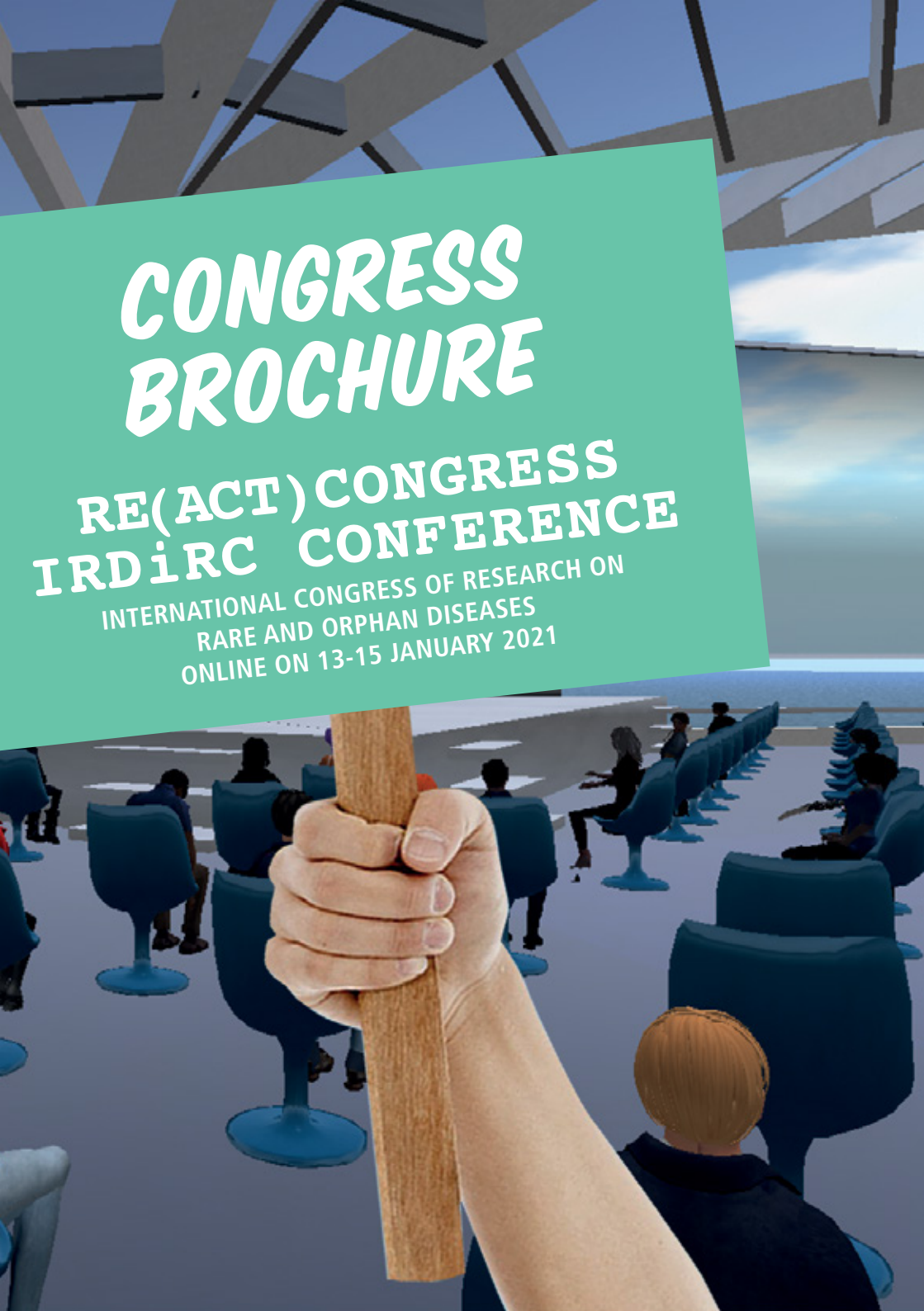

CONGRESS BROCHURE

RE(ACT)CONGRESS IRDiRC CONFERENCE

INTERNATIONAL CONGRESS OF RESEARCH ON RARE AND ORPHAN DISEASES
ONLINE ON 13-15 JANUARY 2021

RE(ACT) CONGRESS
IRDIRC CONFERENCE
INTERNATIONAL CONGRESS OF RESEARCH
ON RARE AND ORPHAN DISEASES
JANUARY 2021

STAND UP FOR SCIENTIFIC RESEARCH

#RAREVOLUTION
#REACTCONGRESS
#IRDiRC
#EJPRD

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WELCOME

Dear Colleagues,

Welcome to the online RE(ACT) Congress and IRDiRC Conference 2021, we are excited to host you for the first time at this joint event.

This joint event will continue the RE(ACT) Congress series (6th edition) and IRDiRC Conference series (4th edition). Over the next few days, a stimulating program awaits with a dedicated, global community of scientists and experts, and many opportunities to discuss progress in rare diseases research. The overall aim of the joint event is not only to bring together scientific leaders, experts, and young researchers with patients, but also to present and promote cutting- edge research on rare and orphan diseases among the general public, industry and policy makers – all with the ultimate goal of enhancing the rapid delivery of new and promising diagnostics and therapies to patients all around the world.

The RE(ACT) Congress – International Congress of Research on Rare and Orphan Diseases – was initiated in 2012 by the BLACKSWAN Foundation to create a forum for and promote scientific cooperation and research on rare and orphan diseases. IRDiRC – launched in April 2011 at the initiative of the European Commission and the US National Institutes of Health – fosters international collaboration on rare disease research by bringing together researchers, funders and patient advocacy organizations that work collaboratively within a multinational consortium.

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

Dr. Olivier Menzel
Chairman and founder
BLACKSWAN Foundation

Dr. Daria Julkowska
Coordinator
EJP RD

Dr. Lucia Monaco
Consortium Assembly Chair
IRDiRC

THE INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDIRC)

With the challenging vision to enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention, the International Rare Diseases Research Consortium (IRDiRC) unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organizations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide. Importantly, the coverage of the Consortium is global and involves stakeholders from Africa, Asia, Australia, North 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 three Scientific Committees (Diagnostics, Therapies and Interdisciplinary) composed of approximately 15 members with balanced expertise and geographical representation. All Committees work together 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. By means of dedicated Task Forces, IRDiRC has tackled specific topics within rare diseases research and proposed solutions through policy recommendations and technical applications. New activities in the 2020 Roadmap will address strategic topics relevant to the development of therapies for neglected rare diseases, to innovative diagnostic tools and to the promotion of access to medicines for all rare diseases patients.

irdirc.org
twitter.com/irdirc
#IRDiRC

THE EUROPEAN JOINT PROGRAMME ON RARE DISEASES (EJP RD)

The European Joint Programme on Rare Diseases (EJP RD), launched in January 2019, brings together the resources in rare diseases (RD) research at the national and European level. It assembles funders, universities, research organisations and infrastructures, hospitals, and patient organisations representing over 130 institutions across 35 countries. Jointly funded by the European Commission and Member States over five years, its purpose is to create a comprehensive and sustainable ecosystem for RD research. The two main objectives of EJP RD are to improve the integration, efficacy, production, and social impact of research on RDs, and secondly to implement an efficient model of financial support for all types of RDs research. In order to successfully achieve its goals, EJP RD is structured around 4 'pillars'. Pillar 1 focuses on the financial support through the implementation of transnational calls for research projects into RDs (including basic, translational, clinical, social and health economic research topics), and a networking support scheme to encourage sharing of knowledge on RDs. Pillar 2 aims to build a comprehensive, FAIR- compliant virtual platform pooling data and resources (e.g., registries, biobanks, databases, bioinformatics tools) that will be findable online and accessible to the whole RD community via a central access point. Pillar 3 aims at capacity building and patient empowerment through the provision of periodic training activities to the RD community. It will deliver an EU-wide education programme on transversal RD research fully available online to all interested stakeholders. Pillar 4 aims at accelerating the translation of research outputs by creating and continuously developing online self-help resources for benefit of any RD researcher involved in translational research. t will also implement the support for funded RD projects by identifying results that can be supported for further funding and development, thereby enhancing their chance of reaching clinical implementation. In its first year of existence, EJP RD already demonstrates how the centralised collaboration between different stakeholders advances RD research for the benefit of patients.

ejprarediseases.org
twitter.com/EJPRareDiseases
#EJPRD

BLACKSWAN FOUNDATION

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

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NOTES

KEY FACTS

Scientific advisory board (alphabetical order):
Stylianos Antonarakis, CH
Gareth Baynam, AUS
Jacques Beckmann, CH
Adam Hartman, USA
Virginie Hivert, FR
Daria Julkowska, FR
Stanislas Lyonnet, FR
Lucia Monaco, IT
Michael Morris, CH
David Pearce, USA
Alexandre Reymond, CH
Hamish S. Scott, AUS

Organizing committee (alphabetical order):
Thomas Amiconi, Amiconi Consulting SA, CH
Daria Julkowska, EJP RD, FR
Olivier Menzel, BLACKSWAN Foundation, CH
Lucia Monaco, IRDiRC, IT

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

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

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

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

NOTES

TIME TABLE

WEDNESDAY, JANUARY 13th

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Opening Ceremony, 13 to 15

Break 15 to 15:30

Session B, 15:30 to 17, "Rare Diseases Foresight: Panel discussion (EU/America/Asia/AU)"

THURSDAY, JANUARY 14th

Session C, 10 to 12, "Diagnostic, WGS, artificial intelligence, new technologies "

Lunch break 12 to 13

Session D, 13 to 15, "Molecular etiology of RD, innovative clinical trials, precision medicine"

Break 15 to 15:30

Session E, 15:30 to 17, "Advanced therapies: gene editing, cell therapy"

FRIDAY, JANUARY 15th

Session F, 10 to 12, "Patients as drivers in drug development and clinical trials"

Lunch break 12 to 13

Session G, 13 to 15, "Access to diagnostic and drugs for all"

Break 15 to 15:30

Session H, 15:30 to 17, "Methodologies to assess the effect of diagnosis and therapies on RD patients"

Closing Ceremony, 17 to 17:30

FULL PROGRAM

WEDNESDAY, JANUARY 13th

Session A**, 9 to 12 (break 10:30 to 11), "Presentation of the Galaxy Guide & Hands-on"**

- Virginie Hivert, FR – Eurordis
- Michela Gabaldo, IT – Fondazione Telethon
- Anneliene Jonker, NL – IRDiRC
- Diego Ardigò, IT – Chiesi

LUNCH BREAK 12 to 13

Opening Session 13 to 15 - Welcome messages

- Irene Norstedt – Director responsible for the Health Directorate within the Directorate General for Research and Innovation, European Commission
- Lucia Monaco – Chair, IRDiRC Consortium Assembly
- Daria Julkowska – Coordinator. European Joint Program Rare Disease
- Olivier Menzel – Chairman and founder BLACKSWAN Foundation, founder RE(ACT) Congress
- Keynote presentation: Alexandre Reymond, Director of the Center for Integrative Genomics and president of the executive board of the European Society of Human Genetics, CH "Genome architecture and diseases: the 16p11.2 paradigm"

BREAK 15 to 15:30

Session B, 15:30 to 17, "Rare Diseases Foresight: Panel discussion (EU/America/Asia/AU)"
Chairs: Lucia Monaco and David Pearce
- Yann Le Cam, FR – Eurordis
- Anne Pariser, USA – NCATS, NIH
- Matthew Bellgard, AUS "Vision of the Asia-Pacific Economic Cooperation (APEC) Rare Disease Network: Multilateral, Multi-stakeholder Rare Disease Policies & Plans"

THURSDAY, JANUARY 14th

Session C**,** 10 to 12, "Diagnostic, WGS, artificial intelligence, new technologies" Chairs: Jacqui Beckmann and Catherine Nguyen

- Short Film presented by Maja Bartoszewicz Moritz: Journey of hope
- Mark Caulfield, UK "The 100,000 Genomes Project Transforming Healthcare"
- Christoffer Nellåker, UK "Deep phenotyping from faces and the Minerva Initiative"
- Uzma Atif, USA "The Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease"
- Peter Krawitz, USA "Next-Generation Phenotyping Using DeepGestalt in Clinic, Research and Variant Analysis"
- Clara van Karnebeek, NL "Diagnostic -omics : what's new in 2021?"

