlyinghuman disease, and intellectual disability (ID) disorders in particular. Using such new technologies, I was able to identify several novel syndromes (e.g. Koolen-de Vries syndrome) and discover multiple disease-genes (e.g. CHD7 for CHARGE syndrome), publishing her findings in high-impact journals. My research also strongly contributed to the implementation of microarray-based comparative genomic hybridization as routine diagnostic test for the detection of submicroscopic alterations in routine clinical practice. The application of this technology allowed me to define the diagnosis for 15% of patients, producing the strong increase the effectiveness of clinical diagnostic services.
In the last 5 years, I demonstrated an exceptional talent for bridging the gap from research to clinic, resulting in a strong record of productive and successful translational research in novel state-of-the-art genome-wide technologies, including exome and genome sequencing for (de novo) mutation detection. The latter fostered fundamental research into mutational mechanisms, significantly shifted paradigms for medical genetic disorders with reproductive lethality, and enabled a diagnosis in ~60% of ID patients. Moreover, I have developed novel (statistical) frameworks to identify novel candidate genes for neurodevelopmental disorders, including large-scalemeta-analysis of existing exome data, clustering of de novo mutations enriched for genes exerting their effect by gain-of-function and/or dominant negative effects, and the use of large-scale re-sequencing technologies to verify the true nature of candidate disease genes. With an H-factor of 70, I have (co-)authored >180 publications in peer-reviewed journals (i10-index 145). Highlights include >10 publications in Nature Genetics, >20 in the American Journal of Human Genetics, and senior authorships in the New England Journal of Medicine, Nature Medicine, Nature Genetics and Nature.
Collectively, my pioneering translational work on the cutting edge of genetic research and clinical diagnostics has significantly changed the field of medical genetics. My unique skills to integrate various genomics technologies has provided novel diagnostic strategies, which allowed the identification of >85 novel disease genes, provided fundamental scientific new insights, but also allowed a conclusive molecular diagnosis to be made in tens of thousands of patients worldwide.

YEPEZ VICENTE

Dr. Vicente Yépez is a researcher and Scientific Manager of the Chair of Computational Molecular Medicine at the Technical University of Munich and is the co-lead of the European Solve-RD RNA-seq analysis working group. Dr. Yépez did his bachelor in Industrial Engineering in Mexico and his MSc in Mathematical Modeling in Engineering in Italy, followed by a PhD in Bioinformatics at the TUM where is currently based.

SPEAKERS' ABSTRACTS

NOTES

WHAT CAN WE LEARN FROM 60 YEARS OF NEWBORN SCREENING AND THE CHALLENGE OF GENOMICS?

DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

Jim Bonham, Sheffield Children's HospitaL, UK

It is more than 60 years since Dr Robert (Bob) Guthrie helped introduce newborn screening for phenylketonuria. During that time more than 750m babies have been tested and an estimated 500,000 children have benefitted from this life changing intervention.

Today around 45 million babies are offered newborn screening, some for up to 60 conditions. While this is recognised as a major public health advance almost 100m babies pa, many in low and middle income, do not have access to this intervention. It is hoped that the recent resolution presented by the WHO during the World Health Assembly in 2024 may help address this inequality.

Meanwhile, newborn screening continues to develop both in the technologies used to detect and treat babies and in the number of disorders included. Most recently, first line genomic testing offers the possibility of increasing the number of disorders from 60 to several hundred. Despite the clear benefits of such an approach, there are some key questions to address about the logistic and interpretative aspects of these exciting new opportunities.

The penetrance and expressivity of the genomic variants identified has largely been established from studies in symptomatic individuals or in families with an affected member. It is therefore likely that, with the current understanding, the significance of the findings from whole population screening of asymptomatic babies may not be fully understood.

The resulting uncertainty could potentially undermine the remarkable public confidence that newborn screening currently enjoys.

In this presentation we will explore the unique aspects of newborn screening which mark its difference from the typical diagnostic and clinical scenario and explore ways in which we can support the careful growth and development of newborn screening while ensuring that it continues to deliver 'more good than harm at reasonable cost'.

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FROM DATA TO DIAGNOSIS: THE SOLVE-RD STORY

DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

Steven Laurie, Centro Nacional de Análisis Genómico (CNAG), ES

Solve-RD – Solving the unsolved Rare Diseases was a six-year Horizon 2020 initiative with primary goals of diagnosing previously unsolved rare disease cases and establishing a framework for continental scale -omics analyses and interpretation, to expedite diagnoses. The project involved over 300 researchers and clinicians, from 40 different centres and hospitals across Europe, working in close collaboration with six European Research Networks for rare disease. It combined clinical, technical, and biological expertise to build a complete workflow for facilitating and enhancing rare disease diagnoses.
We approached these challenges through a multifaceted strategy including:
(i) Reanalysis of over 20,000 exome/genome sequencing datasets, and accompanying phenotypic data from approximately 12,000 undiagnosed individuals, and family members
(ii) Applying novel multi-omics analyses to a subset of cases that remained unsolved
(iii) Fostering pan-continental data sharing and collaboration, in conjunction with the application of cutting-edge assays and up-to-the-minute expert clinical interpretation.
In this presentation, I will highlight some of the successes, and the ongoing challenges still to be overcome, as we work towards the IRDiRC goal of ensuring that every individual with a rare disease receives a diagnosis within one year of coming to medical attention. This work underscores the transformative potential of collaborative, data-driven research for rare disease diagnostics.

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WHEN THE OUTLIER IS THE SIGNAL: RNA-SEQ BASED DIAGNOSTICS OF RARE DISORDERS

DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

Vicente Yépez, University of Munich, DE

Over the last few years, sequencing the transcriptome has emerged as a complementary path in the field of Mendelian disease diagnostics. RNA sequencing allows to test directly the functional impact of variants and can further lead to the discovery of variants missed by DNA analysis. Here, I will present statistical methods that we have developed to find aberrations in the transcriptome, specifically to detect aberrant gene expression and splicing. These methods usually report only a handful of genes per sample and, in combination with rare variants from DNA and matching phenotype, allow to examine just the most relevant candidates. Finally, I will showcase specific examples of diagnosed cases and discuss limitations and future directions of this approach.

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LONG READ SEQUENCING AS FIRST-TIER DIAGNOSTIC TEST FOR RARE DISEASES

DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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INNOVATIONS FROM LMIC

DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

Christian J Hendriksz, A Rare Cause, UK

The diagnostic odyssey is a well-known concept for those affected by rare disease and multiple attempts has been made to reduce this journey. Traditionally this has been by biochemical newborn screening and now whole genome sequencing is also being introduced in some areas. AI has become the "new kid" on the block that will solve everything, but it does hold promise for some areas.

However, for many living in Low- and Middle-Income Countries (LMIC) this is only a pipe dream for the privileged nations.

My focus will be on the work that we have been doing in LMIC to build the Africa Roadmap – simple diagnostics network to help develop epidemiology which can be used to develop potential screening studies in the future. The limitations of sample logistics and how we may be able to overcome them for those in LMIC.

Medical education programs and networking to promote awareness being part of the Nngwe project based in South Africa.

Rolling out of a diagnostic algorithm in LMIC to support phenotypic diagnosis and interpretation of whole genome sequencing data to deal with high incidence of VUS in LMIC.

Developing an AI radiology tool which may have the potential to use simple x rays as more advanced diagnostic and monitoring tools.

Development of a Federated AI patient held registry to enhance research and evidence generation for rare disease which have started in Sri Lanka.

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ACCELERATING RARE DISEASE TREATMENT: THE ROLE OF DATA SHARING IN THE RDCA-DAP

EMPOWERING DATA

Nicole Vasilevsky Critical Path Institute, US

The search for new or repurposed drugs for rare diseases remains a top priority, yet significant challenges persist. Patients and families frequently face difficulties in obtaining accurate diagnoses and effective treatments for approximately 10,000 unique rare diseases worldwide. While clinical data exists that describe patient phenotypes, genotypes, and other relevant features, it is often disparate, heterogeneous, and siloed. Initiatives aimed at standardizing, harmonizing, and disseminating this data to wider communities can facilitate research, clinical trials, and development of new therapies for these conditions.

The Critical Path Institute (C-Path), a non-profit public-private partnership with the US Food and Drug Administration (FDA), seeks to accelerate the development of treatments for rare and underserved diseases. A key initiative of this effort is the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP). The RDCA-DAP aggregates curated data to facilitate rare disease characterization and the development of new therapies in an accessible data portal for researchers, clinicians, and patients.

Patient-level data, including clinical trials, patient registries, and natural history studies are contributed by various organizations. Data undergoes a rigorous curation workflow to ensure integrity, security, and compliance with the FAIR principles (findable, accessible, interoperable, and reusable). Metadata is made available for user access on the platform, and data is then further curated and key data elements are mapped to a standardized data model (Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)) and aligned with biomedical ontologies such as Human Phenotype Ontology (HPO). Data and metadata are integrated into a knowledge graph which facilitates exploration and querying across the aggregated patient data. Users can freely search for data through the 'FAIR Data Services' platform after completing a data access request. The platform features 'Workspaces' that provide cloud-based infrastructure for data analysis and insights generation.

By providing semantically annotated data in the RDCDA-DAP platform, this initiative aids in understanding the characteristics of diseases (e.g., symptom presentation over disease course, potential subgroups within a disease), which may have utility in improving future study designs, running sample size calculations, and better interpretation of endpoints for clinical trials.

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THE SWISS PERSONALIZED HEALTH NETWORK- FROM CLINICAL ROUTINE DATA TO FAIR RESEARCH DATA

EMPOWERING DATA

Sabine Österle, SIB Swiss Institute of Bioinformatics CH

The Swiss Personalized Health Network (SPHN) facilitates health research by building a system that helps researchers to find, organize, and reuse health data. This system follows the FAIR (Findable, Accessible, Interoperable, Reusable) principles, ensuring data is easy to find, access, and use across different projects.

The process starts with the SPHN Data Exploration and Analysis System (pilot phase currently ongoing) which allows researchers to check what data is available in hospitals, find patient groups for their studies, and run basic analyses while preserving patient privacy. To organize their data, researchers use SPHN Schema Forge, a webservice that enables them to build a blueprint and the technical specifications for their knowledge graph. By designing structured data graphs following the SPHN guidelines, researchers ensure that different types of health data, such as clinical records, biological samples, and genetic information, can be linked and analyzed in a standardized way.Once a data schema is created, the SPHN Connector is used in hospitals and data platforms to transform raw data into this structured format in a consistent manner across different healthcare institutions. After a research project is completed, metadata describing the datasets of a project are stored in the SPHN Metadata Catalog, a central system where other researchers can find existing health datasets and all information for reuse requests. This catalog follows FAIR principles, making it easy to search for relevant datasets. An additional feature, SPHN Schema Scope, helps researchers explore and understand how different graphs are structured and which aspects (concepts), making it easier to find useful information.

By simplifying the process of finding, structuring, and reusing health data, SPHN provides researchers with the systems they need to advance personalized health research.

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A HEALTH DATA ACCESS BODY IN THE NETHERLANDS: POTENTIAL FOR RARE DISEASE RESEARCH?

EMPOWERING DATA

Thomas Hellebrand, Dutch Ministry of Health Welfare and Sport NL

The presentation will elaborate on the current state of affairs of the implementation of the European Health data Space Regulation in the Netherlands with a focus on the realization of a Health Data Access Body. These bodies will be required by law in every EU Member State and are tasked with enabling access to electronic health data for among other things research. Rare disease research is one of the possible areas for which researchers could obtain a permit to gain access to anonymised or pseudonymised data in a supervised secure processing environment. These bodies will cooperate to enable access in several Member States for single research projects with an aim to reduce as much as possible the administrative burden for researchers.

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RESPONSIBLE DATA USE IN RARE DISEASE RESEARCH: AN ETHICAL, LEGAL, AND SOCIAL (ELSI) PERSPECTIVE

EMPOWERING DATA

Marieke Bak, Amsterdam UMC, NL

In rare disease research, the scarcity of cases often necessitates extensive data sharing to advance scientific understanding and develop effective treatments. However, this practice raises ethical, legal, and social issues (ELSI), including patient privacy concerns, challenges around informed consent and anonymization, and the need for harmonized data governance across the European Union. In this presentation, I examine these ELSI dimensions through the philosophical lens of "empowerment", advocating for a shift beyond the conventional debate that pits individual risks against societal benefits. Instead, I propose a focus on relational values such as trust, which underpins the mutual cooperation required among researchers and with data subjects to further responsible rare disease research.

A relational approach to data sharing that promotes empowerment, or collective "power-with" as it is known in feminist philosophy, demands robust democratic engagement with diverse stakeholders. Drawing on empirical and embedded ELSI research within several rare disease and data-sharing consortia—including in the areas of sudden cardiac arrest and pharmacogenomics— this talk substantiates its argument with findings from interviews and multi-stakeholder deliberations with patients, their next-of-kin, data scientists, clinicians, and policymakers. I will end with practical recommendations for meaningful stakeholder participation in different research contexts, illustrated by our recent experiences with the "guidance ethics" methodological framework. By fostering inclusive dialogue and emphasizing trust, data practices can better align with societal expectations and ethical standards—ultimately reinforcing a responsible environment for rare disease research.

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CHALLENGES AND OPPORTUNITIES FOR MRNA THERAPY FOR RARE GENETIC DISEASES

ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

Nick Sireau, AKU Society, UK

This presentation by Nick Sireau will focus on the innovative application of mRNA therapy for treating Alkaptonuria (AKU), a rare genetic disorder characterized by the accumulation of homogentisic acid due to mutations in the HGD gene. With over 7,000 rare diseases and only 5% having approved treatments, there is a significant unmet need for effective therapies. Nick Sireau, through the AKU Society and Sireau Labs, aims to address this gap by leveraging advanced mRNA and LNP technology. He will discuss the challenges and successes in doing so in pre-clinical models and plans for the future. Additionally, the talk will discuss the broader implications of mRNA therapy in the context of rare diseases, expanding the research beyond AKU to include other conditions like Phenylketonuria and Hereditary Tyrosinemia Type 1. The session aims to engage stakeholders in understanding the potential of mRNA therapeutics to transform treatment paradigms for rare genetic diseases.

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CELL SPECIFIC GENE EDITING AS TREATMENT OF ALFA 1 ANTITRYPSIN DEFICIENCY

ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

Tiziana Cremona, University of Bern CH

Alpha1 antitrypsin deficiency (AATD), an autosomal codominant disease that is caused by mutation of the SERPINA1 gene, leads to liver and lung disease. The prevalence of AAT deficiency varies considerably, yet it is estimated that 3 million people carry allele combinations that are associated with severe deficiency. Individuals with AAT deficiency usually develop symptoms of lung involvement at older ages, which include shortness of breath, chronic bronchitis, high prevalence of bronchial obstruction with Forced expiratory volume (FEV1) decline, and progressive emphysematous lung destruction. Current therapeutic options are comprised of either lung or liver transplantation, or life-long intravenous weekly augmentation therapy with commercially available affinity-purified plasma-derived human AAT.

Our aim is to test a novel approach to obtain sustained therapeutic levels of circulating AAT using non-viral targeted cell specific base editing (BE) for hepatocytes. We investigate whether this approach could permanently alter or attenuate the course of the disease. To test our hypothesis, we use cell lines as in vitro system, and we used pallid mice as animal model. Pallid mice carry a genetic deficiency of murine AAT, developing spontaneous emphysema at 8 months of age. Wild type (C57BL6) serves as control. Protospacer sequence (PAM) is designed for DNA base editing that specifically recognize the mutation present in pallid mice to enable editing of the pathogenic base pair. PAM is encapsulated in cell specific extracellular vesicles (EVs) as nanocarriers of about 100 nm in diameter to specifically target hepatocytes. We have standardized induction, isolation, storage, and loading of EVs. We have demonstrated, in vitro and in vivo, that EVs are cell specific and within 24 h more than one extracellular vesicle can be uptake.in vivo after 48 h EVs accumulates in the liver. We demonstrate that after 72 h in vitro 13% of the cells were edited and in vivo after 1 week 6% of the hepatocytes were edited. Further time points need to be tested. Next step will be to used EVs loaded with Base Editors on AATD human hepatocytes, followed by studying time and concentration-dependent expression of AAT after editing.

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DEVELOPING NOVEL THERAPIES FOR DIAMOND-BLACKFAN ANEMIA (DBA)

ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

Johan Flygare, Lund University, SE

Diamond-Blackfan Anemia (DBA) is a genetic bone marrow failure syndrome characterized by severely impaired red blood cell production, primarily caused by mutations in various ribosomal protein genes. This presentation explores two promising therapeutic approaches for DBA: small molecule CDK8-inhibitors and lentivirus-mediated gene therapy of CD34+ hematopoietic stem cells (HSCs), highlighting their potential efficacy and mechanistic similarities.

CDK8 inhibitors, identified through a small molecule screen using a DBA mouse model, demonstrate broad therapeutic potential for DBA patients regardless of the underlying ribosomal protein mutation. These inhibitors, including RVY120, induce ´ significant rescue of proliferation and erythroid maturation in both mouse models and primary DBA patient cells with various ribosomal protein deficiencies (RPS19, RPS26, RPL35a mutations). The therapeutic effect involves reduced activation of p53 and its target genes, partially reversing the DBA phenotype across different genetic backgrounds.

In parallel, a gene therapy approach using lentiviral vectors to express the RPS19 gene in CD34+ cells from DBA patients show very promising results. While this approach initially targets patients with RPS19 deficiency specifically, it demonstrates the potential for mutation-specific treatments. Single-cell molecular analysis revealed that expression of the RPS19 transgene in DBA erythroid progenitors led to significant induction of genes associated with terminal erythropoiesis and, importantly, down-regulation of p53-mediated apoptosis pathways.

Both therapeutic strategies converge on a key mechanism: the reduction of p53 activation, which is a central pathogenic feature in DBA. This shared effect underscores the importance of p53 modulation in alleviating the DBA phenotype. Additionally, the studies uncovered potential new players in DBA pathogenesis, such as RPL22L1 and CD70, which may improve DBA diagnosis and understanding across various genetic subtypes.

In conclusion, CDK8 inhibitors offer a promising broad-spectrum pharmacological treatment for DBA, potentially benefiting patients with diverse ribosomal protein mutations. In contrast, the RPS19 gene therapy approach, while more targeted, provides a potential curative option for a specific subset of DBA patients. Both approaches demonstrate molecular efficacy in rescuing the DBA phenotype by modulating p53 activation, supporting their further development and progression to clinical trials. These findings pave the way for novel, mechanism-based DBA therapies that could address the diverse genetic landscape of the disease.

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DEVELOPING GENE AND CELL THERAPY FOR RARE INFLAMMATORY DISORDERS

ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

Despina Eleftheriou, Great Ormond Street Hospital (GOSH) UK

Rare inflammatory disorders represent a significant unmet medical need, with current therapies often limited to symptomatic management and significant variability in patient outcomes. Gene and cell therapies offer a promising frontier to address the root causes of these diseases by targeting underlying genetic and molecular mechanisms. This presentation explores the development of gene and cell therapies tailored for rare inflammatory conditions, emphasizing the integration of translational research, cutting-edge genomic technologies, and clinical innovation. Key topics include the identification of genetic drivers and molecular pathways in rare inflammatory diseases, the design of gene therapy approaches and the engineering of cell-based therapies such as CAR-T cells . The talk will highlight preclinical and clinical studies that demonstrate proof-of-concept for these novel therapies. It will also address challenges such as ensuring long-term safety, overcoming immune-related complications, and optimizing delivery methods. Collaborative strategies between academia, biotech, and regulatory bodies to expedite development and access will also be discussed. Through this work, we aim to pave the way for transformative, curative treatments that improve survival and quality of life for patients with rare inflammatory disorders.

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ATMPS: ESSENTIAL TOOLS OR ESSENTIAL MEDICINES?

ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

Rimas Orentas, Miltenyi Biotec, Inc., US

The rubric of Advanced Therapy Medicinal Products (ATMPs) has come to represent a new class of cell and gene therapies that has become a useful classification tool for regulatory authorities. The challenge is that these therapies remain in rapid deployment and rapid change. Retroviral, Lentiviral, Crisp-based, and advanced Crispr-based (such as base editing or gene writing) gene vectors are rapidly challenging how we classify these vectors and their effects. And now, in 2025, direct in vivo gene therapy trials with lentiviral vectors has allowed this class of products to enter the drug risk classification afforded to AAV. While gene-modified cellular products are considered as the final drug product by regulators, the gene vector itself is now held to be an ATMP as well. This raises the question if this gene modification tool does indeed need to be classified as such. Given the track record of the vectors themselves, this extra burden has slowed progress. The potential of using a direct in-line device to modify autologous cells with a gene vector, or a shortened ex vivo process that does not need to be frozen, but can be administered in a single outpatient visit, again challenges current classification. Again the question arises if this is a true combination product (cATMP) or an advanced means to facilitate therapy. The need to accelerate and derisk these highly effective therapies has been recognized by regualtory authorities in the US and EU by creating a series of programs to accelerate approval. Here we raise the question if this is sufficient, and are there ways in which the approval process could encourage competition and innovation, with an aim to lower the drug price. With ATMPs comprising the most costly drugs on the planet, the core justice issue of providing medicines to those who need them most, and developing these medicines in the context of the population they are designed to benefit has fallen to the wayside. Thus, we are left with a challenge: do we continue to raise a higher and higher bar, which counterbalances innovation, or can we develop new pathways that provide curative ATMPs to those who would benefit most.

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IMPACT OF A CROSS-SECTOR (INTER-AGENCY) CARE COORDINATION PROGRAM FOR CHILDREN AND FAMILIES LIVING WITH RARE AND UNDIAGNOSED DISEASES (RUDS)

IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES, AND SOCIETY

Sue Baker, Rare Care Centre AU

Children and families living with RUDs have multidimensional needs that impact not only their physical and mental health, but every aspect of their lives including education, finances, social activities, and employment. Consequently, families require services from multiple sectors and government agencies which often results in fragmented care pathways. Where there is no coordination or integration of care across these pathways, patients and families face an even higher burden and therefore it is a priority to deliver and evaluate formalised care coordination programs.