Panel discussion: All speakers and patient representative (Virginie Bros-Facer – Eurordis and Maja Bartoszewicz Moritz)

LUNCH BREAK 12 to 13

Session D, 13 to 15, "Molecular etiology of RD, innovative clinical trials, precision medicine" Chairs: PJ Brooks and Lucia Monaco

- PJ Brooks, USA "Beyond "one disease at a time" so no disease is left behind: "Platform approaches to clinical trials in rare diseases"
- Anna Wedell, SE "Precision Diagnostics of Rare Diseases at the Genomic Medicine Center Karolinska"
- Terence Beghyn, FR "Individualized research program, sustainable approach through drug repurposing"
- Gisou van der Goot, CH "Hyaline Fibromatosis Syndrome: how the study of individual patient mutations drives the molecular understanding of the disease"
- Susan J Ward, USA "Learning from natural history patient data to drive smaller, faster, trials a case study in Duchenne Muscular Dystrophy (DMD)"

Panel discussion: All speakers and patient representative (Christian Rubio – Global Gene)

BREAK 15 to 15:30

Session E, 15:30 to 17, "Advanced therapies: gene editing, cell therapy" Chairs: Joseph Scheeren and Lucia Monaco

- Joseph Scheeren, USA Challenges and considerations in the regulation of gene and cell therapies"
- Alessandro Aiuti, IT "Hematopoietic stem cell gene therapy for monogenic diseases: from experimental studies to approved drugs"
- Hans-Dieter Volk, DE "Immunological challenges in gene and cell therapy"
- Nathalie Cartier-Lacave, FR "Gene therapy for Huntington's disease and spinocerebellar ataxias: from preclinical proofs of concept to first Phase 1 clinical trial"

Panel discussion: All speakers and patient representative (Oxana Illiach – CORD)

FRIDAY, JANUARY 15th

Session F, 10 to 12, "Patients as drivers in drug development and clinical trials" Chairs: Durhane Wong-Rieger, Sharon Terry and Samantha Parker

- François Houÿez, FR "Engaging Patients: The EuroCAB Programme"
- Dimitrios Athanasiou, GR " 25 years of Duchenne Patient Advocacy: Between Hype and Hope"
- Nick Sireau, UK "How patients can lead drug development: the case of the AKU Society"
- Nicola Bedlington, BE "Towards a sustainable patient engagement ecosystem"

Panel discussion: All speakers and patient representative (Sharon Terry – Genetic Alliance)

LUNCH BREAK 12 to 13

Session G, 13 to 15, "Access to diagnostic and drugs for all" Chairs: William Gahl and Durhane Wong-Rieger

- Susanne Weissbaecker, SG "Taking action for Rare Diseases. If we don't, who will?"
- Benjamin Djoudalbaye, ET "Access to diagnostic and drugs for all in the African context"
- Durhane Wong-Rieger, CAN "Access to Rare Disease Drugs in Emerging Health Systems: Pathway for Access to Diagnosis, Treatment, Care and Patient Empowerment"
- William Gahl, USA "Global Access to Rare Disease Diagnostics and Treatment"

Panel discussion: All speakers and patient representatives (Alba Ancochea-Diaz – ALIBER; Ramaiah Muthyala – I-ORD; Samuel Agyei Wiafe – Rare Diseases Ghana; Tanja Collin-Histed – International Gaucher Alliance; Eda Selebatso – BORDIS Botswana)

BREAK 15 to 15:30

Session H, 15:30 to 17, "Methodologies to assess the effect of diagnosis and therapies on RD patients" Chairs: David Pearce and Virginie Hivertw

- David Pearce, USA – Welcome & Introduction
- Daniel Ollendorf, USA "The Economics of Rare Disease: Value Assessment Challenges, Evidence Considerations, and Special-Case Status"
-Vicki Seyfert-Margolis, USA "Patient-centric digital technology to define disease progression and response to therapy: a model that also supports a de-centralized approach for clinical trials in rare diseases"

Panel discussion: All speakers and patient representatives (Dimitrios Athanasiou – World Duchenne Organization; Vanessa Boulanger – NORD)

Closing Ceremony**, 17 to 17:30**

SPEAKERS' BIOGRAPHIES

AIUTI ALESSANDRO

Alessandro Aiuti is M.D., specialized in Immunology, and Ph.D. in Molecular and Cell Biology. In 1998 he obtained the National Board in Hematology.
Heis Deputy Director, Clinical Research Coordinator, and Head of Unit on Pathogenesis and Therapy of PIDof the San Raffaele Telethon Institute for Gene Therapy in Milan; Director of the Pediatric Immunohematology Unit, San Raffaele Hospital, Milan; full Professor of Pediatrics and Director of the Residency Program of Pediatrics, Vita-Salute San Raffaele University in Milan, Italy.
He is author of more than 180 peer reviewed publications (total citations of 10812, h-index Scopus 48). Full list of publications is available at here.
He is board member of the ESGCT since 2012, member of the Inborn Errors Working Party (IEWP) Studies Committee of the European Society for Bone and Marrow Transplantation (EBMT) (since 2015), member of ASGCT Hematologic and Immunologic Gene and Cell Therapy Committee (since 2016), Co-Chair of the Stem Cell and Gene Therapy WP of European Reference Network (ERN) on Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network (RITA) (since 2017), member of IRDiRC Orphan Drug Development Guidebook (ODDG) Task Force (since September 2018), and member (representing clinicians) of the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) (as from July 1, 2019)
His main interests are hematology, immunology and pediatrics, particularly in the study of PID. His main domains of research are: HSC gene therapy for genetic diseases (PI of 5 clinical trials: ADA-SCID, WAS, beta thalassemia, MLD and MPS1), clonal dynamics of hematopoiesis, genetics and pathogenesis of primary immunodeficiencies. He has pioneered the EU market approval of the first ex vivo gene therapy for a genetic disease.

ARDIGÓ DIEGO

Dr. Ardigò is an MD with a specialization in Internal Medicine. He obtained his PhD at the University of Parma (Italy) and did a post-doctoral fellowship at Stanford University (California, US). Before joining the industry, he worked at the University of Parma (Italy) in the field of cardiovascular and metabolic genomics, and as free-lance consultant for various academic institutions. He joined Chiesi in 2010, where acted as Clinical Lead in the registration of the first stem cell therapy in EU and led the cross-company team (with uniQure BV) treating the first patient with a commercial gene therapy in EU. He is currently the Head of the R&D Rare Disease Unit in Chiesi. He is also serving as chairman of the Therapies Scientific Committee of IRDiRC (International Rare Diseases Research Consortium) and board member of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE). He is author of 50 indexed papers and speaker at international medical and industrial congresses.

ATHANASIOU DIMITRIOS

Dimitrios ATHANASIOUholds a BA in Business Administration and an MBA in Financial Management. He speaks three European languages and has more than 25 years' experience with international business projects, working in various countries in consulting, developing and

reorganizing companies. When his son was diagnosed with Duchenne Muscular Dystrophy, a fatal and incurable rare disease, he becomes a strong international patient advocate in Duchenne and Rare Diseases. Having a passionate personality and technocratic background, he educated himself with basic rare disease and advocacy knowledge via the EURORDIS Summer School and then with the 14 month Patient Expert Course of the European Patient Academy of Therapeutic Innovation (EUPATI) acquiring basic biotech and regulatory knowledge, where he served as a Member of EUPATI's Course Committee for the next year, representing the patient voice. Being a EUPATI fellow, he established the Greek EUPATI National Liaison Team. Locally in Greece he is the patient representative of MDA HELLAS, created an active network of patient advocates, and became a board member of the World Duchenne Organization (WDO) promoting a vibrant network of patient organizations where children with DMD will have access to the best care irrelevant to where they live.
In his role as a patient advocate, he interacts with Regulators, HTA authorities, Industry and Academia promoting the rights of patients with rare diseases to have access to the best care possible and to new, safe and affordable drugs for rare diseases.
As a strong and committed patient advocate for DMD and rare diseases, he serves the patient community through various roles. He is a board member of EPF, a EURORDIS EPAC/TAG member, he served on the Board of the European Forum for Good Clinical Practice (EFGCP), Co-Chairing the Children Medicines Working Party (CMWP), Patient Advisor in TREAT-NMD Advisory Committee for Therapeutics (TACT), DIA's Program Committee Member and many others.
In 2014 he was nominated patient expert by EMA for DMD and has participated in several of EMA's Scientific Advice, SAG, Protocol Assistance and CHMP pilot meetings for Duchenne, providing the essential patient representative perspective when companies request regulatory advice or approval.
He currently serves as PDCO member in EMA representing EURORDIS.

ATIF UZMA

Uzma Atif has more than 20 years' experience in the Pharmaceutical industry. She joined Shire US Medical Affairs in 2010 and served as an Executive Medical Science Liaison in the area of rare genetic diseases, contributing to and supporting medical and scientific strategy. Since 2018, she has also been a key contributor to the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. Uzma now serves as the Scientific Director for Innovative Health Partnerships within the Takeda Chief Medical office, R&D Center of Health Equity and Patient Affairs.
Prior to joining Takeda, Uzma was at GlaxoSmithKline for 10 years in various positions including, Principal Education Advisor supporting the development of an Educational Physician Foundation Program, Medical Genetics Advisor in Translational Medicine & Genetics, where she directed and led initiatives in disease genetics, biomarker research and pharmacogenetics, and Head of Predictive Screen Development and Toxicogenomic Mechanisms at Smith Kline Beecham Pharmaceuticals. She managed projects through international collaborative interactions with Academia Sinica, a government-funded academic institute in Taiwan.
Uzma received her Ph.D in Human Molecular Genetics from the University of Newcastle-upon-Tyne, in England and her Bachelor's in Pharmacology & Biochemistry. In pursuing her passion for learning and global health, Uzma received her Certification in Core Public Health concepts, and in 2013 received her Master's in Public Health Leadership, with a major in Global Health, from the Gilling's School of Global Public Health at the University of North Carolina.

BEDLINGTON NICOLA

Nicola Bedlington is Special Advisor at the European Patients' Forum. Until recently she was Secretary General and joined as its first Executive Director in June 2006. She was the Founding Director of the European Disability Forum, an umbrella organisation uniting over 70 European disability non-governmental organisations (NGOs) to advocate for the human rights and inclusion of disabled citizens in Europe (1996 to 1999), and prior to this she worked as an external expert for the European Commission, heading the NGO unit within the HELIOS Programme (1991 to 1996).
From 2004 to 2006, she worked for the Swiss Government, leading the Environment and Schools Initiatives Secretariat, an international government-based network set up by the Organisation for Economic Co-operation and Development focusing on innovation, action research and policy development in the field of Education for Sustainable Development.
Whilst in Switzerland, she has also worked as an independent consultant/evaluator, specialising in European social and development policy and health advocacy.
Nicola studied business and human resource management in the UK and France.
The EPF is an umbrella organisation that works with patients' groups in public health and health advocacy across Europe. Their 74 members represent specific chronic disease groups at EU level or are national coalitions of patients.

BEGHYN TERENCE

Terence is 40 years old, native of Région Hauts-de-France in France. He is pharmacist and holds a Ph.D. in medicinal chemistry. From 2007 to 2014, he is assistant Professor at the Faculty of Pharmacy (University of Lille). Passionate about all drug discovery technologies, he participated in the establishment of several high technology platforms and in the design of the chemical library screening platform of Institut Pasteur de Lille. His research has then focused on the discovery of novel pharmacological activities of drugs already on the market, work funded by two ANR Emergence programs. Envious of enterprise, he co-founded Apteeus with Professor Benoit Deprez to share his expertise and know-how in drug discovery and repurposing at the service of rare monogenic disorders. pharmaRedux project was awarded by the French ministry of research in 2011 and 2012 and led to the creation of APTEEUS in 2014. APTEEUS is particularly innovative through its individualized approach of drug discovery. Terence is currently the CEO and CSO.

BELLGARD MATTHEW

Professor Matt Bellgard is the inaugural eResearch Director at Queensland University of Technology (QUT). Over his career Professor Bellgard has honed his skills in digital transformation (DT) leadership within and across large institutions addressing cross jurisdictional

challenges. He has personally attracted over m in research funding, co-inventor of 5 full/20 provisional patents, designed and commissioned a world's top 100 supercomputer, co-authored over 156 peer reviewed articles in areas including human/animal/plant genomics, bioinformatics, health informatics, AI, biosecurity, eResearch, HASS, remote sensing and radio astronomy. He has led the design and development of digital health solutions and patient rare disease registries for government, industry and academia, addressing policy, privacy, consent issues across multiple jurisdictions.
Professor Bellgard is Chair of the Asia Pacific Economic Cooperation Rare Disease Network, and within 16 months of introducing the Concept Note in August 2017, the 21 APEC governments endorsed the APEC Rare Disease Action Plan that brings together governments, industry, academia, clinicians and patient advocacy groups to support the estimated 200 million individuals living with a rare disease within the APEC economies. On the back of this work, this year, Professor Bellgard and his colleagues were successful in securing m through the Australian Digital Health Cooperative Research Centre to deploy a Clinical Data Analytics Platform to improve clinical outcomes through point-of-care decision support for patients with COVID-19 and in other clinical care settings. Partners for this project include: Queensland Health, NSW Health, Australian Commonwealth Health, QUT, University of Sydney and Monash University.
Previously, Professor Bellgard was the Director of the Centre for Comparative Genomics, a Western Australian State Government Centre of Excellence for over 12 years. The CCG undertakes research in the biomedical and agricultural sciences on themes as diverse as human health, personalised medicine, animal and plant genomics and pathogens and viruses. As CCG Director, he was responsible for the expansion of the Centre into the fields of rare disease and molecular therapy, recruiting a team that has pioneered research on innovative rare disease registries development and novel therapies for muscular dystrophy that have FDA accelerated approval.

BROOKS PHILIP JOHN (P.J.)

Philip John (P.J.) Brooks is a Program Director in the NCATS Office of Rare Diseases Research (ORDR). Dr. Brooks received his Ph.D. in neurobiology from the University of North Carolina at Chapel Hill. After completing a postdoctoral fellowship at the Rockefeller University, Brooks became an investigator in the intramural program of the National Institute on Alcohol Abuse and Alcoholism. He developed an internationally recognized research program focused on two distinct areas: the molecular basis of alcohol-related cancer, and rare neurologic diseases resulting from defective DNA repair, including xeroderma pigmentosum, Cockayne syndrome and Fanconi anemia. Since joining NCATS and ORDR, Dr. Brooks is interested in accelerating clinical trials in rare diseases by moving beyond "one disease at a time" approaches. Examples include the development of therapeutics that target shared molecular mechanisms underlying multiple rare diseases, platform technologies for the delivery of nucleic acid therapeutics, and the implementation of recommendations from the NCATS Cures Acceleration Network regarding the acceleration of gene therapy clinical trials. In addition to his responsibilities at NCATS, Dr. Brooks is the Working Group Coordinator for the NIH Common Fund program on Somatic Cell Genome Editing https://commonfund.nih.gov/editing.

CARTIER-LACAVE NATHALIE

MD, Director of the INSERM lab NeuroGenCell (Gene and cell Therapy for neurodegenerative diseases of adults and children) at Institute for Brain and Spine (ICM) in Hospital Pitié Salpêtrière in Paris.
Engaged in the development of gene therapy applications for neurodegenerative diseases (genetic leukodystrophies, Huntington's disease, Alzheimer disease, Amyotrophic Lateral Sclerosis) Including all translation steps from preclinical proof of concept in animal models to clinical trials in human patients; development of clinical protocol and regulatory aspects.
Investigator in the first gene therapy trial based on autologous transplantation of corrected cells with an HIV vector to correct cerebral forms of Adrenoleukodytrophy and Investigator in the gene therapy trial using AAV gene transfer of arylsulfatase A in brai parenchyma to cure metachromatic leukodystrophy.
Teaching activity :
Professor at the Faculty of Pharmaceutical Sciences (Université Paris Descartes 2010-2013, University Paris Sud since) : Genetics, medical semiology, Biotherapies
Director of the Biotherapy course in the Magistère of Genetics Paris 5-Paris 7
Visiting Professor, University of Massachusetts Medical School : Gene therapy
Expert activity
President of the Société Française de Thérapie Cellulaire et Génique (SFTCG , 2010-2014)
Coordinator of the Domaine d'Intérêt Majeur (DIM) of the Ile de France region for biothérapies (since 2011)
Expert in the French committee for the follow up of clinical trials in Biotherapy if INSERM (COSSEC) since 2008
Expert at INSERM national specialized committee for biotherapies (CSS8, 2008-2013)
Member of the Scientific committee of INSERM (2013-2018)
Former President of the scientific committee of the Fondation Maladies Rares
Member of the scientific committee of AFM (Association Française contre les Myopathies)
Corresponding member of the French Académie Nationale de Médecine (section biology)
Member of the Gene Therapy Working Party (GTWP) European Medicine Agency (EMA)
Member of the scientific committee of the Janssen research fund (2017)
Member of the scientific committee of the Hanover Medical School (2015-current)
Former President of the European Society for Cell and Gene Therapy (ESGCT, European Society for cell and Gene Therapy) : 2014-2016
Honors
Jean Valade award (Fondation de France) (2004)
Thermo Biotherapie award (2007)
Sisley-Lejeune award (2010)
Drieu – Cholet (Académie de Médecine) award (2010)
Chevalier de la Légion d'Honneur (French Government award) (2010)
Mémain-Pelletier de l'Académie des Sciences award (2011)
Corresponding member of the French Academy of Medicine (2012)
Grand Prix de la Fondation pour la Recherche médicale (2019)
Grand prix Lazorthes de l'Académie des Sciences 2019.

CAULFIELD MARK

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

DJOUDALBAYE BENJAMIN

Dr Benjamin Djoudalbaye is Head of Policy and Health Diplomacy at the Africa Centers for Disease Control and Prevention. He was a Senior Health Officer for HIV/AIDS, tuberculosis, malaria and other infectious diseases at the African Union Commission from 2009–2018. He has a strong professional experience in strategic planning, administration, management and evaluation of policies, programs and public health, infectious diseases programs and projects; capacity building and operational research in Africa. Dr Djoudalbaye also has a good knowledge of coordination mechanisms including multidisciplinary and multisectoral teams, partnership development, negotiation skills, advocacy and resource mobilization, multilateral and bilateral cooperation, public & private sector and civil society.

Dr Djoudalbaye specializes in Infectious Diseases (University Claude Bernard Lyon 1), HIV/AIDS and Sexual Reproduction Health (University Denis Diderot Paris 7) and Epidemiology & Biostatistics (University Claude Bernard Lyon 1). He holds a Master Degree in Population Studies and Public Health. He has worked with many organizations; among them are International SOS, Ministry of Health of the Republic of Chad and SOLTHIS.

GABALDO MICHELA

Michela Gabaldo is Head, Alliance Management & Regulatory Affairs at Fondazione Telethon in Milan (Italy) supporting the 2 internal Scientific Institutes SR-TIGET (San Raffaele-Telethon Institute for gene therapy) and TIGEM (Telethon Institute of Genetics and Medicine) through the early development up to the registration and market access of the gene therapy programs developed both internally and in partnership with relevant pharmaceutical industries.
She has 20 years of experience in drug development spanning from chemicals up to ATMP.
She joined Telethon in 2011 where she manages gene therapy projects at different stages of development ranging from preclinical, to clinical, to registration and market access.
Winner of 2017 edition of TopRA Award in the Future category, Michela offers up to date knowledge of the most recent regulations in ATMPs and Orphans.
She's currently a member of the IRDiRC (International Rare Disease Research Consortium) Therapies Scientific Committee.

GAHL WILLIAM

Dr. William A. Gahl earned his B.S. in biology from the Massachusetts Institute of Technology in 1972 and his M.D. and Ph.D. from the University of Wisconsin. He served as pediatric resident and chief resident at the University of Wisconsin hospitals from 1976-80. In 1984, he completed clinical genetics and clinical biochemical genetics fellowships at the NIH's Interinstitute Medical Genetics Training Program, which he directed from 1989 to 1994. Dr. Gahl elucidated the basic defects in cystinosis and Salla disease and helped bring cysteamine to new drug approval by the Food and Drug Administration as the treatment for cystinosis. His group described the natural history of Lowe syndrome, alkaptonuria, autosomal recessive polycystic kidney disease, Chediak-Higashi disease, GNE myopathy, and Hermansky-Pudlak syndrome (HPS), and his lab discovered the genetic bases of gray platelet syndrome, Hartnup disease, arterial calcification due to deficiency of CD73, 3-methylglutaconic aciduria type III, 3 types of HPS, and neutropenia due to VPS45 deficiency. Gahl has published more than 400 peer-reviewed papers and trained over 40 biochemical geneticists. He established American Board of Medical Specialties certification for medical biochemical genetics. He served on the board of directors of the ABMG and American Society of Human Genetics, as president of the Society for Inherited Metabolic Disorders, and was elected to the American Society for Clinical Investigation and the Association of American Physicians. Dr. Gahl received the Dr. Nathan Davis Award for Outstanding Government Service from the AMA, the Service to America Medal in Science and the Environment, the RareVoice Award for a Government Agency Leader, the March of Dimes Pruzansky Lecture Award, and numerous other awards.

HIVERT VIRGINIE

Virginie Hivert joined EURORDIS in 2014 as Therapeutic Development Director.
Virginie is responsible for following the development of orphan medicinal products as an observer on the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency.
She coordinates the group of high-level EURORDIS representatives/volunteers who sit on the various scientific committees/working parties at the EMA, known as the Therapeutic Action Group (TAG) and is herself the alternate member representing patients on the Pharmacovigilance and Risk Assesment Committee (PRAC).
Virginie is responsible for two activity areas in EURORDIS, one being the training of pa-

tients' representatives in therapeutic development activities (EURORDIS Summer School, EUPATI) and the other related to their engagement in these activities (in Protocol Assistance in Scientific Advice Working Party (SAWP) at the EMA for example).
She is also Vice-Chair of the Therapies Scientific Committee of IRDiRC (International Rare Disease Research Consortium).
Prior to joining EURORDIS, Virginie worked for Orphanet as coordinator of data collection of the resources related to rare diseases (such as expert centers, medical laboratories, patient organisations, research projects, clinical trials, etc.) in the 37 countries of the Orphanet Consortium.
Virginie holds a PharmD and a PhD in Biological Sciences and has previously worked in basic research, particularly on pathophysiological pathways in oncology.

HOUŸEZ FRANÇOIS

François Houÿez is working at the European Organisation for Rare Diseases Eurordiswhere he is Director of Treatment Information and Access. He has always been working as a patient advocate since the early 90s, first in the HIV/AIDS advocacy, and in rare diseases since 2003. He pioneered patient advocacy with the European Medicines Agency as part of the first patients' delegation that engaged dialogue with the Agency back in 1996.
He represents Eurordis at the Patients' and Consumers' Working Party at the European Medicines Agency (EMA). He also represents Eurordisin the HTA Network, and he has been involved in EUnetHTA activities since 2010. His expertise includes Community Advisory Boards, compassionate use, drug repurposing, involvement of patients in regulatory and HTA activities, drug shortages, pharmacovigilance, marketing authorisation, HTA, pricing and reimbursement, cross-border care…
He is one of the trainers at EurordisSummer School on clinical development. François is also a patient.

JONKER ANNELIENE

Anneliene Jonker, PhD, is the Funding and Strategy Officer of the TechMed Centre, at the University of Twente, in Enschede, The Netherlands. In this position, she is responsible for setting up funding strategies for different researchers in the personalized medicine-, medtech, and rare diseases domain, working with academic and industrial researchers. In addition she assists in the constitution of new collaborations with different stakeholders, to create new research and implementation projects. Anneliene has previously worked at the IRDiRC Scientific Secretariat, as Project and Communication Manager and has been involved with many of the different tasks of the consortium. Anneliene Jonker has had a long interest in rare diseases, and was trained as a biomedical scientist, obtaining her PhD in genetics and metabolism of Ewing' sarcoma, a rare childhood cancer, at Institut Curie, Paris, France. In addition, she has a master's degree in the history of medicine, dedicated to rare bone diseases, from the Free University of Amsterdam, Amsterdam, The Netherlands. She is currently a member of the IRDiRC (International Rare Disease Research Consortium) Therapies Scientific Committee.

JULKOWSKA DARIA

Daria Julkowska has over 15 years of experience in research and management. She is the Scientific Coordinator of the European Joint Programme on Rare Diseases that brings together different type of stakeholders (researchers, funders, clinicians & patients) from 35 countries from Europe and beyond, and also is responsible for the coordination of the IRDiRC Scientific Secretariat. This position allows her to implement the strategic rare disease research and funding recommendations of IRDiRC to the development of EJP RD which includes the participation of the European Research networks. She is involved in the rare diseases field since 2010, starting from E-Rare, the ERA-Net for Research programmes on rare diseases, where for the first two years she occupied the position of the project manager to finally (April 2013-December 2018) take over the coordination of the programme. As the coordinator, she developed and put into action a set of collaborations facilitating rare diseases research, including the partnerships with European Research Infrastructures and Patients' Organizations. She has an extensive knowledge and understanding of European funding schemes and programmes.
Dr. Julkowska obtained her international PhD in molecular biology at the University of Paris XI, France and University of Gdansk, Poland in 2005. She pursued her scientific vocation by the post-doctoral experience in cellular biology, at Institut Pasteur, Paris and extensive training in communication and European Union counselling. She also holds MSc in Management of Research from the University of Paris Dauphine.

KRAWITZ PETER

Dr. Peter Krawitz became FDNA's Chief Science Officer with the goals of identifying and exploring high-impact and original research fields to further the development and use of NGP technologies, as well as driving the research efforts to create new knowledge that serves to expand the field of genetics. Beyond his role at FDNA, Dr. Krawitz also serves as Director of the Institute for Genomic Statistics and Bioinformatics at the University of Bonn in Germany. Through the use of artificial intelligence in the analysis of big genomic data, his research aims to deepen the understanding of genome biology and advance personalized care.

LE CAM YANN

Yann was one of the founders of EURORDIS-Rare Diseases Europe in 1997. He is the organisation's Chief Executive Officer since 2000.
Yann initiated Rare Diseases International (RDI) in 2009. He is an elected member of the RDI Council and Chair of the RDI Advocacy Committee. He is a founding member of the NGO Committee for Rare Diseases(United Nations, New York) in 2014 and its Vice-Chair. Yann is a Co-Chair of the Global Commission to End the Diagnostic Odyssey of Children with Rare Diseases since its launch in 2018. Yann is a member of the World Economic Forum's Health Stewards Board from 2020 and of its Global Precision Medicine Council since 2019.
Recent past positions include: member of the Management Board of the European Medi-

cines Agency (EMA)2017-2019; Chair of the Therapies Scientific Committee of the International Rare Diseases Research Consortium (IRDiRC), 2013-2017; Vice-Chairman of the EU Committee of Experts on Rare Diseases(EUCERD), 2011 – 2013; and a member of the Commission Expert Group on Rare Diseases, 2014 – 2017; member of the Committee for Orphan Medicinal Products (COMP) at the EMA, served 9 years, two elected mandate as vice-chair for 6 years.
Yann holds an MBA from HEC Paris. He has three daughters, the eldest of whom is living with cystic fibrosis.

MENZEL OLIVIER

Dr. Olivier Menzel graduated (B.Sc.) from the University of Geneva, where he obtained a Master of Medical Genetics (M.Sc.) in 2001 and a Ph.D. in Molecular and Cellular Biology in 2006 from the University of Lausanne and EPFL at the Swiss Institute for Experimental Cancer Research (ISREC). For seven years, he directed the laboratory of pediatric surgery at the University Hospital of Geneva. In parallel, he created the BLACKSWAN Foundation (blackswanfoundation.ch), a Swiss foundation to support research on orphan diseases, and he is the lead organizer/promoter of the bi-annual well-recognized international scientific conference of rare disease research (RE(ACT) Congress; react-congress.org). For two years, he was a director of a company specialized in the identification, acquisition, development, marketing, and sale of research programs for rare and orphan diseases. In 2013 he obtained an Executive MBA from the HEC of Lausanne with a specialization in Management Healthcare. He served as director at the second largest group of private clinics in Switzerland, Swiss Medical Network, then, for two years, he was the managing director and consultant at Think Rare Sàrl and fully involved in the BLACKSWAN Foundation activities. Now he is the Head of Strategic Partnerships at the Health 2030 Swiss Genome Center, a multi-institutional hub to promote genomic medicine. Dr. Menzel sits on the board of the Swiss rare disease patient organization alliance (ProRaris), on the National Steering Board of the Swiss Personalized Health Network (SPHN), and he is a member of the American Society of Human Genetics (ASHG).

MONACO LUCIA

Lucia Monaco is the current Consortium Assembly Chair of the International Rare Diseases Research Consortium (IRDiRC), where she represents Fondazione Telethon, the Italian charity committed to rare genetic diseases research. She is the head of Research Impact and Strategic Analysis and former Chief Scientific Officer of Fondazione Telethon in Milan, Italy. She previously worked as a researcher at the San Raffaele Scientific Institute in Milan and earlier she was senior researcher in the Molecular Biology Laboratory of Farmitalia Carlo Erba in Milan, Italy. She graduated in chemistry at the University of Pavia, Italy and received her training in biochemistry at the University of Iowa in Iowa City, USA and in molecular biology at the European Molecular Biology Laboratory in Heidelberg, Germany. She is/has been member of several international committees and boards, among which: the Policy Board of the European Joint Program on Rare Diseases (EJP RD) and the Horizon 2020 Advisory Group for Societal Challenge 1 – Health, demographic change and well-being.

NELLÅKER CHRISTOFFER

Christoffer Nellaker is a researcher in Digital Phenotyping based at the Big Data Institute at the University of Oxford. His research encompasses broadly extracting biologically meaningful data from imaging modalities. Dr. Nellåker's group is translating the latest developments in computer vision and computational biology to aid diagnosis of rare diseases. The work is a collaborative effort to apply the latest techniques from facial recognition research for disease phenotyping. The aim is to bring this to clinical use to help narrow down the search for a correct diagnosis and to be used together with genome sequencing to identify mutations causing disease.

NORSTEDT IRENE

Irene Norstedt works at the European Commission, where she is Acting Director responsible for the Health Directorate within the DG for Research and Innovation, European Commission. She is also Head of the Innovative and Personalised Medicine Unit.
She has been at the European Commission since 1996, and was instrumental in the creation of IMI in 2008.
From 16 December 2014 to15 September 2015, Irene served as Acting Executive Director of the Innovative Medicines Initiative.
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 biotechnology and polymer science, and holds a Master of Science (MsC) in Chemical Engineering.