Historically care coordination programs integrate the various components of healthcare services such as primary, secondary, and tertiary care. The Rare Care Centre at Perth Children's Hospital in Western Australia has taken care coordination a step further in pioneering an innovative Cross-Sector Care Coordination Program designed to integrate health, school education, welfare, disability, and social services into a holistic Program. The Program provides navigation, coordination, integration and advocacy support mechanisms across the hospital and community, adding value without duplicating existing services.

The Program was co-designed from inception with children and families, representatives from each sector and government agency at both strategic and operational levels, and in partnership with family support organisations.

The Program has impacted parental outcomes in lowering levels of stress, improving wellbeing, and reducing unnecessary visits to the hospital with subsequent cost savings for families. Additionally, the Program has enhanced the overall child and family experience and increased access to disability services, school resources and welfare programs.

The Program has not only improved patient outcomes but is also indicating potential cost savings to the health system through decreased hospital utilisation including reductions in inpatient admissions, outpatient appointments, inpatient bed days, and emergency department presentations. An independent economic analysis has also demonstrated an impressive return on investment, with $4 of social and economic value generated for every $1 spent.

This sustainable and replicable Care Coordination Program offers a blueprint for the future of rare disease care, providing a scalable, evidence-based solution to improve whole of life outcomes for this population.

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CAN HIGHLIGHTING THE SOCIETAL VALUE OF RARE DISEASE TREATMENTS LEAD TO IMPROVED HEALTH?

IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES, AND SOCIETY

Gina Cioffi Loud, Chiesi USA, Inc. US

Research by Chiesi with support from IQVIA demonstrated the economic burden rare conditions impose on individuals, society, and healthcare systems. An aim of the research is to encourage policies that will lead to improved health of rare disease patients.
We examined direct, indirect and mortality-related costs for 23 rare diseases (Figure 1) across five therapeutic areas first in the United States and now in France, Germany and Italy. The 23 rare diseases were selected from multiple sources in collaboration with Patient Advocacy Groups and others and affect approximately 227 000 people in France, Germany and Italy. We benchmarked these costs against those for high-prevalence diseases including diabetes, cardiovascular disease, Alzheimer's disease, arthritis and certain cancers. We explored the burden when treatment is available and provided a scenario analysis to show what the cost would have been if there were no effective treatments available for those diseases. There is a high degree of specificity on the costs for the 23 rare diseases included in this analysis and the calculations are similar across the board in the three geographies. Information from families on their specific financial strains and attributes was not available.

The average burden for the high-prevalence diseases was €7000 per patient per year (PPPY). In comparison, the average burden of the rare diseases we explored was €107 000 PPPY, an increase of more than 15 times. Of this PPPY burden, indirect costs for the 23 rare diseases average 29% of the total burden when treatment is available, rising to an average of 45% when no treatment is available. Significantly, most of the indirect costs (e.g. caregiver burden, home changes and costs of secondary treatments, travelling and accommodation) are borne by families. We directionally estimated that without any treatment options available, the overall burden PPPY would increase by 28% across the 23 diseases in focus. These data suggest that the availability of treatment creates positive value and alleviates financial strain on families and healthcare systems.

The findings provide important insights for patients and patient representatives, as well as policymakers and other stakeholders, on the economic burden of rare conditions on individuals, society, and healthcare systems. Moreover, our findings demonstrate the economic advantage when treatments are made available. The inequity between high-prevalence and rare diseases should be addressed at the country level and in national plans. We encourage further exploration and advocacy focused on the acute gap in research and available treatments and the totality of its impact.

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MENTAL HEALTH AND RARE CONDITIONS: AN INTEGRATED APPROACH TO CARE AND RESEARCH

IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES, AND SOCIETY

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An integrated, holistic approach to care and research of rare conditions should address the whole person. EURORDIS announced their Mental Health and Wellbeing Initiative at the end of 2022, and early results from this work show the importance of making the psychosocial factors to quality of life a priority as well as recognising the intersectional mental health needs of those living with rare conditions. Poor mental health can affect access to diagnosis, care, treatment, clinical trials, and quality of life. A systematic review has highlighted the impact of rarity and living with uncertainty, and the importance of psychosocial care which promotes self-esteem and inclusion, combatting stigma and discrimination. A relational approach which focuses on the whole family and caregiver network is needed to provide the best possible environment for efficacy of care and quality of life over the life course. Psychologically-informed medical care is ideal, within the multidisciplinary team structure, with good communication and shared, person-centred decision making. Celebrating the strengths of those living with rare conditions, while supporting the areas of need, allows a fulsome quality of life for as long as possible.

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SCHOOL ABSENCE LEGISLATION GOVERNING IN NORWAY, SWEDEN, AND DENMARK FOR CHILDREN WITH CHRONIC ILLNESS IN COMPULSORY EDUCATION—A COMPARATIVE STUDY

IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES, AND SOCIETY

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Background
Health and education are interrelated and influence social, economic and lifestyle perspectives. Children with chronic illnesses experience barriers in the educational system regarding school attendance and social isolation. Gaining knowledge of compulsory education and how children with chronic illnesses are supported is crucial for the implications of future education policy and legislation in Scandinavia. This study compares Scandinavian legislation frameworks on compulsory education, chronic illness and school absence to form the basis of future research on education for children with chronic illness.
Methods
The study uses a comparative approach to explore the support of children with chronic illnesses in compulsory education across Norway, Sweden and Denmark. The documents included are 3 education acts and 15 secondary documents, which are notes and guidelines for the education acts. The data were analysed using a manifest content analysis.
Findings
We found four categories and six subcategories: (1) school obligation and rights; (2) chronic illness; (3) school absence: (a) categorisation of absence; (b) registration of absence; and (c) sanction; and (4) education support: (a) Hospital school support; (b) Home instruction support; and (c) technological support.
Conclusion
This study's findings demonstrate the similarities and differences in the Scandinavian compulsory education legislation and guidelines regarding chronic illness and school absence. We found similarities across the countries regarding chronic illness and school absence. Still, the findings showed differences in the systematic registration of school absence and requirements for attendance with compulsory education in Norway and Denmark compared with compulsory schooling in Sweden. This knowledge will inform and enlighten future discussions and decisions in education and public health. The results can contribute to awareness of the opportunities for educational support and perspectives about education for children with chronic illnesses. Future research focusing on the experience of children with chronic illness and educational support is needed.

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ORPHAN DRUGS BARRIERS - APPROVALS TO ACCESS
FUNDING MODELS

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An insight into orphan drug approval trends by the FDA and EMA, funding barriers with case studies on successes and setbacks with orphan applications.

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NOT PROVIDED
FUNDING MODELS

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ORPHAN DRUGS R&D PRODUCTIVITY AND PROBABILITY OF SUCCESS

FUNDING MODELS

Samantha Parker, Italfarmaco FR

In 2011, the International Rare Disease Research Consortium (IRDiRC) was formed to boost the global research and innovation ecosystem, and subsequently to help accelerate rare disease drug development, approvals and diagnosis, and to better support the needs of people living with a rare disease and their families (1,2). IRDiRC brings together international governmental, non-profit, industry and patient groups to foster global collaboration for rare disease research. In 2023, IRDiRC set up a Funding Models for Rare Diseases Research Task Force to assess funding models most frequently observed in the clinical development of an OD and identify potential funding gaps and priorities to further accelerate their development (3).

In support of this goal, we desired to explore if specific attributes might provide greater value in predicting the success of drug development programs. The approach we undertook was a retrospective analysis of drugs designated as orphan drugs (ODDs) in 2017 by the FDA & EMA. 2017 provides a 7 to 8-year window of opportunity from the designation to current timeframe during which the therapeutics could have advanced or been terminated. This approach allowed us to perform a thorough quantitative analysis of the success rates of the progression to an advanced clinical trial phase and the attrition rates in each stage, as well as a comparative assessment across different classes of ODs. We were also able to better understand different derisking factors, to further stimulate orphan drug development.

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CHALLENGES IN ALIGNING FUNDING INITIATIVES IN RARE DISEASE: FONDAZIONE TELETHON EXPERIENCE

FUNDING MODELS

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Aligning funding initiatives for rare diseases presents numerous challenges. The IRDiRC Funding Models for Rare Diseases (RD) Research Task Force was established to examine the funding landscape in RD research which is complex due to various strategic goals among funders. Like IRDiRC's earlier study on what drives company investments in RD research, this Task Force identified return on investment (ROI) as a key factor. However, the definition of ROI varied among different RD funders. Investors should address scientific quality, human resources, sustainability, and health economics when setting funding priorities. This involves evaluating which stage of product development aligns with the investor's expertise and meets the requirements of the RD community. Investment strategies often involve partnerships between various types of funders, as these allow for shared risks and minimally overlapping risk tolerance. This complex scenario highlights knowledge gaps that need to be addressed through targeted research. Finally, funding catalyzes advancements in economically disadvantaged areas, transforming unmet needs into opportunities. Individuals living with rare diseases will significantly benefit from ongoing transparent dialogue and innovation among all relevant stakeholders. As an example of collaborations in the research funding landscape, Fondazione Telethon has formed partnerships with both a private bank foundation and a public foundation and patient associations to support the drug development process from basic research to preclinical studies.

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DRUG REPURPOSING IN RARE AND INFECTIOUS DISEASES - LESSONS LEARNT FROM EU PROJECTS ON HOW TO IDENTIFY AND PROGRESS SMALL MOLECULE BASED THERAPIES TO THE CLINIC.

DRUG REPURPOSING IN RARE DISEASES

Philip Gribbon, Fraunhofer ITMP, DE

Drug repurposing (also called drug repositioning) is an alternative approach to identify novel therapies. It is defined as the identification of new indications for drugs that are already in clinical use. The advantage of drug repurposing is that it can bypass several steps of classical drug development. For example, safety studies can be limited to a minimum because the drugs are already in clinical use, and development time and cost can be reduced to a great extent, especially regarding preclinical development and early clinical trials. For some drugs, that have already been in clinical use for years or decades, there is plenty of pharmacological information and pharmacovigilance from a large number of treated patients available and adverse effects in patients are well known and documented. In this presentation practical case studies of drug repurposing for infectious and rare disease related settings will be presented based upon work performed in the REMEDI4ALL, EXSCALATE4COV and KCNQ2 research consortia.

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CHALLENGES AND OPPORTUNITIES FOR DRUG REPURPOSING IN RARE DISEASES

DRUG REPURPOSING IN RARE DISEASES

Catriona Crombie, LifeArc Rare Disease Translational Challenge UK

he repurposing of medicines with known mechanisms of action and toxicity can offer an expedited route to deployment in new disease areas. There is significant hope that for rare disease with insufficient market potential to justify expensive drug discover operations that the use of existing approved drugs could provide an answer. However, the journey to approval and reimbursement for a new indication is not trivial. This presentation will cover some of the initiative put in place to support the repurposing of medicines with some case studies.

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SLC6A1: A DRUG REPURPOSING JOURNEY

DRUG REPURPOSING IN RARE DISEASES

Lindsay Randall, Arthur's Quest UK

SLC6A1 is a rare genetic neurodevelopmental disorder or developmental and epileptic encephalopathy, depending on the phenotype. SLC6A1 encodes for GAT-1, a major GABA transporter whose function is the re-uptake of GABA from the extra cellular space in the synapse. Mutation in the SLC6A1 gene causes loss of function at varying degrees, the impact of which is a host of devastating comorbidities including refractory epilepsy, learning disabilities, speech and language delay/absence, autism, ADHD, challenging behaviour, hypotonia.

SLC6A1 is represented by a global network of patient organisations run by parents who chose to fight for their children's lives. Facilitating a globally collaborative scientific network for research and development focused on understanding the disease, and creating therapy options for those with the mutation. SLC6A1 Connect funded an open label drug repurposing trial in 2021, leading to positive outcomes for patients around the world. Since then, we continue to push the repurposing needle for SLC6A1, funding Zebra fish projects for screening drug libraries, observational studies in an over the counter medication with successful outcomes in other rare diseases, and other projects for repurposing drugs in the hope of finding promising solutions to address the existing unmet needs of this disease community.

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DELEGATES' ABSTRACTS

MITOCHONDRIAL DNA METHYLATION IN PLATELETS MEASURED BY LC-MS/MS.

ABSTRACT N° A001 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Purpose: Mitochondria are critical for cellular energy, reactive oxygen species (ROS) production, calcium buffering, and apoptosis. Mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) affecting mitochondrial function can lead to various disorders, though in some cases, the genetic cause remains unknown. Recent findings suggest that enhanced mtDNA methylation (mtDNAme) levels are associated with decreased ATP production in patients with myopathy without detected DNA mutations (Mposhi, doi: 10.3390/ijms23042197). Measuring MtDNAme is challenging due to contamination with nDNA. The aim of this study is to isolate and analyze platelet MtDNAme with minimal nDNA contamination and sufficient analytical sensitivity using LC-MS/MS, potentially offering a non-invasive approach for mitochondrial disorder screening.

Methods: Platelets were isolated from EDTA-anticoagulated blood samples (method adapted from Doormaal, doi: 10.1007/BF00264763), and processed using TRIzol and phenol-chloroform for (mt) DNA isolation. LC-MS/MS (HILIC-Shimadzu LC-0AB U(H)PLC-SCIEX API 4500QQQ system; method adapted from Zhou, doi: 10.1016/j.foodchem.2013.10.143) was used to measure global MtDNAme, ensuring minimal nDNA contamination.

Results: Platelet isolation using multiple centrifugation-washing steps resulted in the lowest leukocyte contamination. The TRIzol RNA phase isolation yielded lower MtDNAme than genomic phenol-chloroform DNA isolation, likely due to reduced nDNA contamination.

Conclusion: The TRIzol RNA phase method is effective for mtDNA isolation with minimal nDNA contamination, and LC-MS/MS proved suitable for MtDNAme measurement. Additional studies utilizing patient samples are needed to evaluate whether mtDNA methylation can serve as a noninvasive biomarker for mitochondrial dysfunction, neurodegenerative disorders (e.g., Parkinson's, Alzheimer's), Diabetes, Cardiology, or Aging.

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CHANGING RARE DISORDERS OF LYSINE METABOLISM (CHARLIE) – MOUSE PHENOTYPING IN A MULTIDISCIPLINARY ENDEAVOR

ABSTRACT N° A002 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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CHARLIE is an international research consortium comprising six countries focused on developing and validating novel therapies and biomarkers for rare inborn disorders of lysine metabolism, specifically pyridoxine-dependent epilepsy (PDE-ALDH7A1) and glutaric aciduria type 1 (GA1-GCDH). Both diseases, due to neurotoxic substrate accumulation, lead to debilitating neurological symptoms that require lifelong care from an early age including dietary lysine reduction therapy proving difficult to implement and often ineffective. The CHARLIE consortium has focused on developing patient recommendations, digital tools for dietary adherence, a patient registry, newborn screening and a research program utilizing various models including iPSC cells, zebrafish and mouse models.

A part of the project is dedicated to the inhibition of the key upstream enzyme aminoadipic semialdehyde synthase (AASS) in the lysine breakdown pathway using gene-editing technologies in Aldh7a1 and Gcdh deficient mouse models for PDE and GA1 diseases, respectively.

The German Mouse Clinic (https://www.mouseclinic.de/) has generated and phenotyped the Gcdh single knockout (KO) mouse model for GA1 and the Aass-Gcdh double knockout (DKO) mouse model within the CHARLIE consortium. Histopathological evaluation of hematoxylin and eosin-stained brain sections of Aass-Gcdh DKO mice revealed no vacuolation of brain tissue in contrast to the known spongiotic findings observed in Gcdh_KO mice. Metabolomic analysis of the brain recently performed at the Radboudumc Translational Metabolic Lab uncovered a significant reduction in the accumulation of glutaric acid and 3-hydroxyglutaric acid in Aass-Gcdh DKO mice, in comparison to Gcdh KO mice.

In a Aass-Gcdh DKO mouse model, through inhibiting AASS, it is possible to restore the abnormal biochemical alterations linked to Gcdh deficiency. The inhibition of the flux through the lysine degradation pathway by CRISPR deletion of the Aass gene is a potential therapeutic option for GA-1, with potential applications to other inborn errors of lysine metabolism.

The synergetic effort of the CHARLIE consortium provides an example of empowering world-class research and medical institutions with resources to perform disease-specific collaborative studies advocating for therapeutic recommendations, genetic-editing technologies and newborn screening.

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THE BIRTH OF VENUS: A CORRECT DIAGNOSTIC ASSUMPTION AS A KEY POINT IN THE NATURAL HISTORY OF A RARE DISEASE PATIENT

ABSTRACT N° A003 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Introduction: When studying the diagnostic journey of patients with rare diseases, researchers usually assume that definitive testing is immediately followed by an accurate diagnostic suggestion. Therefore, the primary way to accelerate their diagnosis is to increase doctors' awareness of rare diseases and their high likelihood in complicated clinical cases.

An analysis of real diagnostic odysseys shows that the relationship between the occurrence of a correct diagnostic assumption and its confirmation is much more complex.

Material & Method: We consider the natural history of two patients with prolonged diagnostic journeys.

The first of them suffered for years from manifestations of Chronic Inflammatory Demyelinated Neuropathy (CIDN). The atypical clinical picture of the disease did not allow neurologists to recognize his illness and led to inadequate treatment. Only contacting a specialized medical center experienced in diagnosing neuropathies made it possible to formulate the correct diagnostic assumption and confirm it with successful treatment.

In the second case, the family physician assumed a diagnosis of multiple endocrine neoplasia (MEN I), drawing attention to the patient's combination of several unrelated diseases. However, local endocrinologists consistently rejected his diagnostic suggestion. Only two years later, when the patient was investigated by a medical facility specializing in neuroendocrine neoplasms, the diagnosis was confirmed clinically and then genetically.

Conclusion: This case study highlights the importance of establishing the timing of the correct diagnostic hypothesis to explore the reasons for a prolonged diagnostic journey. It indicates that, in addition to the delay in assuming the correct diagnosis, the cause of the diagnostic odyssey may be a tendency for the health system to reject it.

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RAPID WHOLE GENOME SEQUENCING IN A PAEDIATRIC INTENSIVE CARE AND NEONATAL UNIT

ABSTRACT N° A004 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Rapid genetic diagnostics in paediatric intensive care units (ICUs) and neonatal units is gaining momentum. The increasing need for timely genetic diagnostics in intensive and neonatal care is particularly critical for the evaluation and management of rare diseases with ambiguous clinical presentations. Here we present a one-year experience of integrating rapid whole genome sequencing (rWGS) at the Division of Paediatrics, University Medical Centre Ljubljana, Slovenia, highlighting its impact in genomics laboratories, ICUs, and neonatal units.

Following the initial clinical assessment and referral to the genomics laboratory of the Clinical Institute of Special Laboratory Diagnostics (CISLD), rapid WGS was performed using a PCR-free library preparation protocol with the Illumina NovaSeq 6000 sequencing platform. Bioinformatic analysis adhered to the GATK Best Practices pipeline, ensuring robust and standardized data processing.

Among 2066 referrals received for genetic testing at CISLD, rapid and urgent WGS referrals accounted for just over 2% of cases. Of these, 46% were analyzed as family trios, and nearly two-thirds yielded positive genetic results. The median age of patients was 3.3 years, ranging from 1 day to 16 years. The most common referral categories were epilepsy and epilepsy-related neurological disorders, haematological and immune system disorders, and hepatopathies with metabolic abnormalities. The mean time-to-result was 10.5 days, ranging from 5 to 20 days.

Our one-year experience demonstrates the critical role of rapid whole genome sequencing (WGS) in neonatal and paediatric intensive care settings for timely genetic diagnostics of rare diseases with unclear symptoms. The high diagnostic yield, with nearly two-thirds of cases providing positive genetic results, underscores the value of rapid WGS in guiding clinical decision-making and improving patient outcomes. The diversity of referral reasons, spanning neurological, haematological, and metabolic disorders, highlights the broad applicability of this approach. Continued integration of advanced genomics into paediatric care holds promise for addressing the growing demand for urgent genetic insights, particularly in critically ill children, and sets a benchmark for similar initiatives in other healthcare settings.

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IMPROVING AGE-AT-ONSET ESTIMATION IN HUNTINGTON'S DISEASE USING A MACHINE LEARNING MODEL

ABSTRACT N° A005 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Huntington's disease (HD) is a rare neurodegenerative disorder that is inherited in a dominant manner and is caused by a prolonged CAG repeat in the huntingtin gene. HD is characterised by motor, behavioural and cognitive abnormalities. Age-at-onset (AAO) in HD refers to the time when symptoms first appear. HD is an incurable condition, which makes the determination of AAO crucial in identifying factors that can modify it, and in developing and evaluating therapies aimed at delaying its onset. The AAO is inversely correlated with the number of CAG repeats representing the most significant factor in estimating the AAO. Current models for AAO prediction are based on the length of the CAG repeat as the primary predictor variable. However, the CAG repeat accounts for about 60% of the variation in the HD population, indicating that there should be more factors influencing the AAO.

In this study, we developed machine learning (ML) models to improve the current estimation of the AAO as well as models that can provide estimations for individual symptom onset. To achieve this we used the Enroll-HD dataset which collects observational data (baseline and follow-up) from multiple study sites, in both manifest and premanifest stages of the disease. Study population was defined as patients enrolled as pre-manifest and those up to 3 years after symptom onset. In addition to the CAG repeat, we included lifestyle factors as well as comorbidities and (non) pharmacological interventions. We performed feature selection to select the most critical variables for our prediction model.

Results indicated that, ML model in conjunction with Enroll-HD, generated more accurate predictions of HD AAO, outperforming the current method. ML model achieved a performance of 77% with an average error of 4.4 years, compared to the 60% performance of the Langbehn formula (used as baseline model). We also developed additional ML models to predict various symptom onsets such as motor, apathy, and cognitive impairment onset. The study also examined the relative importance of the various variables that influence these onset domains on an individual basis, highlighting factors such as marital status, education level or the use of certain medications (such as cardiovascular). This is very important for prognosis and patient stratification in clinical trials that focus on neuroprotective treatments. Timely treatments can result in a better quality of life for HD patients and their caregivers.