OLLENDORF DANIEL

Dan Ollendorf is Director of Value Measurement and Global Health Initiatives at the Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts University. His research interests include expanding the use of health technology assessment in low- and middle-income economies, as well as refinement of value assessment tools in the US and other high-income settings. Prior to joining CEVR, Dan was Chief Scientific Officer for the Institute for Clinical and Economic Review (ICER) for over 10 years, where he was responsible for the conduct of assessments of the clinical effectiveness and economic value of high impact health care technologies as well as coordination of the broader health technology assessment process. His 30 years of experience also include work in the hospital, informatics, insurance, and consulting sectors.
Dan holds a Ph.D. in clinical epidemiology from the University of Amsterdam, a Master's of Public Health from Boston University, and a Bachelor of Arts from the University of Rochester. Dan currently serves as a non-resident Fellow at the Center for Global Development, is a member of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) HTA Council Working Group, and is the Chair of the Health Technology Assessment International (HTAi) Global Policy Forum. From 2015-2019, he served on the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC).

PARISER ANNE R.

Anne Pariser, M.D. is the director of the Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Sciences (NCATS) NIH. ORDR is dedicated to accelerating rare diseases research to benefit patients, through rare diseases programs such as the Rare Diseases Clinical Research Network, Genetic and Rare Diseases Information Center (GARD), and the NCATS Toolkit for Patient-focused Therapy Development. Important translational science research initiatives for rare diseases at ORDR include establishing best practices and tools for good quality natural history studies, data standards and sharing initiatives, the development of diagnostic support tools, and rare diseases therapeutics development, as well as translational and basic science research grants and collaborative programs. Dr. Pariser came to NCATS in 2017, and before this, she worked for 16 years at the US Food and Drug Administration Center for Drug Evaluation and Research, where she founded the Rare Diseases Program in FDA CDER's Office of New Drugs in 2010 and served as a Medical Officer and Team Leader for rare diseases drug and biologics product development, review and regulation. Dr. Pariser has 20 years of experience in rare diseases research, and her current research interests include "many diseases at a time" research approaches, such as platforms for gene therapies and other rare disease product development, and informatics approaches to diagnosis.

PEARCE DAVID A.

David Pearce is President of Innovation and Research for Sanford Health. He completed his undergraduate Bachelor of Science Degree with honors in biological sciences at Wolverhampton Polytechnic in 1986. He gained his PhD in 1990 at the University of Bath, UK, and did postdoctoral training at the University of Rochester, U.S., and Oxford University, UK.
Dr. Pearce heads the leading lab in Juvenile Batten disease research. He has been researching Juvenile Neuronal Ceroid Lipofuscinosis (Batten disease) since 1997. His research has led to the first clinical trial for Juvenile Batten disease. He has published over 100 research papers on Batten disease. He also oversees a national registry for rare diseases known as the Coordination of Rare Diseases at Sanford (CoRDS). He has served on numerous NIH review committees, has organized rare disease workshops for the National Institute for Neurological Disorders and Stroke (NINDS) arm of the National Institutes of Health (NIH) and is currently the vice chair of the consortium assemble for the International Rare Diseases Research Consortium (IRDiRC).
In his role as President of Innovation and Research at Sanford he is responsible for overseeing the development of research programs across Sanford's nine-state footprint, including more than 450 researchers, eight research centers and more than 300 ongoing clinical trials. With this, he is also responsible for commercialization of select research strategies, as well as integrating Sanford Research operations into Sanford Health International Clinics. Driven by Dr. Pearce's passion for developing patient-centered, impactful research programs Sanford Research is uniquely positioned to provide translational research that can bring important discoveries from bench to bedside, improving the quality of care.

REYMOND ALEXANDRE

Alexandre Reymond carried out his thesis in the laboratory of Dr. Viesturs Simanis at the Swiss Institute for Experimental Cancer Research (ISREC) and received his Ph.D. from the

University of Lausanne in 1993. After completion of his postdoctoral training with Dr Roger Brent in the Department of Molecular Biology, Massachusetts General Hospital and in the Department of Genetics, Harvard Medical School in Boston, he moved to the Telethon Institute of Genetics and Medicine (TIGEM) in Milan in 1998 to lead a research group. He joined in 2000 the Department of Genetic Medicine and Development, University of Geneva Medical School. He moved to the Center for Integrative Genomics in October 2004 and became its Director in 2015. He is the President of the European Society of Human Genetics.
His laboratory has assessed the functional impact of genome structural changes, such as CNVs and balance rearrangements. His team demonstrated that expression levels of genes within CNVs tend to correlate with copy number changes, and that structural changes influence the expression of genes in their vicinity – an effect that may extends over the entire length of the affected chromosome. They provided initial evidence that CNVs shape tissue transcriptomes on a global scale and thus represent a substantial source for within-species phenotypic variation. His laboratory participated in disentangling the natural history of the 16p11.2 rearrangements, i.e. their evolution, associated phenotypes and identification of major driver genes.

SCHEEREN JOSEPH

Dr. Scheeren started his pharmaceutical industry career in 1982 with Servier in Paris, responsible for Regulatory Affairs Northern and Eastern Europe, and Clinical Development in Munich from 1986 – 1987. In 1991, he was appointed Head of Worldwide Regulatory Affairs at Serono, Geneva. In 1992, he took over responsibility of the Global Regulatory Affairs department of Roussel UCLAF in Paris. In 1996, he moved to New Jersey to head the Global Marketed Product Regulatory Affairs Department of Hoechst Marion Roussel. After the merger with Rhone Poulenc Rorer in 2000, he was nominated to a similar position.
Dr. Scheeren joined Bayer Pharmaceuticals as Senior Vice President, Head of Global Regulatory Affairs (GRA), in 2004, responsible for development in the US and in 2009 became Site Head US in Montville, NJ. In 2012, he assumed in addition to his responsibilities as Head of GRA, the position of Head of Global Development Asia in Beijing and in 2015, was appointed Head of GRA Pharma and Consumer Care of Bayer Healthcare, Basel. In January 2018, he was appointed Senior Advisor R&D, Bayer AG in Berlin and left Bayer AG at the end of 2018. Since January 2019, he is Adjunct Professor at Peking University for Regulatory Sciences in the Department of Clinical Research. Dr. Scheeren holds many memberships and designations, serving on Advisory Boards at the Center for Innovation in Regulatory Science, the Regulatory Affairs track at Yale University, the Center of Regulatory Excellence in Singapore. He is also a foreign member of the Academie Nationale de Pharmacie, France, and a lecturer at Yale University. Dr. Scheeren studied pharmacy at the University of Leiden.

SEYFERT-MARGOLIS VICKI

Vicki Seyfert-Margolis, CEO and Founder of My Own Med, Inc., has published and presented in top journals and numerous conferences about the transformative nature of digital technologies and novel clinical trial designs. Prior to founding My Own Med, Inc., Vicki

was appointed in the Obama Administration as the Senior Advisor for Science Innovation and Policy in the Office of the Commissioner of the US Food and Drug Administration. While at the FDA, she worked on a myriad of regulatory and leading-edge science issues, including mobile technologies, innovation in drug development, companion diagnostics, and a whole range of regulatory science initiatives and policies working with industry and academic leaders. Prior to the FDA, she served as Chief Scientific Officer at the Immune Tolerance Network (ITN), a non-profit consortium of researchers seeking new treatments for diseases of the immune system. At ITN, Dr. Seyfert-Margolis oversaw the development of over 20 leading-edge assay development and centralized laboratory facilities. Over the course of her career, including time at ITN, she designed and implemented over 35 innovative Phase II and registration clinical trials incorporating biomarker discovery and qualification. Prior to this, she served as Director of the Office of Innovative Scientific Research Technologies at the National Institute of Allergy and Infectious Diseases at NIH, where she worked to integrate emerging technologies into existing immunology and infectious disease programs. Dr. Seyfert-Margolis completed her PhD in immunology at the University of Pennsylvania's School of Medicine, and her post- doctoral fellowship work at Harvard University and the National Cancer Institute. Vicki also serves on Board of Directors for the EveryLife Foundation for Rare Diseases, and Eureka Institute for Translational Medicine.

SIREAU NICK

Dr Nicolas Sireau is the CEO and Chair of Trustees at the AKU Society, a patient group that helps people with AKU (short for alkaptonuria), a rare genetic disease affecting both his children. He is also co-founder and Chair of Findacure, an organisation that helps rare disease patient groups. Previously, Nick was the CEO of SolarAid, an NGO working in Africa. He is a fellow of the Ashoka Fellowship of Social Entrepreneurs and has a PhD in the social psychology of social movements. 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' (Findacure 2016).

VAN DER GOOT GISOU

Gisou van der Goot is the Head of the Laboratory of Cell and Membrane Biology at EPFL (Ecole Polytechnique Fédérale de Lausanne) in the School of Life Sciences of which she is the Dean since 2014.
Before joining EPFL, she was Group Leader at the Faculty of Sciences of the University of Geneva (UNIGE) and subsequently Associate Professor at the Faculty of Medicine of the same university.
She studied engineering at the Ecole Centrale de Paris, then did a PhD in Molecular Biophysics at the Nuclear Energy Research Center, Saclay, France, followed by a postdoc at the European Molecular Biology Laboratory (EMBL) in Heidelberg.
She obtained an EMBO Young Investigator award in 2001, a Howard Hughes International Scholar award in 2005 and the Swiss Prix Marcel Benoist in 2009, the same year she was elected EMBO member (European Molecular Biology Organisation).
She is a leader in the fields of molecular and cellular understanding of bacterial toxins, the organization of mammalian membranes, in organelles biology as has become and expert over

the last 15 years in studying the molecular mechanisms of several rare diseases such as Hyaline Fibromatosis Syndrome.
Professor van der Goot is or has been member of many scientific boards such as the Swiss National Science Foundation, the Swiss Council for Science and Technology, the European Research Council (ERC), the Louis Jeantet Foundation or the Bettencourt-Schuller Foundation.

VAN KARNEBEEK CLARA

Professor Clara van Karnebeek is head of the metabolic diseases department in the Radboud University Medical Centre in Nijmegen and principal investigator at the Amsterdam University Medical Centres, The Netherlands and the University of British Columbia in Vancouver Canada.
Clara's work as a pediatrician and biochemical geneticist focuses on early diagnosis and innovative treatment of neurometabolic diseases in a P4-medicine model. Her international team integrates genomic and metabolomics technologies to unravel the cause of degenerative brain conditions in children, discovering novel genetic conditions and treatment targets. She implements this knowledge in the management of her patients, via clinical trials with personalized outcomes.
Translating new knowledge into expanded newborn screening, as well as useful information and action for the patient and family, using digital applications, are the ultimate goals of her multi-disciplinary team's effort.
She is the Director of United for Metabolic Diseases (www.umd.nl), a Dutch consortium uniting all 6 academic metabolic expertise centers and the patient organizations to optimize research and care.
She published over 180 peer-reviewed journal articles, multiple clinical guidelines and chapters in textbooks. She is a dedicated teacher and mentor for clinical and research trainees at different stages. For her contributions to research and clinical care and commitment to translational science she received the Canadian Organization for Rare Diseases Scientist Award.

VOLK HANS-DIETER

Hans-Dieter Volk, MD, is Professor of Immunology and head of the both Institute of Medical Immunology, Charité Berlin and BIH Center for Regenerative Therapies (BCRT) as well as deputy spokesman of the Berlin-Brandenburg School for Regenerative Therapies (BSRT) (all Berlin, Germany). In addition, he is scientific head of the division Immunology of the Labor Berlin Charité Vivantes GmbH, Berlin. His focus lies on implementation of new concepts in diagnosis and therapy of immunological diseases. Hans-Dieter Volk is an expert in coordinating and conducting clinical trials by biomarker development, monitoring new cell therapies, performing proof-of concept and investigator-initiated trials (all phase I/II). Moreover he was/is co-editor/editorial board member of several high-impact journals (e.g. Am J Transpl, Transplantation) and board member of several scientific medicine societies (e.g. German Society Immunology, German Society Sepsis).
Scientific development: 1974-1980 Studies of Medicine, Berlin; 1982 M.D. (Dr. med.) Department of Immunology, Charité Berlin; 1987 Habilitation (PhD) and Senior Lecturer „Clinical Immunology", Charité Berlin; since 1994 Head of Institute of Medical Immunology, C3 Professorship "Immunology"; since 2007 Head of BIH Center for Regenerative Therapies (BCRT)

and W3 professorship; since 2009 Deputy spokesman of the Berlin-Brandenburg School for Regenerative Therapies (BSRT); since 2011 Head of the Div. Immunology, Labor Berlin Charité Vivantes GmbH
Expertise/Projects:

- Development of regenerative therapies (several BMBF grants, DFGSFB TR36, EU-FP7 "One Study")
- Biomarker development and validation (EU-FP7: "Bio-DrIM" and "BioCog", >40 industry-sponsored studies)
- Transplant immunology (DFG, foundation)
- Board member of several scientific

WARD SUSAN J

Recognizing the urgency of finding new approaches to clinical trial design and analysis in rare disease, in 2015 Dr. Ward founded the collaborative Trajectory Analysis Project (cTAP), a dynamic pan-stakeholder alliance applying advanced data science to the largest collection of patient clinical data in Duchenne Muscular Dystrophy http://ctap-duchenne.org
A pharmaceutical executive, scientist, consultant and educator whose career is marked by innovation in solving tough cross-disciplinary challenges. Dr. Ward was a prominent pain researcher before joining Wyeth (now Pfizer) where she became the first woman in the industry to head R&D in the U.K.. A member of the Wyeth global executive team, she pioneered project management in drug discovery, halving time to initiate clinical trials, and subsequently oversaw development and world-wide approval of innovative products including Enbrel, Rapamune, and the first toxin-antibody conjugates developed in cancer. As an officer of Millennium Pharmaceuticals (now Takeda) from 2000, Dr. Ward led strategy, productivity and the technology platform, with annual revenue exceeding M. As a consultant, she developed Alnylam's research strategy, introduced a pioneering quality-based productivity platform at Novartis, and served as a business advisor to innovative technology companies. Dr Ward is a member of the MGH-Harvard Rare Disease Think Tank, is an experienced independent board director of emerging Biotech, and served for 6 years as a Trustee and Finance Chair of the Cambridge School of Weston, a leader in progressive education. Dr. Ward earned her Ph.D. from the University of Manchester, UK, has authored over 60 articles in peer-reviewed journals, and holds 9 patents.