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A MULTIDISCIPLINARY AND PATIENT-CENTRED STUDY PROTOCOL TO DEVELOP A DIAGNOSTIC PATHWAY FOR PEDIATRIC PATIENTS WITH SUSPECTED DIAGNOSIS OF A RARE DISEASE (RD)

ABSTRACT N° A006 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Rare diseases (RDs) are complex, heterogeneous, and frequently disabling conditions that affect over 300 million people worldwide. Approximately 75% of these diseases affect children, many of whom experience prolonged and challenging diagnostic journeys with sequential referrals to numerous specialists and frequently invasive diagnostic procedures. This diagnostic odyssey can have serious consequences for the physical and mental health of these children, and for their families' psychosocial and financial wellbeing. According to the 2022 EURORDIS Rare Barometer survey and the ALAN position paper, 60% of the 76 respondents from Luxembourg reported having consulted more than 5 healthcare professionals to receive a diagnosis, 47% declared lacking psychological support, and 64% had insufficient coordination of their diagnostic pathway. Given the lack of coordinated care during the diagnostic journey, there is an urgent need to develop an integrated diagnostic pathway for paediatric patients. Therefore, with this project we aim to develop a streamlined diagnostic pathway that guides patients from their first symptoms to a confirmed diagnosis, ensuring they receive timely, coordinated and appropriate care. We will use a systematic approach to develop the diagnostic pathway, based on three core elements: scientific evidence, clinical expertise, and the needs and preferences of patients. First, we aim to understand what is out there in the literature: we will conduct a scoping review to understand what diagnostic pathways have been published in literature, whether they demonstrate to improve the quality of the diagnostic process and whether they can be transferred to Luxembourg. Additionally, we will conduct a qualitative research study, where we will conduct semi-structured interviews with patients and caregivers, and focus groups (FGs) with healthcare professionals, to collect data on the diagnostic experiences and unmet needs of patients and caregivers, as well as on the perspectives of healthcare professionals. We aim to identify barriers, facilitators and potential areas for improvement during the diagnostic process, and ultimately develop an integrated diagnostic pathway with the focus on patients' unmet needs and preferences. The proposed diagnostic pathway will be refined together with an advisory committee composed of members from the various institutions involved in the diagnostic process (CHL, LNS, UL, and ALAN Maladies Rares Luxembourg).

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BRIDGING-RD: STRENGTHENING RARE DISEASE RESEARCH THROUGH INTERNATIONAL COLLABORATION

ABSTRACT N° A007 / DIAGNOSING RARE DISEASES: FROM NBS TO MACHINE LEARNING

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Research into rare diseases (RD) is challenging for a number of reasons, primarily due to the limited number of affected individuals and the scarcity of data, knowledge, and expertise for any specific condition. Hence, to accelerate progress, collaboration between domain experts is essential. While Europe is at the forefront of RD research, significant disparities exist in genomic research and innovation capabilities between countries across the continent. The BRIDGING-RD project aims to close this gap for Serbia by fostering knowledge and expertise exchange between the Institute of Molecular Genetics and Genetic Engineering (IMGGE, Belgrade, Serbia), and three world-class counterparts, the National Center for Genomic Analysis (CNAG, Spain), the Karolinska Institute (Sweden), and the Autonomous University of Madrid (Spain).
Key objectives of BRIDGING-RD include:
(1) Enhancement of the IMGGE RD Biobank, including full integration of genetic and phenotypic data, in order to increase and strengthen participation in transnational research and innovation projects focussed on improving human health
(2) Optimising bioinformatics workflows used in RD analyses to increase diagnostic yield and case resolution in the IMGGE RD Biobank
(3) Advancing disease modelling and drug testing, by expanding capabilities for modelling of metabolic diseases and testing small molecule drugs to accelerate translational research
BRIDGING-RD will achieve these goals through a variety of initiatives, including exchange visits, expert training sessions, workshops, and annual joint summer schools showcasing and disseminating what has been learned throughout the 3-year duration of the project. Furthermore an exploratory research initiative, involving the engagement of all partners, will aim to identify and initiate development of a novel pharmacological chaperone therapy for a selected metabolic RD.
Through these international collaboration and capacity-building efforts, BRIDGING-RD will strengthen Serbia's role in rare disease research, ultimately improving diagnostics and advancing new therapeutic options for patients.

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ILIAD: THE ERN ITHACA FEDERATED REGISTRY

ABSTRACT N° B001 / EMPOWERING DATA

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Objectives: In 2017, following the EU directive on the application of patient's rights in cross-border healthcare, the European Commission established the European Reference Networks (ERNs). These are pan-European healthcare providers networks that specialize in a set of rare diseases, with the objective of pooling together clinical expertise, knowledge and resources available on rare and complex diseases. ERN ITHACA is the reference network for rare malformative conditions, intellectual disabilities and neurodevelopmental disorders. ERN ITHACA has developed a "meta-registry" called ILIAD, connecting 71 HCPs, databases, and biobanks across the EU for patients with dysmorphic/multiple congenital anomalies 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.

Methods: The registry is built on MOLGENIS open-source software, providing flexible rich data structures, user friendly data import and querying, and FAIR interfaces for programmatic data exchange. ILIAD consists of 2 components: a central, web-based registry and a network of linked satellite/client registries forming the ERN ITHACA registry federation. To date, two client installations have been successful and at least six more are ongoing. Data is modelled adhering to international interoperability standards from JRC and EJP-RD.

Results: In addition to the core registry, ILIAD includes thematic sub-registries of patients with biologically proven monogenic or genomic (chromosomal) diagnoses, under the supervision of ERN-based curation teams. ILIAD has adopted a data access policy, for requesting access to the data and the governance of the registry is in place to ensure compliance with applicable legal and regulatory requirements on the use of Personal Data.

Conclusion: We are well underway to share ERN ITHACA patient data, yielding high-quality epidemiological insights and expert consensus statements, informing policy decisions that impact rare disease patients in general and care for ERN ITHACA patients in particular.

Grants: ERN ITHACA has been funded by the European Union, under the grant agreement number 101156387.

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A DATA PLATFORM FOR CHINESE PEDIATRIC RARE DISEASES BASED ON LARGE LANGUAGE MODELS

ABSTRACT N° B002 / EMPOWERING DATA

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Background and Objectives
Pediatric rare diseases are challenging due to low incidence, difficulty in early diagnosis, and poor follow-up compliance. These factors hinder the establishment of high-quality, long-term, large-sample cohorts. This study aims to develop a rare disease data platform for Chinese children, using large language models and artificial intelligence technologies.

Methods
We selected two types of hospitals in China: pediatric specialty hospitals and large general hospitals, to build a rare disease data platform. Specific rare diseases were chosen at pediatric hospitals, while all rare diseases listed in the national catalog were included at general hospitals. Using this platform data, we analyzed pediatric rare disease visit trends and patient proportions over the past 20 years, integrating large language models to assess their effectiveness in assisting diagnosis and research.

Results
The pediatric rare disease platform has distinct features compared to adult and common disease platforms: (1) multidimensional and interdisciplinary data collection, (2) intelligent long-term tracking of pediatric patients, and (3) AI-assisted diagnosis. Approximately 100,000 patient records were collected, with pediatric rare diseases making up 0.0009% of the total. Outpatient visits were much higher than inpatient visits, with outpatient visits 11.4 times higher than inpatient visits, and outpatient patients 4.8 times more numerous. Most rare disease diagnoses in pediatric patients were not listed as primary diagnoses. If only primary diagnoses were considered, inpatient visits would drop by 46.7%, and outpatient visits by 79.5%. In the pediatric specialty hospital, 50 children with mucopolysaccharidosis (MPS) were analyzed, and a large language model based pre-diagnosis analysis predicted disease likelihood with 90% accuracy.

Conclusions
Research on pediatric rare diseases faces key challenges: unclear etiology, diagnostic difficulties, lack of effective treatments, and management issues. The pediatric rare disease platform developed in this study provides tools for big data analysis, ensuring long-term data collection and maintenance. The platform also integrates AI models, significantly advancing research and treatment strategies for pediatric rare diseases, improving diagnosis, treatment, and health management for pediatric patients.

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COMPREHENSIVE ANALYSIS OF LONGITUDINAL SV95C MEASUREMENT, AN E-DIGITAL MOBILITY ASSESSMENT IN REAL-LIFE AMBULANT DMD POPULATION IN GNT-014-MDYF NATURAL HISTORY STUDY

ABSTRACT N° B003 / EMPOWERING DATA

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Duchenne Muscular Dystrophy (DMD) is a rare neuromuscular disease with significant clinical heterogeneity. Hospital based physiotherapist-assisted functional assessments such as the North Star Ambulatory Assessment (NSAA), the Six Minute Walk Test (6MWT) and the Timed Function Tests (TFTs) are commonly used for monitoring in clinical and research settings. Stride Velocity at the 95th Centile (SV95C) captures daily ability using a wearable device in a real-life setting and therefore relies less on patient collaboration with assessment (e.g., young patients) or inter-evaluator variability. It was qualified by the European Medicines Agency (EMA) as a primary endpoint in ambulant DMD. This analysis aims to explore the validity and normative data of SV95C in a natural history (NH) study.

DMD boys aged 5-9 years, receiving steroid and achieving a NSAA ≥18 were enrolled in a prospective NH study (GNT-014-MDYF). The SV95C (from a record period of 30 days) and other clinical functional outcomes (NSAA, TFTs and 6MWT) are measured every 6 months. This analysis included data from 77 patients. Data were described for age subgroups (5-8Y and >8Y). SV95C accuracy was analysed and compared to age-matched healthy (N=66) and DMD population (n=107) in EMA SV95C Qualification Dossier. Reliability was assessed by intra-class correlation coefficient (ICC) with SV95C separated by 2 half recording periods. Spearman's correlation was used to evaluate the consistency between different outcomes. Over 2 years, SV95C was highly reliable (ICC ranged 0.96 to 0.98). The mean of SV95C in DMD patients was clearly separated from the healthy control, and comparable with the published data. At 1-year, mean changes in SV95C were -0.068 m/s and -0.193 m/s for 5-8Y and >8Y in GNT-014-MDYF patients (vs -0.263 and -0.226 m/s in respective age group of DMD patients in the EMA Dossier). Numerically lower mean changes in GNT-014-MDYF population could be explained by the difference of baseline function status and the age distribution.

Good correlations were observed between the SV95C and other physiotherapist-assisted outcomes (Correlation coefficient from 0.56 to 0.83). This analysis demonstrated the validity of SV95C in a NH study with standardized follow-up, and its consistency with published data. SV95C was sensitive to detect clinical change and correlated well with other clinical measurements, supporting its application in the development of treatment for this rare disease.

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LEVERAGE DATA TO IMPROVE ACCESS TO ESSENTIAL MEDICINES FOR RARE DISEASES

ABSTRACT N° B004 / EMPOWERING DATA

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Introduction: Access to medicines is a fundamental component of achieving Universal Health Coverage for Persons Living With a Rare Disease. The World Health Organization Model List of Essential Medicines (EML) stands as a fundamental tool in facilitating access to safe, effective, medicines globally, and for national public health planning. Rare Diseases International (RDI) has set up a dedicated Working Group with the objective to analyze relevant successful and failed rare disease medicine applications to the EML, identifying pitfalls and lessons, and to advocate for appropriate assessment of essential rare disease medicines.

Methods: The RDI Essential Medicines Working Group was set up via an open call of expression which welcomed patient representatives from RDI member organizations and members of RDI members. The Working Group is composed of RDI Secretariat and 12 representatives from eight countries located in four continents. The Working Group mapped a list of stakeholders who had made applications or used the EML for rare diseases, using the electronic EML and community contacts as sources of information. A long list of more than 40 potential stakeholders to interview was gathered, encompassing patient organizations, academia, non-profit organisations and pharmaceutical manufacturers. Prioritization was applied to the list for conducting semi-structured interviews. An interview guide was designed to capture the experiences of stakeholders.

Results: Preliminary analysis of the interviews identified common challenges related to the nature of rare disease and availability of data. The challenges were categorized and organized into three macro-areas: application preparation process, challenges encountered, and EML impact and value. Significant amount of data is required to build a successful EML application: including evidence from clinical trials and long-term studies, comparative effectiveness to existing standard of care, regulatory, and cost-effectiveness or Health Technology Assessment studies. It is important to include data from various regions of the world to provide a thorough global perspective. A factsheet was developed and publicly released to facilitate the understanding of the EML and its relevance for rare diseases.

In the next phase, will compile the lessons learnt and develop recommendations as a basis to build capacity about the utility of EML and discussions with WHO regarding gaps in the EML for rare diseases.

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APPLYING GENETIC DATABASE ANALYSIS TO ESTIMATE THE PREVALENCE OF LATE-ONSET FABRY DISEASE

ABSTRACT N° B005 / EMPOWERING DATA

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Objective Fabry disease is a rare X-linked lysosomal storage condition caused by pathogenic alleles in the GLA gene. As with many rare diseases, Fabry prevalence estimates vary widely, from 1 in 170,000 based on reported clinical cases, to 1 in 1,250 from newborn screening studies. Such widely varying estimates present major challenges for companies developing therapies. This study applied genetic database analysis to estimate the prevalence of Fabry disease in the US in 2024 by analysing selected GLA variants associated with late-onset Fabry disease, projecting the allele frequencies to the US population, and applying penetrance data to determine the number of symptomatic carriers.

Methods The study included 8 causal variants for prevalence analysis: rs28935197, rs797044776, rs869312163, rs372966991, rs104894828, rs727503950, rs869312389 and rs797044749. Allele frequencies were obtained from gnomAD v4.1. The size and demography of the US population in 2024 were obtained from the US Census Bureau. gnomAD v4.1 ancestry groups were mapped to US Census groups. Carrier counts by sex and ethnic group were calculated by projecting the summed allele frequencies calculated to the US population using the Hardy-Weinberg equation and considering the X-linked mode of inheritance.

Results Pathogenic alleles are found in the gnomAD v4.1 sample for all variants in the non-Finnish European ancestry group, for 2 variants in the South Asian ancestry group, and for 1 variant in the African/African American and East Asian ancestry groups. The highest pathogenic allele carrier frequencies were in the European (non-Finnish) ancestry group, followed by the South Asian, East Asian and African/African American ancestry groups. Using reported penetrance figures of 100% for males and 70% for females, the carrier and symptomatic populations of Fabry disease in the US in 2024 based on the 8 variants analysed are: 24,845 female carriers, of whom 17,392 will develop symptoms, and 12,024 male carriers, all of whom will develop symptoms.

Conclusion Analysing just 8 of the 100s of potential causal variants within the GLA gene, this study suggests Fabry disease may be over 3 times as prevalent as current estimates suggest. This work highlights the potential of genetic databases to study rare genetic diseases. To our knowledge, this is the first study to estimate the number of causal Fabry disease carriers and the symptomatic population in the US using data from gnomAD v4.1.

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DM1-HUB: BUILDING A NATIONAL HUB FOR MYOTONIC DYSTROPHY TYPE 1 IN SPAIN

ABSTRACT N° B006 / EMPOWERING DATA

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The DM1-Hub project aims to create a national network in Spain that will provide insights into the natural history of patients with Myotonic Dystrophy Type 1 (DM1) and define genomic and proteomic markers or characteristics for the development of precision medicine protocols.

DM1 is a rare neuromuscular disease of genetic origin, with a global prevalence of 1:10,000 (1:4000 in some Spanish regions), and highly heterogeneous clinical manifestations. It can debut at any stage of life and affects multiple organs, leading to a significant reduction in both quality and length of life for patients. DM1 is the most prevalent myopathy in adults and children, and currently, only palliative treatments are available to mitigate some of its symptoms. No curative or disease-modifying drug has yet been approved, although several candidates are in advanced evaluation stages. This highlights the fact that there are still major challenges to address in DM1. Healthcare professionals currently lack tools to help them determine which patients will experience greater clinical severity, who is at higher risk of complications in specific organs or systems, or whether it is possible to optimize patient selection for clinical trials. For the first time in Spain, DM1-Hub will integrate a network of 80 professionals who will actively collect prospective lifestyle and clinical data, including—novel to this approach—neuropsychological data, from a cohort of 3,000 DM1 patients. Additionally, blood samples will be obtained to conduct a large-scale (epi)genomic study using third-generation sequencing and proteomic studies through mass spectrometry. By conducting a comprehensive analysis of all these data, we aim to address the challenges previously mentioned, including the identification of new therapeutic targets—another key aspect to be investigated in this pathology. The DM1-Hub project aspires to be the cornerstone for a substantial transformation in the healthcare protocols for monitoring these patients, ultimately improving their quality of life and/or life expectancy. At the same time, DM1-Hub will promote intensive communication efforts, emphasizing the importance of early diagnosis, clinical follow-up, and patient registry participation. This outreach will target the general public, healthcare professionals, and patient associations through press releases, personal communications, as well as talks or interviews in the media.

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DEVELOPMENT OF PRECISION GENE ENGINEERED B CELLS AS A TREATMENT FOR HEMOPHILIA B

ABSTRACT N° C001 / ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

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Despite advances in treatment options for hemophilia B, significant unmet needs remain, notably disease and treatment burden. Terminally differentiated human plasma cells derived from genetically engineered B cells (B Cell Medicines, BCMs), offer decade long natural longevity, capacity for high levels of protein secretion, ability to engraft without preconditioning, and are re-dosable, thus making them an attractive platform to provide durable protein replacement therapy in both adults and children. BE-101 is an investigational autologous B cell-derived ex vivo gene edited cell therapy comprised of expanded and differentiated B lymphocyte lineage cells that have been genetically engineered to express and secrete FIX. BE-101 is in development as a potential treatment for hemophilia B. In this study, primary human B cells were isolated, activated, and engineered by CRISPR/Cas9 genome editing followed by AAV-mediated homology directed repair insertion of human F9 gene (Padua variant) into the C-C chemokine receptor type 5 safe harbor locus. The cells were then expanded and differentiated towards the plasma cell lineage, resulting in FIX-producing BCMs. Vitamin K-dependent activated partial thromboplastin time using the one stage clotting and immunocapture chromogenic assays were employed to verify biological activity of BCM-produced FIX. FIX-expressing BCMs were transferred into immunodeficient NOG-hIL6 mice, with FIX production demonstrated in vivo across multiple different lots of BE-101. A single intravenous dose of BE-101 resulted in sustained hFIX levels in plasma over the course of the 28-week study. Biodistribution studies using a human Alu gene family qPCR assay confirmed rapid and sustained bone marrow engraftment with clearance from non-target/homing tissues. A robust nonclinical program of studies has confirmed BE-101's mechanism of action and demonstrated a favorable safety profile, with no BE-101 related safety findings across any of the in vivo studies. Furthermore, a second dose of BE-101 at 7 weeks post-infusion resulted in an additive increase in FIX levels, demonstrating potential for re-dosability. In summary, we have developed an ex vivo precision gene engineered BCM, BE-101, that produces durable levels of active FIX in vivo. IND application and CTA of BE-101 were cleared by the US FDA and Health Canada, respectively. The initial clinical trial, the BeCoMe-9 Study, is now recruiting participants at multiple centers in US (NCT06611436)

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A FUNCTIONALISED NANO-INK FOR CONTROLLED GENE KNOCKDOWN IN FGFR2-RELATED SYNDROMES

ABSTRACT N° C002 / ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

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Hydrogels are highly hydrated 3D mesh networks exploited for time- and space-controlled drug delivery in diseased tissues and cells. In this study we have developed a moldable nanoparticle-laden hydrogel for in situ delivery of small interfering RNAs (siRNA) targeting the mutant FGFR2 allele, hence reducing the abnormal osteogenic cascade leading to early suture ossification in craniosynostosis syndromes (i.e. Crouzon, Apert, Pfeiffer, etc).
Based on our previous research recently published, we designed small interfering RNAs (siRNA) able to interfere selectively with the mRNA transcribed from the mutant FGFR2 allele in 6 non-related patients. We produced PLGA nanoparticles and characterized them via dynamic light scattering and scanning electron microscopy. Their biocompatibility was assessed through cell viability assays. The intracellular trafficking of fluorescently-labeled NPs was examined through live imaging and confocal microscopy. The knockdown efficacy of siRNA-NP complexes was studied in vitro using qPCR and western blotting. Finally, fluorescently-labeled PLGA NPs were 3D-printed within a hydrogel scaffold, and the scaffold's efficacy was evaluated in vitro using patients' cells. The designed therapeutic siRNA mitigated FGFR2 cascade downregulating phosphorylation of FGFR2 (48%) and of its key effector ERK1/2 (77%) as RUNX2 protein levels (34%) in patient-derived cells. NP biocompatibility was confirmed in CMSCs. Intracellular trafficking showed that NPs are distributed in cell's cytoplasm and escape lysosomal degradation. Live-cell microscopy demonstrated sustained intracellular release of PLGA NPs from the hydrogel in CMSC culture.
Our findings indicate that PLGA nanoparticles are suitable for drug delivery in CMSCs, and hydrogel-PLGA-NPs bioink allows controlled release of NPs to surrounding cells. This approach holds promise for in situ delivery of therapeutic molecules in an extended number or diseases caused by gain-of-function pathogenic variants and requiring ATMP to be implemented in tissue engineering.