WEDELL ANNA

Anna Wedell, MD, PhD, is a Clinical Geneticist and Professor of Medical Genetics at the Department of Molecular Medicine & Surgery and Science for Life Laboratory (SciLifeLab), Karolinska Institutet, and Head of the Centre for Inherited Metabolic Diseases (CMMS) at Karolinska University Hospital. Her multidisciplinary team provides nationwide diagnostics, including newborn screening, as well as expert clinical advice on all aspects of inherited metabolic diseases. A strong focus is on mitochondrial medicine, where in-house methods for detailed biochemical evaluation of live muscle mitochondria have been developed. During 2010 – 2013, she was Clinical Director at SciLifeLab in Stockholm, establishing a collaboration for development of tools and workflows for clinical whole genome sequencing which has subsequently been implemented at the Karolinska University Hospital, forming the basis for the Genomic Medicine Center Karolinska (GMCK) Rare Diseases, chaired by Wedell. Results are dramatic as large numbers of patients now receive specific molecular diagnoses and treatment in early disease stages, improving outcome. Wedell has discovered a number of novel monogenic diseases affecting brain metabolism, opening novel avenues for treatment. In 2015, she established a KI-Max Planck laboratory for Molecular Metabolism at Karolinska Institutet, together with Professor Nils-Göran Larsson and Dr Anna Wredenberg. Anna Wedell is a member of the Nobel Committee for Physiology and Medicine and served as its chairman during 2016-2018. She is also a member of the Royal Swedish Academy of Sciences and the Royal Swedish Academy of Engineering Sciences.
Dr Ward is a member of the MGH-Harvard Rare Disease Think Tank, is an experienced independent board director of emerging Biotech, and served for 6 years as a Trustee and Finance Chair of the Cambridge School of Weston, a leader in progressive education. Dr. Ward earned her Ph.D. from the University of Manchester, UK, has authored over 60 articles in peer-reviewed journals, and holds 9 patents.

WEISSBAECKER SUSANNE

As Global Head of Access to Medicines Susanne is leading Takeda's strategy to enhance access and strengthen evolving healthcare systems with a focus on low-and middle-income countries. Prior to this role, Susanne was Head of Patient Access and Services in Takeda Europe and Canada and successfully developed and implemented patient engagement programmes for Entyvio and Ninlaro. As a medical physician with a degree in business, Susanne has been working for about 15 years in healthcare and the pharmaceutical industry in various roles. Before joining Takeda, she engaged cross-sectorial partners from the public, civil society and private sector to move the health agenda in Non-Communicable Diseases and value-based Healthcare leading the Healthcare Community at the World Economic Forum. Her broad knowledge and experience in access and patient programs has been developed in more than 10 years, when she worked as a Consultant in Emerging Markets including South East Asia, the Middle East and North Africa.
Susanne has been living and working in Western Europe, the US, the Middle East, and is currently based in Singapore.

WONG-RIEGER DURHANE

DURHANE WONG-RIEGER, PHD is Chair of Rare Disease International, Vice-Chair of Asia Pacific Rare Disease International, member of the Editorial Board of The Patient- Patient Centred Outcomes Research, member of the Global Commission to End the Diagnosis Odyssey for Rare Diseases and member of Health Technology Assessment International Patient /Citizen Involvement Interest Group. In Canada, she is President & CEO of the Canadian Organization for Rare Disorders, Chair of the Consumer Advocare Network, President & CEO of the Institute for Optimizing Health Outcomes and Chair of Canadian Heart Patient Alliance. She is a certified Health Coach.
Dr. Wong-Rieger has served on numerous health policy advisory committees and panels and is a member of Ontario's Rare Disease Implementation Working Group and member of Genome Canada Steering Committee for the Rare Disease Precision Health Initiative. Durhane has a PhD in psychology from McGill University and was professor at the University of Windsor, Canada. She is a trainer and frequent lecturer and author of three books and many articles.

SPEAKERS' ABSTRACTS

GENOME ARCHITECTURE AND DISEASES: THE 16P11.2 PARADIGM

OPENING SESSION

Alexandre Reymond, Director, Center for Integrative Genomics,
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The recurrent 600 kbp deletions and duplications at human chromosome 16p11.2 are among the most frequent genetic causes of neurodevelopmental and psychiatric disorders, as they are found in 1% of individuals with autism spectrum disorders and schizophrenia. These rearrangements cause reciprocal defects in head size, body weight and as described below age of menarche (AaM). These rearrangements are mediated by human-specific duplications that appeared at the beginning of the modern human lineage, suggesting that their expansion has a possible evolutionary advantage that outweighs the accompanying chromosomal instability. These duplications include BOLA2, a gene involved in the maturation of cytosolic iron-sulfur proteins. To investigate the potential advantage provided by its rapid expansion, we assessed hematological traits in individuals who have lost or gained copies of BOLA2. The 16p11.2 deletion is strongly associated with anemia (P=4e-7, OR=5) and upon stratification by BOLA2 copy number, we found an association between low BOLA2 dosage and anemia (P=2e-3). Consistent with human data, the 16p11.2 deletion mouse model and Bola2-deficient mice showed early evidence of iron deficiency. The rapid expansion of BOLA2 might have evolved to protect humans against iron deficiency as our species successfully expanded its ecological range at the cost of increased predisposition to rearrangements associated with autism. We leveraged biobank-scale phenotype data, Mendelian randomization and animal modeling to identify causative genes in a GWAS locus for AaM. The dosage of the 16p11.2 interval is correlated with AaM and an increase in reproductive tract disorders. Likewise, 16p11.2 mouse models display perturbed pubertal onset and structurally altered reproductive organs. Further, we report a negative correlation between the 16p11.2 dosage and relative hypothalamic volume in both humans and mice, intimating a perturbation in the gonadotropin-releasing hormone (GnRH) axis. Two independent assays identified candidate causal genes for AaM; Mendelian randomization and agnostic dosage modulation of each 16p11.2 gene in zebrafish gnrh3:egfp models. ASPHD1, expressed predominantly in brain and pituitary gland, emerged as a major phenotype driver; and it is subject to modulation by KCTD13 to exacerbate GnRH neuron phenotype. Together, our data highlight the power of an interdisciplinary approach to elucidate disease etiologies underlying complex traits.

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THE 100,000 GENOMES PROJECT – TRANSFORMING HEALTHCARE

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Caulfield, Genomics England, UK

The UK 100,000 Genomes Project has focussed on transforming genomic medicine in the National Health Service using whole genome sequencing in rare disease, cancer and infection. Genomics England partnering with the NHS established 13 Genomic Medicine Centres, the NHS whole genome sequencing centre and the Genomics England Clinical Interpretation Partnership (3500 researchers from 24 countries). We sequenced the 100,000th genome on the 5th December 2019 will complete an initial analysis for all participants by the end of July 2019. Alongside these genomes we have assembled a longitudinal life course dataset for research and diagnosis including 2.6 billion clinical data points for researchers to work on to drive up the value of the genomes for direct healthcare. In parallel we have partnered the NHS to establish one of the world's most advanced Genomic Medicine Service where we re-evaluated 300,000 genomic tests and upgraded 25% of tests to newer technologies with an annual review. The UK Department of Health have announced the ambition to undertake 5 million genome analyses over the next 5 years focused on new areas tractable to health gain.

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DEEP PHENOTYPING FROM FACES AND THE MINERVA INITIATIVE

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

C. Nellåker, University of Oxford, UK

New deep learning approaches hold great promise for changing clinical pathways through making new tools for data interrogation for clinicians. Perhaps no patient group stands to benefit more than those undergoing investigations for rare diseases. There are multiple ongoing efforts to utilize facial imaging and morphometrics for phenotyping of patients in clinical settings. I will present the latest effort to deploy deep learning approaches for phenotyping from ordinary photographs. Deep learning models are vulnerable to learning biases in data sets and this is potentially detrimental to their utility. Difference in lighting, pose, age, sex, and different ancestral background can all drive predictions for clinical metrics in unexpected directions. This is an ethical dilemma in that this can propagate systematic disparities in access to accurate diagnoses. I will discuss some of the strategies to ameliorate the influence of such biases on deep learning models for rare diseases. Central to all the challenges and promise of using facial recognition style approaches for clinical phenotyping of rare diseases is however data access and sharing. The fundamental need to identify similarities and cluster ultra-rare disease patients can't be resolved without addressing this issue. We present the Minerva Initiative, an effort to build a framework for secure, ethical and open data sharing across academic and commercial platforms, and across legal and international borders.

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THE GLOBAL COMMISSION TO END THE DIAGNOSTIC ODYSSEY FOR CHILDREN WITH A RARE DISEASE

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Uzma Atif, Takeda Pharmaceutical, USA

Individual diseases may be "rare," but over 6,000 affect 300+ million people. Most rare diseases are genetic and 70% start in childhood. An accurate, timely diagnosis can be the linchpin for a long and healthy life, yet the search for a diagnosis often takes 5-7 years.
In 2018, Takeda, Microsoft and EURORDIS-Rare Diseases Europe launched the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease (the GC) – a multidisciplinary group of advocates, researchers, physicians and technologists. In 2019, the group issued a report outlining major barriers and opportunities to accelerate rare disease diagnosis. The GC is now working towards 3 goals over the next 5 years: Foster global collaboration to speed up time to diagnosis; Develop new standards of practice for diagnosing rare diseases, leveraging advances in technology and genetics; Support an ecosystem that engages families and healthcare providers to accelerate diagnosis.
The GC has made great progress by supporting pilot projects:

- Machine learning to recognize symptom patterns: Foundation 29 in Spain is developing a tool that leverages AI to identify and connect rare disease symptoms and support referrals for diagnostic testing. The platform has engaged 400 physicians and initial research has found that performance evaluation correctly predicted 79% of cases based on a cohort of previously diagnosed patients.
- Intelligent Triage Tool: Children's National Hospital in Washington, DC, is piloting innovative tools to re-think the genetic consultation. The pilot includes a Rare Disease Opinion app that leverages virtual communication tools allowing pediatricians to submit a referral to a specialist electronically to increase access to genetic consultation and to reduce the time/cost burden to patients for in-person consultations.
- Tools to empower "questioning" families: The GC is piloting a campaign to increase awareness of rare disease as a consideration among families searching for a diagnosis for their child. In partnership with medical experts and patient organizations, the campaign will provide personalized tools, resources and guides to help facilitate informed discussions with PCPs. The campaign is set to launch in San Diego, CA in early 2021.

NEXT-GENERATION PHENOTYPING USING DEEPGESTALT IN CLINIC, RESEARCH AND VARIANT ANALYSIS

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

P. Krawitz, FDNA, USA

Artificial intelligence and facial analysis technologies have recently surpassed the capabilities of expert clinicians in syndromic phenotypes identification. To date, these technologies could only identify phenotypes of a few diseases, limiting their role in clinical settings, where hundreds of diagnoses must be considered.

DeepGestalt, using computer vision and deep learning algorithms to highlight numerous genetic syndromes correlating with patients phenotypes analyzed from unconstrained 2D images, achieves 91% top-10-accuracy in identifying over 200 different genetic syndromes and has outperformed clinical experts in three separate experiments.

We suggest that this form of artificial intelligence is ready to support genetics in clinic, research and variant analysis practices and will play a key role in the future of precision medicine.

In this talk I will review DeepGestalt and will demonstrate its use in each aspect.

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DIAGNOSTIC-OMICS: WHAT'S NEW IN 2021?

DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

Clara van Karnebeek, Radboud University Medical Center, Nijmegen, The Netherlands and Amsterdam University Medical Centers, Amsterdam, The Netherlands

The era of high-throughput technologies and expanding bioinformatics capacity promises to accelerate the scale of P4 medicine (preventive, predictive, personalized, and participatory) for rare disease patients dramatically. Genomics, transcriptomics, epigenomics, proteomics, glycomics, metabolomics, and lipidomics offer an amazing opportunity for holistic investigation and contextual pathophysiologic understanding of rare genetic diseases for precise diagnosis and tailored treatment. While each of the -omics technologies is important to systems biology, some are more mature than others. Exome sequencing has emerged as a reimbursed test in many but not all clinics around the world, and untargeted metabolomics can serve as a single biochemical testing platform. The challenge lies in the integration and cautious interpretation of these big data, with translation into clinically meaningful information and/or action for our patients. A daunting but exciting task for rare diseases professionals; I will provide clinical cases to illustrate the importance of a close connection between physicians, laboratory experts and researchers in the basic, computer, and clinical sciences. Open collaborations, data sharing, functional assays, and model organisms are key in the validation of -omics discoveries. Having all the right expertise at the table when discussing the diagnostic approach and individualized management plan according to the information yielded by -omics investigations (e.g., actionable mutations, novel therapeutic interventions), is the stepping stone of P4 medicine. Patient participation and the adjustment of the medical team's plan to his/her and the family's wishes most certainly is the capstone. Let's go for it together in 2021!

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BEYOND "ONE DISEASE AT A TIME" SO NO DISEASE IS LEFT BEHIND: PLATFORM APPROACHES TO CLINICAL TRIALS IN RARE DISEASES

MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

P.J. Brooks, ORDR, NCATS, NIH

At the current rate of translation in the rare disease space, it will take about a thousand years to achieve an approved treatment for all rare diseases. Therefore, there is clearly a need for fundamentally different approaches to the problem. In this presentation, I will focus on some possible approaches. First, while there are thousands of rare genetic diseases, the number of underlying diseases etiologies is much smaller, and many of these are therapeutically actionable. For monogenetic diseases, the major etiologies are premature stop codons, misfolded proteins, abnormal splicing, and dominant (gain of function mutations). Corresponding potential therapeutic approaches for these etiologies are stop codon readthrough compounds, proteastasis pathway modulators, splice modifying oligonucleotides, and siRNAs. As proposed previously (Brooks, Tagle, and Groft, Nature Biotechnology 2014, PMC4548299), a more efficient approach to clinical trial design would be to enroll patients into trials on the basis of underlying disease etiology rather than traditionally defined disease. Such an approach would have the advantage of providing access to clinical trials to patients with diseases that are so rare that disease specific clinical trials are highly unlikely. Importantly, this basket trial approach (e.g. N Engl J Med 2018; 378:731-739) is now the state of the art in oncology, and has resulted in regulatory approvals (https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0). Gene therapy and gene editing are also inherently platform approaches of direct relevance to rare diseases. I will also discuss ongoing NIH efforts on gene therapy and gene editing.

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PRECISION DIAGNOSTICS OF RARE DISEASES AT THE GENOMIC MEDICINE CENTER KAROLINSKA

MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Anna Wedell, MD, PhD, Professor, Department of Molecular Medicine and Surgery, Science for Life Laboratory, Karolinska Institutet and Centre for Inherited Metabolic Diseases, Genomic Medicine Center Karolinska, Karolinska University Hospital

Science for Life Laboratory (SciLifeLab) is a Swedish national center for large-scale molecular biosciences with focus on health and environmental research, a joint effort between Karolinska Institutet, the Royal Institute of Technology (KTH), Stockholm University and Uppsala University. Through a close collaboration with the Karolinska University Hospital, a facility for Clinical Genomics was established in Stockholm in 2013 and tools have been developed allowing rapid, quality assured, comprehensive clinical whole genome sequencing. This includes a bioinformatics pipeline which produces ranked candidate lists of potential disease causing variants (MIP), a visualization, analysis and data sharing tool (Scout), and a tool for calculation and presentation of coverage (Chanjo), ensuring continuous quality assessment. HPO terms are being included in the system, to further facilitate systematic analyses and collaborative efforts. The concept is being spread within the hospital and a collaborative community has been established, where multidisciplinary teams focusing on different disease groups collaborate and share genome data, evaluate findings in the context of biochemical and clinical data, and translate the results all the way to individualized care. This unique concept forms the basis of the Genomic Medicine Center Karolinska (GMCK) that was established in 2017. More than 6000 rare disease samples have to date been analyzed. Average turnaround times are 10-12 days, in selected cases this can be shortened allowing rapid diagnosis even in acute situations. Within the area of metabolic medicine, around 1240 patients have been analyzed, with a diagnostic rate of 36% representing 283 different disease genes, illustrating a striking heterogeneity. A dozen novel diseases have been discovered, and mechanistic studies have opened novel possibilities for treatment. Taken together, the results are dramatically improving our possibilities to prevent severe handicaps and early death.

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INDIVIDUALIZED RESEARCH PROGRAM, SUSTAINABLE APPROACH THROUGH DRUG REPURPOSING

MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Terence Beghyn, CEO Apteeus, France

Precision medicine, which is booming in the field of cancerology, is an approach that must be fully explored in the field of rare genetic diseases. Indeed, genetic mutations make each patient a unique case. It is not easy to take into account the individuality of each patient in drug research programs, even less when there too few patients for the approach to be sustainable. Apteeus is integrating those constraints in its research programs.
We allow individuals to search for their own treatment amongst the world drug directory. We are screening two thousand molecules approved for a human use directly on primary cells which phenotype is relevant of the pathology and we explore the opportunities for drug repositioning. Apteeus has already initiated several compassionate uses of drugs and intend to develop its first drug candidate for a broad impact on the community of rare patients.
We will present a full program that has resulted in a personalized treatment.

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HYALINE FIBROMATOSIS SYNDROME: HOW THE STUDY OF INDIVIDUAL PATIENT MUTATIONS DRIVES THE MOLECULAR UNDERSTANDING OF THE DISEASE

MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

F. G. van der Goot, Global Health Institute, School of Life Sciences, EPFL, Lausanne, Switzerland

Hyaline Fibromatosis Syndrome (HFS; OMIM #228600) is a monogenic genetic disease caused by mutations in the gene encoding anthrax toxin receptor 2 (ANTXR2), also known as Capillary Morphogenesis Gene 2 (CMG2). It is a severe, often fatal, autosomal recessive disorder. The hallmark of the disease is an augmented connective tissue, particularly of the skin and periarticular tissues, followed by the relentless formation of large extracellular matrix (ECM)-containing subcutaneous nodules. We recently found that CMG2, which is a transmembrane surface protein, is a receptor for the extracellular matrix protein collagen VI. So far 40 different patient mutations have been identified. We have performed an in depth molecular analysis of each that allowed to classify them into 4 categories, which have clear therapeutic implications. Our recent analysis of a group of mutations that map to an exon encoding a cytoplasmic region of the protein have allowed an exquisite molecular dissection of the signaling that CMG2 mediates and which is impaired in patients, providing unprecedented understanding of the disease mechanism.

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LEARNING FROM NATURAL HISTORY PATIENT DATA TO DRIVE SMALLER, FASTER, TRIALS – A CASE STUDY IN DUCHENNE MUSCULAR DYSTROPHY (DMD)

MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

Susan J Ward, cTAP, USA
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As in many rare disorders, longitudinal heterogeneity in disease progression in patients with DMD leads to in high variance in clinical trials, confounding results and resulting in an unacceptably high rate of statistical failures. Regulators urge drug companies to repeat failed placebo-controlled clinical trials with yet larger studies, while patient advocates champion replacing placebo-controlled trials with single arm studies using natural history (NH) or real world data (RWD) as an external control. For 'precision' drugs in particular, where patient numbers are even smaller, the need to solve the problems arising from heterogeneity in disease progression is paramount.

The collaborative Trajectory Analysis Project (cTAP) is an innovative, multi-stakeholder platform formed in 2015 to find statistical solutions to heterogeneity-driven issues, thereby enabling "smarter" clinical trials that yield clear, unambiguous understanding of the efficacy of a new therapy.

When using NH/RWD as an external control, the potential for bias (between patients in trials vs those under routine care) is real, especially in situations, as in DMD, where clinical outcome measures are somewhat subjective, or when standards of care are evolving rapidly.

Through collaborative studies conducted by cTAP, this presentation will demonstrate that minimum requirements to reassure oneself that the apparent efficacy of a treatment in an externally-controlled trial is 'real' can be met, even in the face of high heterogeneity of disease progression. Thus, we have i) demonstrated that functional progression in NH/RWE is consistent with that seen in placebo, ii) identified prognostic factors that predict trajectory of functional progression, and iii) shown these prognostic factors are consistent across data sources.

Moreover, these tools enable adjustment for any observed imbalances at baseline between drug-treated and placebo arms, and provide the basis for confident matching of patients in a drug treated arm to NH/RWE control.

A similar approach is being used to build evidence to support pan-genotypic controls for precision drugs (studies ongoing).

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CHALLENGES AND CONSIDERATIONS IN THE REGULATION OF GENE AND CELL THERAPIES

ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

Joseph Scheeren Pharm.D., President and CEO Critical Path Institute

The field of gene and cell therapy have advanced rapidly over the last decade, offering great potential benefits to patients and their caregivers. The paradigm shift from preventions and treatments to cures is in motion. This is particularly true in the area of rare and orphan diseases, where early clinical trials have indicated promising results with innovative gene and cell therapies and even some early approvals. Submissions for these therapies are expected to grow substantially as the field continues to mature. With these scientific successes, however, come regulatory challenges around approval, manufacturing, safety, long-term safety, and efficacy and monitoring. These challenges necessitate innovative new approaches in how therapies are developed and approved. One of the critical topics for the development of new therapies is an optimized characterization of diseases and understanding of their progression. C-Path, together with NORD, has recently initiated the Rare Disease Cures Accelerator Data Analytics Platform (RDCA-DAP), with funding from the FDA. This project is an example of how intelligent data curation, sharing, and analysis can accelerate and de-risk the development and approval of these therapies and help regulators to provide safe, effective treatment. In the talk we will provide a historical perspective, review the development challenges and give an overview of the RDCA-DAP initiative with the need of data accessibility and transparency to support patients in need.

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HEMATOPOIETIC STEM CELL GENE THERAPY FOR MONOGENIC DISEASES: FROM EXPERIMENTAL STUDIES TO APPROVED DRUGS"

ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

Alessandro Aiuti, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy

Abstract has not been provided

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IMMUNOLOGICAL CHALLENGES IN GENE AND CELL THERAPY

ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

Volk HD, Reinke P, Wendering DJ, Amini L, Jülke K, Akyuz L, Wagner DL, Schmück-Henneresse M. BIH Center for Regenerative therapies (BCRT), Berlin Center for Advanced Therapies (BeCAT), Charité-Universitätsmedizin Berlin, D-13353 Berlin, Germany

Immunotherapies are used either to reshape undesired immune reactions (to support endogenous regeneration and engraftment of biological replacement therapies), or to reconstitute the protective immune response to cancer and severe infections. Adoptive T cell therapy is a promising option with curative potency for these approaches. Despite promising first clinical data and first products launched at the market, we have to face several challenges. New gene editing technologies allow molecular "tuning" of our T cell products to increase safety but most importantly sustainable efficacy. Some approaches and challenges will be discussed:

1. Enhancement of migration, activation and fitness of protective T cells, particularly to solid cancer and severe infections to reach sustainable therapeutic effects in almost all patients There are three major hurdles to fight sufficiently solid tumors: i) efficient migration to the tumor/site of infection, ii) adequate intra-tissue activation of the effector T cells, and iii) prevention of T cell exhaustion. Clinical trials testing anti-cancer T cells resistant to checkpoint molecules (e.g. PD-1) by gene editing is ongoing. We present here another novel method to enhance intra-tissue migration and activation and to use less differentiated T cells naturally resistant to checkpoint inhibition.
2. Stabilization of immunomodulatory potency of regulatory T cells to reshape undesired immunity. First-in-Human studies of 1st-generation Treg cell products particularly in hematopoetic stem cell and solid organ transplant patients showed high safety and hints for efficacy (partial weaning of immunosuppression feasible). Based on these data, next generation Treg therapy approaches (modified manufacturing, support of engraftment) are in preparation. The concept of the Reshape consortium (horizon 20202) and first data will be presented.
3. One challenge of gene and cell therapy approaches is the immunogenicity of vectors or transgenes but also of the CRISPR/Cas system. We show data on preformed cell-mediated immunity and solutions to overcome this problem. Finally, the need for a European large-scale initiative for boostering progress in this area is discussed and the RESTORE concept (restore-horizon.eu) is presented.

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GENE THERAPY FOR HUNTINGTON'S DISEASE AND SPINOCEREBELLAR ATAXIAS: FROM PRECLINICAL PROOFS OF CONCEPT TO FIRST PHASE 1 CLINICAL TRIAL

ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

Nathalie Cartier-Lacave, NeuroGenCell, Institute of Brain and Spine (ICM), Hôpital Pitié-Salpêtrière, Paris

Brain cholesterol homeostasis defects in the adult brain are closely linked to neurodegenerative diseases, such as Niemann-Pick C, Alzheimer and Huntington's diseases (HD). In HD, cholesterol homeostasis defects involve a general perturbation in the expression of cholesterol biosynthesis enzymes. 24S-hydroxycholesterol (24OH-Chol), the catabolite of cholesterol metabolism, is decreased in HD patients plasma. CYP46A1, the rate-limiting enzyme, which catalyzes the production of 24OH-Chol in neuronal cells, is decreased in the striatum of HD patients and HD mice models (1). CYP46A1 plays major roles in activating brain cholesterol turnover and is a key stress response factor in neurons. Restoring CYP46A1 expression in vivo by adeno-virus-mediated (AAV-CYP46A1) delivery in the striatum of two HD mouse models (R6/2 and ZQ175) resulted in significant improvement in motor behavior associated with decreased huntingtin-positive aggregates, restored key neuronal functions and connectivity and induced neuroprotection (1, 2). Based on these results we extended our proofs of concepts to other rare polyQ diseases, Spinocerebellar Ataxias (Machado Joseph disease) (3). We propose a first phase I/II clinical application to evaluate the efficacy and safety of a single administration of AAV-CYP46A1 in the striatum of Huntington patients at an early stage of disease progression . 1 Boussicault et al, Brain 2016 2 Kacher et al, Brain 2019 3 Nobrega et al, Acta Neuropathologica 2019.

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ENGAGING PATIENTS: THE EUROCAB PROGRAMME

PATIENT ENGAGEMENT IN DRUG DEVELOPMENT AND CLINICAL TRIAL

François Houyez, Rob Camp, Eurordis

Introduction When developing a health technology that requires clinical studies, developers institute working relations with clinical investigators. In certain diseases areas, patients' representatives create their own advisory boards, which proved their utility in the early 90s, in particular for the development of products to treat HIV infection. Inspired by this model, where patients with a same disease join and meet with relevant developers and discuss all aspects of the research, the European Organisation for Rare Diseases (EURORDIS) proposes a new programme of such Community Advisory Boards for Rare Diseases (CAB). Methods For this programme, EURORDIS invites developers to sign a Charter of principles when engaging with patients, and provides guidelines on CABs, together with a mentoring programme for patients' networks that are less experienced with the development and the evaluation of health technologies. CABs are driven by patients who set their agenda, who sign a Memorandum of Understanding with each developer, and who organise the sessions. Sessions typically last for two to four days during which different meetings with different developers can take place, or trainings. All meetings can take place under confidentiality arrangements, and minutes are written to keep track and to follow-up with all points discussed. Participants and agendas are made public Results As of 2019, five CABs exist and operate (for tuberous sclerosis complex, for scleroderma, for cystic fibrosis, for Duchenne muscular dystrophy, for lymphomas) and 16 others are in discussion with many due to start in 2019-20. Topics discussed cover the target population, the study feasibility, the endpoints including patient reported outcomes, the comparator choice and/or the acceptance of a placebo controlled trial, the quality of life, the practical aspects of the trials, and the identification of previously unknown or unmet patient needs/preferences. For products which are more advanced in their life-cycle, discussions can also cover compassionate use, pricing policy, relative efficacy etc. Conclusions This represents a well-structured programme for the engagement of patients, where collective thinking and exchange between different patients ensure high quality dialogue with developers and can inform regulators and HTA also.