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GNT0004, GENETHON'S AAV8 VECTOR-DELIVERED MICRODYSTROPHIN GENE THERAPY FOR DUCHENNE MUSCULAR DYSTROPHY: DOSE ESCALATION AND PRELIMINARY LONG-TERM FOLLOW-UP DATA OF GNT-016-MDYF ALL-IN-ONE CLINICAL TRIAL IN AMBULANT BOYS

ABSTRACT N° C003 / ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

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Duchenne Muscular Dystrophy (DMD) is a rare, X-linked disease caused by mutations in the dystrophin gene that results in muscle degeneration and early death.
GNT0004 is a recombinant serotype 8 adeno-associated virus (AAV8) vector gene therapy containing a shortened but functional dystrophin gene (hMD1). Driven by the Spc5.12 promoter, hMD1 transgene targets skeletal and cardiac muscles.
The pharmacodynamic (PD), safety, and efficacy of GNT0004 are being evaluated in the clinical trial GNT-016-MDYF. This all-in-one Phase 1/2/3 international trial combines: a first-in-human dose escalation (Part 1), a quadruple-blind, placebo-controlled, pivotal Phase 3(Part 2). Patients enrolled in Parts 1 and 2 will roll-over to long-term follow-up (Part 3).
Ambulant DMD boys aged 6 to 10 years, with a stable or early declining North Star Ambulatory Assessment (NSAA) score, on stable steroid treatment, without neutralising antibodies to AAV8 and being followed for ≥ 6 months in a natural history (NH) study were included. hMD1 expression was measured by muscle biopsy before and 8 weeks after GNT0004 dosing.
Data from Part 1 with long-term follow-up of these patients were summarized descriptively. Comparisons with an external control from the NH study were performed.
A total of 5 patients were enrolled in Part 1, two at dose 1 (1x1013vg/kg) and three at dose 2 (3x1013vg/kg). As of cut-off, total follow-up was 10.5 patient years. After dosing, the mean number of hMD1-positive fibres were 1.96% at dose 1 and 53% at Dose 2. The mean Vector Copy Number per nuclei (VCN) were 0.2 at dose 1 and 1.2 at dose 2. Serum creatine kinase (CK) significantly decreased after dosing which sustained over long term (- 50% to - 90% at dose 2). With dose 2, clinical functional parameters were stable or improved. The change from baseline at one year was clearly separated from the natural trajectory in favour of GNT0004 treated patients, consistent through efficacy parameters (e.g., delta of 4.7 points on NSAA and 0.1 m/s on SV95C). Administration of GNT0004 was well tolerated with few manageable adverse events.
GNT0004 at dose 2 provided efficient transgene transduction in skeletal muscle. hMD1 expression appeared to be significant and correctly localised. The early and sustained decrease in CK suggests sarcolemma stabilisation with evidence of clinical benefit. GNT0004 administration was safe and well tolerated. Dose 2 (3x1013vg/kg) was selected to proceed to pivotal phase 3.
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CRISPR/CAS9-BASED PRECISION B CELL GENE ENGINEERING PRODUCES ACTIVE TISSUE NONSPECIFIC ALKALINE PHOSPHATASE FOR THE POTENTIAL TREATMENT OF HYPOPHOSPHATASIA

ABSTRACT N° C004 / ATMPS: CHALLENGES AND OPPORTUNITIES OF TODAY

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Hypophosphatasia (HPP) is an inherited disorder characterized by defective bone mineralization, caused by deficiency of tissue nonspecific alkaline phosphatase (ALP). ALP is a dimeric zinc-containing metalloenzyme which hydrolyses inorganic pyrophosphate (PPi) and a variety of organic phosphates. Lack of functional ALP leads to elevated levels of PPi, which in turn inhibits bone mineralization, leading to osteomalacia/rickets (soft bones) and can be lethal without treatment. Currently, the only treatment for HPP is enzyme replacement therapy (ERT), asfotase alfa, requiring subcutaneous injections 3 to 6 times per week which is accompanied by injection site reactions including lipodystrophy. Terminally differentiated human plasma cells derived from genetically engineered B cells (B Cell Medicines, BCMs), offer decade long natural longevity, capacity for high levels of protein secretion, ability to engraft without preconditioning, and are re-dosable, making them an attractive platform to provide durable therapeutic proteins in adults, as well as children. We sought to harness the power of BCMs by engineering B cells to produce active ALP protein for HPP. In this study, primary human B cells were isolated, activated, and precision engineered by CRISPR/Cas9 genome editing followed by AAV-mediated homology directed repair insertion of human ALPL gene into various loci, including CCR5 (a safe harbor locus) and JCHAIN (a gene highly expressed in plasma cells). The cells were then further expanded and differentiated towards the plasma cell lineage, resulting in ALP-producing BCMs. Guided by an artificial intelligence-based protein structure design engine (i.e., AlphaFold2), ALP protein constructs were optimized for activity and stability by fusing ALP with different Fc fragmentscoupled via a variety of linkers. A pharmacokinetic study in the mouse model showed in vivo stability of AI designed ALP proteins comparable to the current approved ERT, asfotase alfa. Ex-vivo engineered BCMs secreted active ALP proteins up to 200 ng/1e6 cells/24hr as measured by Legendplex assay. BCM produced ALP (ALP-BCM) showed enhanced specific activity to asfotase alfa and can abolish PPi induced mineralization inhibition in an in vitro osteoblast cell-based model. In summary, we demonstrated successful production of active ALP from our novel BCM platform. The potential therapeutic application of this unique biologic delivery system could afford a new treatment modality for HPP.

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RARE DISEASE COORDINATION IN THE FRENCH PART OF SWITZERLAND

ABSTRACT N° D001 / IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES AND SOCIETY

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This poster presents the rare disease information platform that has been developed to facilitate the access to undiagnosed and/or specialized consultations in the French speaking part of Switzerland, as listed in the Orphanet knowledge database. This platform is a partnership between Geneva and Lausanne University Hospitals. The poster also presents the Rare Disease Center's activities and its collaboration with the national coordination (kosek) in order to implement specialized reference centers and improve interdisciplinary care pathways for patients.

Useful links: https://www.kosekschweiz.ch/fr/kosek

https://orphanet.site/switzerland

https://www.chuv.ch/fr/medecine-genetique/gen-home/patients-et-familles/nos-consultations/centre-maladies-rares

https://www.hug.ch/medecine-genetique/maladies-rares

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PATIENT-CENTRIC INNOVATIONS IN THE RARE DISEASES REGULATORY DECISION-MAKING

ABSTRACT N° D002 / IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES AND SOCIETY

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The INVENTS project aims to advance the development of medicines in rare and paediatric diseases by introducing regulatory-compliant innovative clinical trial methodologies. A key element of this initiative focuses on integrating ethical and regulatory provisions as well as patients' needs and experiences, to ensure that they can join the development of the research and decision-making processes around the care that concerns them. This approach acknowledges the value of patient experiences in shaping effective and equitable healthcare solutions.

The patient-centered efforts in INVENTS aim to design and implement structured tools and guidelines that incorporate patient-reported experiences into regulatory frameworks, including those for marketing authorization and health technology assessment of rare disease treatments. Central to this initiative was the establishment of adult and paediatric Patient Expert Groups (PEGs), which combined multidisciplinary expertise to train and empower patients on topics such as modern clinical trial designs, real-world data applications and in-silico trials.

The PEG will contribute to the design and validation of a decision tool, to identify and standardize the integration of patients' preferences. Key steps include reviewing existing tools and criteria used for assessing patient perspectives in regulatory processes; engaging the PEG, their caregivers, and relevant stakeholders through structured discussions to identify unmet needs and priorities; and co-constructing a tool that incorporates patient preferences while addressing heterogeneity in diseases and treatment outcomes.

Ethical considerations are implemented to ensure that patient engagement aligns with their rights, legal and societal expectations.

The developed tool(s) will be tested across INVENTS rare diseases use cases including juvenile idiopathic arthritis and paediatric multiple sclerosis, leveraging on the re-use of clinical trials data of major drugs developed for these two rare conditions, and the combination with in-silico approaches developed by INVENTS.

This approach bridges technical advancements with the lived experience of patients, fostering collaboration and trust. It integrates patient experiences into the co-construction of rare disease research and regulatory landscapes, ensuring alignment with ethical principles and practical needs.

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BURDEN OF ILLNESS AND UNMET NEED AMONG PATIENTS WITH CIDP: RESULTS FROM A REAL-WORLD SURVEY

ABSTRACT N° D003 / IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES AND SOCIETY

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Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated neurological condition marked by distal/proximal weakness. Evidence on the burden of illness and unmet need among CIDP patients remains limited.

Objective: To gain insights from physicians and patients on CIDP's clinical burden, societal impact, treatment burden, and unmet needs.
Methods: A secondary analysis was conducted using data from the Adelphi Real World CIDP Disease Specific Program, a cross-sectional survey of neurologists and their CIDP patients in France, Germany, Italy, Spain, and the UK (Sep 2022-Apr 2023). Neurologists (N=83) completed electronic record forms for 542 patients. Of these, 199 completed outcome measures and reported data on burden of illness.
Results: Based on physician-reported data, mean time from symptom onset to first consultation was 7.4 months, and from first consultation to CIDP diagnosis was 6.5 months. Over one-third of patients were initially misdiagnosed, most frequently with Guillain-Barré syndrome (37%), fibromyalgia (13%), and diabetic polyneuropathy (11%). Most used maintenance treatments were intravenous immunoglobulin (IVIg, 47%) and corticosteroids (45%), rituximab (11%), and subcutaneous immunoglobulin (SCIg, 8%). Despite treatment, over half of patients experienced moderate-severe symptoms, including peripheral numbness (68%), distal muscle weakness (65%), and peripheral tingling (64%).
Mobility aids were needed by 47% of patients, while 27% required support from a caregiver, with 41% of caregivers changing their working status due to caregiving. Depression and anxiety occurred in 9-24% of the patients, increasing with symptom severity.
Half of all patients (46%) were employed full-time, 42% were not (12% part-time, 30% unemployed/retired/long-term sick leave). Of those not working full-time, 53% cited CIDP as the reason. Among employed patients, 32% reported absenteeism within the last 7 days due to CIDP (mean 1.8 hours).
Mean EQ-5D-5L utility values were lower in CIDP patients (0.63) than in the general UK population (0.86). Physicians were more often very satisfied with treatment outcomes than patients (51% vs. 12%) and reported less often poor symptoms control (29% vs. 34%).
Conclusion: CIDP imposes a substantial burden, affecting patients' daily lives, work, and health-related quality of life. Discrepancies in treatment satisfaction between physicians and patients highlight unmet needs.

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

ABSTRACT N° D004 / IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES AND SOCIETY

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European Reference Networks for rare diseases and complex conditions (ERNs) have been established in 2017 following the European Directive on the application of patients' rights in cross-border healthcare. Their establishment has been deemed by the rare disease global and European stakeholders as an unprecedented move in improving the healthcare management of patients suffering from rare diseases. The ERN-ITHACA brings together specifically experts in rare multiple congenital anomalies and rare neurodevelopmental disorders (NDD), the latter field mainly covering intellectual disability (ID) and autism spectrum disorder (ASD). ITHACA's field of expertise covers the clinical and biological/genetic diagnosis of these developmental anomalies, the coordination of their multidisciplinary care and their treatment, and also their prenatal diagnosis and fetal pathology. The name ITHACA stands for Intellectual disability, TeleHealth, Autism and Congenital Anomalies. It also echoes the diagnostic odyssey experienced by so many patients with developmental anomalies. Led by Prof. Alain VERLOES at APHP-Robert DEBRE University Hospital since March 2019, the network today consists in more than 70 Clinical Genetics Departments, coming from 25 Member States, as well as 47 European Patient Advocay Groups (ePAGs). By networking patient representatives, clinical experts and researchers, we aim to improve early diagnosis, care and cure of patients with rare developmental anomalies. Here are some of the projects we've completed or are currently working on with our members: producing clinical guidelines and consensus statements on rare developmental disorders (such as the Phelan McDermid, Rubinstein-Taybi, Cornelia de Lange syndromes, polyhandicap, and more); developing a "meta" patient-registry called ILIAD, connecting 37 HCPs, databases, and biobanks in 13 countries for patients with dysmorphic/MCA syndromes and/or ID, in order to provide an infrastructure for diagnosis, highly specialised multidisciplinary healthcare, and collection of secure patient data; supporting the development of telemedicine tools to allow collegial discussion of complex situations between referring doctors and RD experts who are scattered in the EU, like the CPMS (Clinical Patient Management System); producing e-learning tools dedicated to health professionals or lay persons; organising webinars, conferences and workshops at the European level for experts and/or patients representatives.