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25 YEARS OF DUCHENNE PATIENT ADVOCACY: BETWEEN HYPE AND HOPE

PATIENT ENGAGEMENT IN DRUG DEVELOPMENT AND CLINICAL TRIAL

D. ATHANASIOU, WORLD DUCHENNE ORGANIZATION / UPPMD, MDA HELLAS, EPF

Duchenne Muscular Dystrophy was first described by the French neurologist Guillaume Benjamin Amand Duchenne in the 1860s, but until the 1980s, little was known about the cause of any kind of muscular dystrophy. Mostly driven by parents of Duchenne boys, at end of the 1950s the first NMD Patient Organizations were founded both in Europe and US and started to fund small research projects and improve care. By the 1980s Duchenne and Becker Patient Organizations have been created all over the world, starting small mostly to ease the life of boys with Duchenne and promote awareness of rare diseases. Mid 2000s they have evolved to a vibrant global network of advocacy groups that shaped a lot of the rare disease advocacy into the new millennium, changing the why that the other stakeholders view, interact and work not only with the Duchenne Community but with the rare community overall globally. At the dawn of 2020, the Duchenne Community is not any more the grassroots collective of desperate parents that were trying to save their children. Although it keeps its strong drive, can-do mentality and passion it more closely resembles a well-oiled advocacy machine that finances and shapes medical innovation and ATMs, co designs and influences Regulation and Policy in a global level. The DMD community is operating on a global level funding more than 80 million Euros per year in various levels from basic Research to Care like: Disease Prognostic Models Preclinical research support In Silico Development A.I. and Machine learning Animal models Virus Development ATM research like Gene and Cell Therapies, Gene editing and Exon skipping technologies Biotech and Spin-off seed funding Regulatory Guidelines for DMD Developers Clinical Trails Simulation Tools development Duchenne Platform Trials development New outcome measures development PROMs and PROs development and validation Care Guidelines development HTA and Reimbursement Models development Exoskeletons and Supportive Digital Applications Still this did not happen in the vacuum, the pathway is marked with many success and failures. The boys live longer, have a better a life but still lose the fight with Duchenne. With the active support and investment of the Duchenne Community, Clinical Trials have been increased exponentially offering hope to the families. Balancing between Hype and Hope the community still fights to keep the boys alive while keeping the Rare Disease in the centre of R&D and Regulatory discussions.

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HOW PATIENTS CAN LEAD DRUG DEVELOPMENT: THE CASE OF THE AKU SOCIETY

PATIENT ENGAGEMENT IN DRUG DEVELOPMENT AND CLINICAL TRIAL

N. Sireau, AKU Society, UK

In 1902, Sir Archibald Garrod described alkaptonuria as inherited for the first time. For the following hundred years, there was no research into a treatment for this life-changing disease that affects 1 in 250,000 people worldwide. The AKU Society was founded in 2003 to find one. In 2012 the AKU Society founded a pan-European consortium, called DevelopAKUre. This was made up of 12 members including hospitals, a pharmaceutical company, universities, biotechs and national AKU patient groups from all over Europe. They shared one aim: to prove that a repurposed drug called nitisinone works in reducing the acid that causes the symptoms of AKU. Together, DevelopAKUre applied for funding through the European Commission's Seventh Framework Programme (FP7) in order to develop and run the trials. The funding secured for this programme included €6 million from the European Commission, with an additional €4 million in co-financing (for in-kind costs such as the drug supply). Armed with this funding, the consortium launched three studies into the efficacy and safety of the drug. The last one, SONIA 2 (Suitability of Nitisinone in Alkaptonuria 2) was a phase 3 study. It finished in January last year and data released to the consortium at the end of 2019 showed that it had been successful. Sobi, the pharmaceutical company that owns the rights to nitisinone, will now apply for a license for the drug's use to treat AKU across Europe. This is the first time an effective treatment for AKU has been found. Nitisinone has now been proven to reduce the acid that causes the symptoms of AKU by up to 99%. If given early enough, the drug could prevent the symptoms from developing at all.

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TOWARDS A SUSTAINABLE PATIENT ENGAGEMENT ECOSYSTEM

PATIENT ENGAGEMENT IN DRUG DEVELOPMENT AND CLINICAL TRIAL

N. Bedlington, European Patients Forum, Belgium

Nicola Bedlington is co-lead of the IMI project PARADIGM, The European Patient Academy on Therapeutic Innovation (EUPATI) and a board member of Patient Focused Medicines Development (PFMD) . These are all European/ global initiatives driving forward patient education and patient engagement in therapeutic innovation. In her presentation she will introduce these briefly and outline the impact they are making together. She will describe the three pillars of sustainable patient engagement: culture change; agreed processes; and resources. Culture change requires trust and a true sense of the 'return 'on engagement to ensure buy-in from all stakeholders. Tried and tested processes that are co-created by all the players across the life cycle are also key. The third pillar – resources – is also crucial – to invest in capacity building, and in ensuring patient organisations are seen as equal partners and can play their unique role. Nicola will then explore patient engagement beyond therapies; to digital and medtech, systems and social innovation and exciting developments in this arena.

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ACCESS TO DIAGNOSTICS AND MEDICINES FOR ALL: TAKING ACTION – IF WE DON'T, WHO WILL?

ACCESS TO DIAGNOSTIC AND DRUGS FOR ALL

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Today, more than 350 million people are estimated to be impacted by rare diseases, accounting for around 5% of the world's population. Some 7,000 rare diseases have been identified, however, only 5% of the diseases have a licensed treatment. Significant progress has been achieved to broaden access to medicines in rare diseases, while mobilizing for the UN2030 Agenda and Sustainable Development Goals. However, there is still a high unmet need for rare disease diagnostics and access to medicines, even more so in low- and middle-income countries. The challenges are complex and relate to awareness, availability, and affordability – on a health system level as well as on an individual patient level. Overall, this results in delayed diagnosis of rare diseases – much beyond the 5-7 years' time to diagnosis we observe in the established countries. Until today we have seen many good attempts of actors across the sectors to drive change – to advance policy as well as to broaden access. For example, at Takeda we established a Charitable Access Program for Lysosomal Disease Orders including Gaucher and Fabry diseases as well as MPSII. This program provides access to medicines in low – and middle-income countries, complemented by capacity building initiatives across the entire patient journey to strengthen diagnosis, treatment and general standards of care. In our program, we address many of the access barriers across the 14 countries we are active in. Even with a comprehensive program that strengthens health systems and supports individual patients, we fall short in addressing the treatment gap in rare diseases in low- and middle-income countries effectively. It is a good and necessary evolution to move towards multi-partner initiatives across the rare disease community to tap into potential synergies and coordinate our efforts for highest impact. Our collective experience and the complex access challenge in rare diseases, calls for action. We need to explore new inclusive and sustainable models that gather a variety of actors, e.g. in a global consortium, to elevate the debate and drive access to rare diseases with tangible impact in the countries that need our help most.

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ACCESS TO DIAGNOSTICS AND DRUGS FOR ALL IN THE AFRICAN CONTEXT

ACCESS TO DIAGNOSTIC AND DRUGS FOR ALL

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African healthcare systems face severe challenges which negatively impact on access to affordable quality healthcare and lead to morbidity and mortality from eminently treatable conditions . The challenges are complex and include a disproportionately high infectious disease burden, a growing chronic disease burden, a shortage of the requisite human resources and the necessary infrastructure to deliver healthcare services, as well as significant funding and budgetary constraints . To address these, the African Union Commission developed the Africa Health Strategy . Furthermore, African Union Heads of State and Government in 2013 , recognized the urgent need to put in place a Specialized Agency to support Member States in their efforts to strengthen health systems. The Commission was requested to work out the modalities of establishing the Africa Centres for Disease Control and Prevention (Africa CDC). Subsequently, Africa CDC was established and officially launched in January 2017. The Heads of State and Government also adopted the treaty for the establishment of the African Medicine Agency (AMA) in 2019 to regulate the access to safe, effective, good quality and affordable essential medicines and health technologies. Africa's health agenda cannot be achieved without creating sustainable access to diagnostics and drugs. The WHO prequalification of products is a very important process for maintaining quality of laboratory diagnostics and their performance and provides guidance to countries in selecting laboratory diagnostics to be implemented. However, local context and reality must be factored in and for many diseases prioritized for health security agenda in Africa, laboratory diagnostics are either absent or are not WHO prequalified. Cognizant of these Africa CDC and partners launched the Africa Collaborative to Advance Diagnostics (AFCAD) in 2018 aiming to promote and advocate for increased access to and manufacturing of diagnostics in Africa. Under this initiative, Africa Union recognized the strategic importance of a healthcare sector that promotes access to and uptake of affordable quality essential diagnostics and the need for manufacturing in Africa.

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ACCESS TO RARE DISEASE DRUGS IN EMERGING HEALTH SYSTEMS: PATHWAY FOR ACCESS TO DIAGNOSIS, TREATMENT, CARE AND PATIENT EMPOWERMENT

ACCESS TO DIAGNOSTIC AND DRUGS FOR ALL

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Regardless of the sophistication of the healthcare environment, access to and the effective use of rare disease drugs are predicated on appropriate diagnosis of rare conditions, access to expert clinical care, drug management and support programs, including administrative and infrastructure support, monitoring and following programs, and research support. While these are challenges for access across all conditions, rare and non-rare, the issues are more difficult to address when the patient populations are very small, accurate diagnosis may be complex, limited, and complex, expertise and centers of care are in very short supply and usually not found in low-and-middle-income countries, and health system infrastructure for rare conditions mostly non-existent. Global Access Initiatives provide important lessons as to "what works well and not so well" across diseases and economies. Examples include:

1. Compassionate Access (Max Foundation and cancer drugs)
2. Medicine Redistribution (Blood products through World Federation of Hemophilia)
3. Government purchase (Chelation therapy in Asia Pacific) Diagnostic (Newborn Screening) testing programs in emerging healthcare systems may be tied to availability of therapeutic options. Examples include the NBS programs in Asia Pacific and Latin American countries. Specific examples are the NBS programs for metabolic disorders in Taiwan and Thailand. Across emerging and developed healthcare systems, the case for diagnostic testing for spinal muscular atrophy is tied to availability of new drug therapies. Several global initiatives that may be leveraged to increase rare disease programming, including diagnosis, centers of care and treatment and access to medicine are: • United Nations Declaration for Universal Healthcare which specifically references need to include rare diseases • WHO-Rare Disease International Memorandum of Understanding with specific objectives of definition (awareness), centres of excellence and registries • Asia Pacific Economic Cooperation (APEC) Rare Disease Framework.

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GLOBAL ACCESS TO RARE DISEASE DIAGNOSTICS AND TREATMENT

ACCESS TO DIAGNOSTIC AND DRUGS FOR ALL

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In 2008, the National Institutes of Health (NIH) established the Undiagnosed Diseases Program (UDP). Its goals were to help undiagnosed rare disease patients finally reach an accurate diagnosis, and to make new discoveries about medicine, biochemistry, and cell biology. In 2013, the success of the UDP prompted NIH funding of the Undiagnosed Diseases Network (UDN), a consortium of clinical UDP sites and supporting cores at medical centers throughout the United States. In 2014, the UDN and UDP expanded to establish the Undiagnosed Diseases Network International (UDNI), which has held 8 conferences throughout the world and which is dedicated to data sharing, rare disease diagnosis, and new disease discovery. A goal of the UDNI is to help provide diagnoses for desperate patients more broadly. The UDP, UDN, and UDNI are heavily engaged with patient advocacy groups. Diagnosis, however, does not always translate to therapy, and treatments often remain unavailable for rare disease patients, especially in low-and-middle-income countries. Reasons for this include lack of financial support for therapies and onerous regulatory requirements for approval of drugs. Other barriers include lack of reimbursement, administrative infrastructure, and knowledge about diagnosis and drug treatment options. One goal of the International Rare Disease Research Consortium (IRDiRC) is to "leave no one behind", meaning that access to treatments should be made available for all rare disease patients. Hence, IRDiRC has approved the establishment of a Working Group on Rare Disease Treatment Access. Initially, the Working Group will create a list of standard-of-care products for rare diseases and make the list available to countries throughout the world. The list will be updated periodically. At the same time, the Working Group will begin to identify the barriers to accessing rare disease drugs, particularly in low-and-middle income populations. The treatment list will be circulated for endorsement by major health organizations.

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THE ECONOMICS OF RARE DISEASE: VALUE ASSESSMENT CHALLENGES, EVIDENCE CONSIDERATIONS, AND SPECIAL-CASE STATUS

METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSTICS AND THERAPIES IN RD PATIENTS

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The development of diagnostic and treatment innovations for rare diseases is seeing unprecedented growth, due in no small part to government incentives provided to companies to encourage their development. Regulators worldwide have sped these innovations to market, but there remain challenges in how health technology assessment organizations and payers should consider very limited clinical evidence at the time of approval. These evidentiary concerns translate into potential problems in how to assess the economic value brought by rare-disease treatments given their typically high price, often in the hundreds of thousands of dollars per year, and the prospect for new diagnostic tools to broaden the candidate population for intervention. In addition to evidence, health systems struggle with the ethical justification of relaxing evidence and cost-effectiveness standards for rare-disease treatments, given the potential for sacrificing overall population health. This presentation will describe the landscape for evidence synthesis, economic evaluation, and creation of special considerations for rare-disease interventions worldwide, and consider possible paths forward for encouraging further innovation in an affordable and sustainable fashion.

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PATIENT-CENTRIC DIGITAL TECHNOLOGY TO DEFINE DISEASE PROGRESSION AND RESPONSE TO THERAPY: A MODEL THAT ALSO SUPPORTS A DE-CENTRALIZED APPROACH FOR CLINICAL TRIALS IN RARE DISEASES

METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSTICS AND THERAPIES IN RD PATIENTS

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Symptomatic presentation of rare diseases is often variable and changes over time as the disease progresses. Assessments of disease progression and therapeutic response therefore requires a standardized means to capture patient-generated data reliably, easily and over time in order to best assess outcomes measures. Importantly, outcomes also should align with the patient's perception and understanding of their disease in order to best test therapies and to optimize their use in the clinic.

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DELEGATES' ABSTRACTS

ZEBRAS OR HORSES? - HOW COMMON ARE RARE DISEASES ON A MEDICAL SYMPTOM CHECKER, ADA?

ABSTRACT N° C001_2020 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Statement of purpose: One reason rare diseases are underdiagnosed is lack of awareness and systematic questioning to rule out more common conditions. One digital tool that people turn to is Ada, a conversational text-based app that uses AI with a database of doctor-curated medical knowledge to alert people to the possibility of diseases (including rare diseases) based on a constellation of user-reported symptoms and health factors.. We sought to understand what proportion of conditions suggested to our users were "rare" under the common European definition of <1 / 2,000. Methods: Exploration of online health app database Results: Ada has more than 8 million users who have completed over 15 million assessments. Rare conditions were suggested as the number 1 conditions in 4% of assessments and were among the top 5 suggestions in 17% of assessments. The most frequent suggestions were infectious diseases (e.g. shigella), followed by rheumatological conditions (e.g. systemic lupus erythematosus), and endocrine conditions (e.g. Cushing syndrome). A subset of the estimated 7,000-10,000 rare diseases have so far been coded in our medical knowledge database, including those coded in response to user feedback. Conclusion: As people increasingly use digital tools to understand their symptoms and support clinical decisions there is much potential for a tool such as Ada to support, and potentially shorten the diagnostic odyssey of people suffering from rare diseases. Those with a rare or complex journey may be more predisposed to searching for support through such tools as they encounter long waits and being passed between multiple medical professionals. This would be in line with our finding that rare diseases feature relatively frequently as suggestions given by Ada, though in line with epidemiological studies suggesting that some 2-4% of the general population live with a rare disease. There is potential to positively influence the diagnostic odyssey for patients through signposting to appropriate care pathways in line with national guidance on standards of care. Future work should therefore increase the breadth of rare diseases coded, improve understanding of the impact on referral pathways, and further validate the sensitivity and specificity of these tools.