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ERN ITHACA WEBINARS: ADVANCING KNOWLEDGE AND COLLABORATION IN RARE MALFORMATIVE AND NEURODEVELOPMENTAL DISORDERS

ABSTRACT N° D005 / IMPACTS OF RARE DISEASES ON PATIENTS, FAMILIES AND SOCIETY

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Background and Objectives: The Teaching & Training Workgroup of ERN ITHACA has initiated a webinar programme with the aim of providing highly specialised knowledge on rare congenital malformations and neurodevelopmental disorders. The programme is aimed at healthcare professionals, patients and their families and covers topics such as fetal surgery, newborn screening, care of older patients and guideline methodology. The webinars are also made relevant and inclusive through input from the ITHACA Patient Advisory Board. ERN ITHACA currently links 71 expert clinical centres and over 49 European Patient Advocacy Groups (EPAGs) in 26 countries. Its mission is to improve patient care, research and access to information through collaboration, and the webinar programme exemplifies this mission by facilitating knowledge sharing and engagement without travel, promoting inclusivity and convenience.

Methods: Each webinar, hosted on Microsoft Teams, includes a one-hour presentation by an expert, followed by a question-and-answer session for interaction between participants and presenters. Approximately ten webinars are held each year, with topics suggested by ERN ITHACA experts and stakeholders, including patient representatives. Collaboration with entities such as the European Society of Paediatric Neurology (EPNS); Young Geneticists Committee (ESHG-Y) and other ERNs to ensure diverse perspectives and produce joint webinars. Sessions are recorded and made available on the ITHACA website for wide access. Impact is measured through upstream and downstream surveys, which are regularly analysed. Within the network, each HCP is committed to producing at least one webinar during the grant period.

Outcomes and impact: The programme has successfully delivered webinars on topics such as ageing with intellectual disability, innovation in newborn screening and integrated care for rare diseases, fostering cross-border collaboration, improving patient advocacy and providing professional development opportunities. The programme includes tailored sessions, from open-access webinars for the public to technical sessions for professionals, to increase accessibility and impact. This programme demonstrates how virtual education can bridge knowledge and collaboration gaps across Europe, integrating patient voices and leveraging technology.

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THE GROWING GAP IN ORPHAN DRUG APPROVALS BETWEEN THE US FOOD AND DRUG ADMINISTRATION AND EUROPEAN MEDICINES AGENCY: RETROSPECTIVE COHORT STUDY 2011-2020

ABSTRACT N° E001 / FUNDING MODELS

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In this retrospective cohort study spanning the decade from 2011 to 2020, we aim to shed light on the substantial and growing disparity in orphan drug approvals between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Our analysis is grounded in an extensive collection of data on FDA orphan drug approvals, compared with EMA.

Results indicate a notable and widening gap between the FDA and EMA since 2011. Within the specified period, the FDA granted orphan designation approvals to a total of 569 drugs. Notably, only 27% of these received the orphan designation and marketing authorisation from the EMA. Additionally, 35% secured approval from the EMA without being designated as orphan products, while 38% didn't gain approval from the EMA.

This divergence is attributed in part to the surge in FDA approvals for neoplastic diseases. Large companies demonstrated a propensity to introduce their products into European markets without the orphan designations. US small companies faced a particularly challenging situation, with two-thirds of their FDA orphan drug approvals not approved by the EMA, while EU small companies experienced a 50% non-approval rate.

Considering the exorbitant pricing associated with orphan drugs, our analysis raises pertinent inquiries regarding the rationale behind the FDA's prolific grant of approvals compared to its European counterpart. This incongruity prompts a critical evaluation of how European consumers are impacted, positively or otherwise, by the absence of many of these orphan drugs within the EU market. In summary, this study underscores the pressing need to address the growing gap in orphan drug approvals between the FDA and EMA. It is imperative to explore the underlying factors and implications of this divergence, as it holds significant consequences for patients, healthcare systems, and pharmaceutical stakeholders on both sides of the Atlantic.

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IDENTIFYING KEY THERAPEUTIC TARGETS IN FACIOSCAPULOHUMERAL DYSTROPHY TO INFORM THE SELECTION OF INNOVATIVE THERAPIES

ABSTRACT N° F001 / DRUG REPURPOSING IN RARE DISEASES

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Facioscapulohumeral muscular dystrophy (FSHD) is a rare, progressive muscle disorder caused by the aberrant activation of the DUX4 gene, for which no approved therapy exists. Understanding the mechanisms of muscle degeneration in FSHD remains a significant challenge, as the extent of muscle impairment varies not only between patients but also across different muscles within the same individual, with the rate of disease progression being entirely unpredictable. Skeletal muscle integrity relies on the interplay of various cell types, and we hypothesize that disruptions in this network contribute to FSHD-associated degeneration. Muscle-resident non-myogenic mesenchymal cells play critical roles in tissue regeneration and have been identified as potential therapeutic targets in neuromuscular disorders, although their role in FSHD remains poorly characterized. In this context, our project aims to investigate altered mechanisms within these cells in FSHD patients to uncover degeneration processes and identify novel therapeutic targets, thereby guiding the development of new therapies.
Muscle specimens were obtained via needle biopsies following muscle MRI examination to identify both early-affected and apparently unaffected muscles in FSHD patients. Non-myogenic mesenchymal cells were isolated as the CD56- cell fraction. Cells from muscles of healthy volunteers were used as controls. Our findings showed that patient-derived cells exhibited heightened proliferation rates and altered differentiation capacities compared to control cells. During adipogenic and fibrogenic differentiation, these cells reactivated DUX4 target genes, a feature absent in control cells. Co-culture experiments further revealed that FSHD-derived non-myogenic mesenchymal cells differentially influenced the proliferation and differentiation of control myoblasts, underscoring their regulatory role in myogenesis. Finally, bulk RNA sequencing analysis revealed a unique gene expression profile in cells from FSHD-affected muscles, highlighting numerous pathways differentially modulated between cells from affected and unaffected muscles in FSHD patients and controls.
Together, these findings confirm that non-myogenic mesenchymal cells exhibit distinct regenerative properties between affected and seemingly spared muscles in FSHD patients, and that targeting specific pathways in these cells could guide the development of tailored or combined therapies.

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A NOVEL THERAPEUTIC APPROACH FOR BRODY MYOPATHY: A TRANSLATIONAL PERSPECTIVE IN RARE DISEASE RESEARCH

ABSTRACT N° F002 / DRUG REPURPOSING IN RARE DISEASES

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Brody myopathy is an ultra-rare autosomal recessive disorder that affects skeletal muscle function in humans. It results from a deficiency of the Sarco(Endo)plasmic Reticulum Ca^{2+} - ATPase isoform 1 (SERCA1) due to mutations, in the ATP2A1 gene. Currently, neither specific therapy nor a mouse model exists for Brody myopathy. Bovine pseudomyotonia (PMT) is a very-rare skeletal muscle disorder that, like Brody myopathy, is an autosomal recessive inherited condition, caused by missense variants in the atp2a1 gene. These mutations lead to misfolded but catalytically active SERCA1 proteins, which are subsequently ubiquitinated and prematurely degraded by the ubiquitin-proteasome system. Bovine PMT, despite unconventional, is currently the unique mammalian model of Brody disease. We have recently proposed a new pharmacological approach based on the repositioning strategy of Cystic Fibrosis Transmembrane Regulator (CFTR) correctors (EU 2925317 and US 9987256 B2 patents). These correctors have been extensively studied for the treatment of Cystic Fibrosis, a disease that shares with bovine PMT and consequently with Brody myopathy, a similar pathogenic mechanism.
Our research has demonstrated the efficacy of the C17 corrector in restoring the expression of mutated SERCA1 in both in vitro and in vivo models. To validate in vivo the efficacy of C17 CFTR corrector, the molecule was locally administered in superficially located muscles of PMT-affected calves. However, this approach has proved to have some limitations. To overcome these limitations, and in the absence of an ideal mouse model, in order to assess the efficacy and safety of our therapeutic approach, we adopted two strategies:
1) we used the commercially available SERCA1 natural mutant zebrafish Accordion and generated new zebrafish mutant lines introducing mutations in SERCA1 found in bovine PMT, by CRISPR/Cas9-mediated genome editing;
2) we developed cheap and easy-to-obtain 3D muscle models based on two different scaffolds, (de-cellularized extracellular matrix from bovine diaphragm and collagen-based scaffold derived from non-processed sea urchin food waste), both re-cellularized with primary myoblasts, to use in parallel with in vivo animal models.
Our objective is to translate the use of the CFTR C17 small molecule into a therapeutic solution for Brody patients with mutated SERCA1 retains its catalytic activity.

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ADVANCING PERSONALIZED MEDICINE IN HEREDITARY SPASTIC PARAPLEGIAS THROUGH MOLECULAR MODELING

ABSTRACT N° F003 / DRUG REPURPOSING IN RARE DISEASES

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Hereditary Spastic Paraplegias (HSPs) are rare, genetically heterogeneous disorders linked to over 80 genes. As medicinal chemists, we focus on small organic molecules that bind protein structures to modulate function. However, the vast variety of mutations makes traditional drug discovery unsustainable when relying solely on experimental methods. Given that many HSP-related proteins lack experimentally determined 3D structures, we believe state-of-the-art molecular modeling can aid in designing personalized therapies. We present three cases demonstrating how modeling mutant protein variants provides insights into pathogenic mechanisms and potential treatments.

The spastic paraplegia, intellectual disability, nystagmus, and obesity syndrome (SINO, OMIM#617296) results from heterozygous mutations in KIDINS220, encoding a membrane-associated scaffold protein. We compiled a dataset of known mutations and predicted their effects on protein stability, surface properties, and membrane interactions. Structural modeling helped rationalize pathogenic mechanisms and aggregation phenomena.

Spastic paraplegia 50 (SPG50, OMIM#612936) is an autosomal recessive HSP caused by mutations in AP4M1, which encodes a subunit of the AP-4 adaptor protein complex, involved in vesicular trafficking. Due to the lack of resolved 3D structures, we modeled the entire AP-4 core and analyzed patient mutations, ranking them by druggability. The R367Q variant was particularly destabilizing. Virtual screening identified the glycoside Rutin as a potential molecular glue stabilizing the complex.

Infantile-onset ascending hereditary spastic paralysis (IAHSP, OMIM#607225) arises from ALS2 mutations, affecting the protein Alsin. We modeled its active homotetrameric form to assess variant impact. Like SPG50, we identified a druggable mutation and, via virtual screening, found vitamin MK4—an approved drug—as a potential therapy. Patient-derived fibroblast models, omics analyses, and advanced microscopy confirmed its efficacy. Given its safety profile, MK4 was approved for compassionate use in Italy.

These cases illustrate the power of molecular modeling in HSP research: for SINO, it provided mechanistic insights; for SPG50, a mutation-specific therapy; and for IAHSP, an approved treatment. Our approach highlights how computational strategies can bridge gaps in personalized medicine for rare diseases.

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NOTES

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