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WHOLE GENOME SEQUENCING IN ROUTINE DIAGNOSTICS OF RETINAL DISEASES

ABSTRACT N° C002_2020 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Purpose: Exome sequencing has evolved to a highly precise diagnostic tool and significantly improved the diagnostic yield and our understanding of the genetic bases of rare diseases. However, a significant portion of likely genetically determined cases remains unresolved, indicating that extended and more sensitive approaches are required. Towards this end we tested the feasibility and efficacy of deep whole genome sequencing (WGS, 42x coverage) in a clinical routine diagnostic setting. Methods: Within one year, we performed genome sequencing on 417 index cases with different retinal disorders. In addition to standard SNVs and indel analysis we implemented the detection of structural and copy number variations from WGS data and optimized their visualization and clinical interpretation by our clinical decision support system. Results: So far, we have fully analyzed 308 out of 417 collected cases. In n=223 cases (72 %) we established a firm (n=155) or likely (n=68) diagnosis. Among the clearly pathogenic changes (class 4 or 5), 20 % were in regions that are not targeted by exome sequencing including changes in the 5'UTR (n=1), introns and intergenic regions (n=8) as well as locus control regions (n=1). Furthermore, we identified 18 index cases with disease-causal deletions or duplications as well as causal inversions combined with complex rearrangements in an additional 2 cases. Conclusion: Routine application of whole genome sequencing has the potential to narrow the diagnostic gap and diagnose a significant number of affected individuals with genetic defects that are otherwise missed in current exome sequencing approaches. Implementation of the required infrastructure and functionality of appropriate decision support systems and databases for clinical data interpretation is challenging and requires large numbers of sequenced individuals. Additional layers of information derived from e.g. RNAseq might be necessary for comprehensive interpretation of all identified genetic variation such as deep-intronic variants affecting splicing.

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ANALYZING THE MITOCHONDRIAL GENOME OF OVER 7000 CASES USING CLINICAL GRADE MTDNA SEQUENCING

ABSTRACT N° C003_2020/ DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Mitochondrial diseases are heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. The circular 16.5-kb mitochondrial genome (mtDNA) contains 37 genes, which are essential for normal mitochondrial function. Cells contain multiple copies of mitochondria and mutated mtDNA may coexists with wild type mtDNA, phenomenon called heteroplasmy, which is important in considering the severity of mitochondrial diseases. Thus, reliable and sensitive mtDNA analysis is crucial for accurate diagnostics of mitochondrial disease. We developed a highly sensitive and clinically validated mtDNA assay based on hybridization-based capture of mtDNA and next-generation sequencing (NGS) that is able to detect very low heteroplasmy levels of SNVs, INDELs and deletions. Sequence homology of NUMT "nuclear mitochondrial DNA" segments, may interfere the sequence alignment and impact sensitivity. To distinguish a mitochondrial signal from nuclear signal, a sample from cells devoid of endogenous mitochondria was used. Furthermore, we developed mitochondrial quality score (MQS) that allows to control possible low level heteroplasmy (<10%) false positives raising from NUMT segments. The mean read depth for the mitochondrial genome was 18 224x, and 100% of base pairs were covered at least 1000x. Sensitivity to detect SNVs and INDELs with over 10% heteroplasmy was 100%. For SNVs with 5-10% and <5% heteroplasmy levels the sensitivity was 93.3% and 88.9%, respectively. Detection of single large and multiple low heteroplasmy deletions (mitochondrial DNA deletion syndrome) is central for mitochondrial disease diagnostics. To call these deletions a combination of coverage and breakpoint based analyses was used. Our sensitivity to detect simulated 500bp - 5kb deletions all the way down to 10% heteroplasmy level was 99.7%. In addition, five out of five mitochondrial DNA deletion syndrome samples that harbor different deletion loads were detected. We analysed mtDNA variants from over 7000 cases. In total 188330 variants were called, of which 157702 where defining haplogroups and 20194 other polymorphies, leaving 10434 heteroplasmic variants (1,47 variants per case on average). In 62 cases an established pathogenic variant was detected (at any heteroplasmy level). Not surprisingly, the most common recurrent variants in this study set were the m.3243A>G underlying MELAS (26) and m.1555A>G associated with aminoglycoside induced hearing loss (15).

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A DE NOVO FAIRIFICATION PROCESS FOR RARE DISEASE REGISTRIES

ABSTRACT N° C004_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Due to the low prevalence of Rare Diseases (RD), research on RD would benefit from cross-database analyses. It is, however, difficult to connect RD registries as they are mostly not interoperable. Initiatives such as implementing the FAIR data principles improve semantic data interoperability and enable machine-readable rich metadata annotations. This way, connecting data from registries to analyze genotype-phenotype relationships and perform natural history studies becomes simple. Different methods to implement the FAIR principles exist. Envisioning sustainability, we aimed to develop and apply a de novo FAIRification process to the Registry of Vascular Anomalies (VASCA), a Vascular Anomalies European Reference Network (VASCERN) member.
The process consists of five phases: 1) pre-FAIRification, 2) facilitating FAIRification, 3) data collection, 4) generating FAIR data in real-time, and 5) using FAIR data. Firstly, we selected the set of Common Data Elements (CDEs) as variables to be collected, and the Data Catalogue (DCAT) metadata elements to describe the registry. In phase two, we designed an electronic Case Report Form (eCRF) within Castor EDC. Next, a semantic model defining the CDEs (and its relationships), and a tool that automatically converts data entered into the eCRF to a machine-readable language were created and implemented in Castor. In the data collection phase, we obtained informed consent and started entering data into the eCRF. Subsequently, data and metadata were automatically converted to RDF Turtle (a format that supports data and ontological annotations), stored, and then exposed in the FAIR Data Point (FDP) deployed by Castor EDC. The final phase regards the reuse of the FAIR data, where authentication and authorization procedures take place inside Castor EDC FDP, and data becomes available for queries.
The de novo (from conception) FAIRification process enables FAIRification upon data collection by transforming eCRF data into a machine-readable language in real-time.
We successfully set up a de novo FAIRification process for an RD registry that can be adopted by other registries. The VASCA registry is up and running in one hospital, and currently being set up in other participating institutions. This de novo process mitigates the need for (repeated) post-hoc transformations for FAIRification purposes. We believe that connecting RD registries in real-time facilitates diagnosis and improves treatment options for RD patients.

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A DIGITAL HEALTH APPROACH: REDUCING THE DIAGNOSTIC ODYSSEY OF HEREDITARY HEMORRHAGIC TELANGIECTASIA USING UK PRIMARY CARE ELECTRONIC HEALTH RECORDS

ABSTRACT N° C005_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare multisystemic disease that is poorly understood1. Under-diagnosis is common due to the disease's complexity and low physician and patient awareness2.

Here we show that a digital health tool may lead to earlier diagnosis by scanning pseudo-anonymised Electronic Health Records (EHRs) across a population to highlight patients for further investigation who may have HHT.

Methodology

This digital health tool uses peer-reviewed disease criteria and maps these to the appropriate SNOMED CT codes to create a digital criteria algorithm. The algorithm for HHT was derived from the Curaçao diagnostic criteria3. Patients who meet 3 or 4 criteria can be diagnosed with definite HHT, those who meet 2 criteria as possible HHT, and those with 0 or 1 criteria are unlikely to have HHT3. This digitised criteria algorithm was applied to the primary care EHRs of 936,148 patients (434,960 Biobank and 501,188 from a single primary care practice federation), highlighting those that match the algorithm.

We analysed the EHRs of the patients that both matched the HHT algorithm and who also already had a diagnosis of HHT based on the presence of the SNOMED CT code for HHT (21877004) to explore how such cases presented to their General Practitioner prior to the diagnosis being made.

Results

61 EHR's had a SNOMED CT code for HHT (21877004).

125 patients' EHRs matched the digitised criteria, of which 7 patients' had a previous diagnosis of HHT. Of these 7 already diagnosed patients, 4 would have matched the digitised criteria in advance of the HHT diagnostic code appearing in their EHR.

3 patients matched the digitised criteria with 2 points (possible diagnosis) 1, 2, and 20 years before the diagnostic code for HHT appeared on their record.

1 patient matched the digitised criteria with 3 points (definite diagnosis) 7 years before the diagnostic code for HHT appeared on their record.

Conclusion

This approach has the potential to highlight patients with HHT earlier than current clinical practice with important implications for clinical management, allowing for earlier surveillance and prevention of potential complications; like congestive heart failure, brain abscesses, pulmonary and intracerebral haemorrhage.

Further prospective studies are planned to evaluate the specificity and sensitivity of this digital approach and its implementation as an adjunctive tool in routine clinical practice.

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IDENTIFYING POTENTIAL CASES OF JUVENILE POLYPOSIS - HEREDITARY HAEMORRHAGIC TELANGIECTASIA (JP-HHT) SYNDROME USING PRIMARY CARE ELECTRONIC HEALTH RECORDS IN THE UK

ABSTRACT N° C006_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Introduction

Juvenile polyposis syndrome (JP) is an autosomal dominant condition characterised by >5 gastrointestinal (GI) hamartomatous polyps and predisposition to GI cancer. Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia with increased risk of arteriovenous malformations (AVMs).

A rarer combined syndrome, JP–HHT, caused by variants in SMAD4, was recently recognised which includes features of both diseases. No formal diagnostic criteria currently exist to identify patients with this combined syndrome.

We hypothesised that early identification of patients with JP-HHT could improve their clinical management. By using a digital health tool, we sought to identify patients who may have JP-HHT from a cohort of HHT patients.

Methodology

We analysed 936,148 electronic health records (EHRs) from a primary care network and research database to select those with the diagnostic code for HHT (SNOMED CT code: 21877004). These EHRs were then analysed to identify patients who also carried diagnostic SNOMED CT codes indicating GI polyposis. Despite a lack of a formal diagnostic criteria for JP–HHT, this allowed us to highlight patients with features suggestive of both conditions for further evaluation.

Identified patients were analysed for metrics related to both conditions including age of polyp finding, location of polyp, GI malignancy, anaemia, age of HHT diagnosis, presence of AVM, telangiectasia and epistaxis.

Results

61 EHRs were identified with a diagnosis of HHT. 7 of these EHRs also had 1 or more codes indicating GI polyposis.

All 7 identified EHRs had GI polyps located in the colon along with their diagnosis of HHT. 1 EHR exhibited codes related to anaemia, cerebral AVM and abscess, pulmonary AVM, epistaxis, colonic polyps and family history of cancer, indicating significant complications potentially related to JP-HHT.

4 out of 7 EHRs had no record of a genetics consultation (absence of the associated SNOMED code) also indicating further evaluation may still be required for these individuals.

Conclusion

Using a digital health tool to identify a subset of patients within a rare disease cohort is a potentially valuable use of such technology. Refining diagnosis of more complex forms of rare disease such as JP-HHT would enable further evaluation of this subset of affected individuals. This could help improve diagnostic precision and therefore facilitate improved clinical care.

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DEVELOPMENT OF AN ANNOTATED CORPUS OF RARE DISEASES TO PROMOTE AN ACCURATE DIAGNOSIS

ABSTRACT N° C007_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Rare diseases share as part of their problematic, the delay in diagnosis and the sparse information available for the clinicians and patients. Collectively, rare diseases affect the lives of an estimated 30 million people across the European Union. In total, more than 6000 different rare diseases exist and, hampering even more their detection, many of these diseases result in different manifestations among same disease patients. Due to the intrinsic low incidence of these rare diseases and the limited interest of big pharmas, the information available of rare diseases generally is dispersed and sometimes centered in few altered genes or one drug proposal, anyway little differential research has been done on this field, resulting in low efficient diagnosis and highly challenging treatments choices for these patients.
These facts explain the need of more structured information about rare diseases. Natural Language Processing (NLP) can help us to extract relevant information about rare diseases to facilitate their diagnosis and treatments. Development and evaluation of NLP tools requires manually annotated corpora. With this purpose, our project aims to create a gold standard corpus annotated with rare diseases, diseases and their symptoms and signs, as well as, some relations between these concepts. The corpus also contains a small sample of 109 texts about skin rare diseases.
This corpus will not only relate diseases with the symptoms and sings they produce, but also different relationships between diseases. The entities (disease, rare disease, skin rare disease, symptom, sign and anaphor) and the relationships (produces, is_a, is_acron, is_synon, increases_risk_of, anaphora) were annotated in a total of 1041 English texts. These texts were extracted from different sections of the Rare Disease Database (created by the National Organization for Rare Diseases (NORD)). Later, the collected texts were firstly annotated automatically and later reviewed and completed manually by two independent annotators.
This corpus suppose a significant step for the field since there is a scarcity of available corpus of rare diseases, opening the door to further NLP applications such as information retrieval, information extraction and question answering systems, which will facilitate the diagnosis and treatment of these rare diseases and, therefore, improving dramatically the quality of life of these patients.

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EJP RD FAIRIFICATION STEWARDS TO HARMONIZE FAIR IMPLEMENTATIONS ACROSS ERN RARE DISEASE REGISTRIES

ABSTRACT N° C008_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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The FAIR principles help computers to Find, Access, Interoperate, and Reuse data with minimal human intervention. They enable seamless federated discovery and reuse of data in registries across and within European Reference Networks of rare disease expert centres (ERNs) and associated institutes under defined, transparent conditions. To empower rare disease research and diagnostics, the European Joint Programme on Rare Diseases (EJP RD) aims to facilitate the FAIRification of patient data registries from 24 ERNs. Due to the heterogeneous ERN registry landscape, it is challenging to harmonize the FAIRification procedures among them. The EJP RD therefore introduced the FAIRification stewards group to act as a liaison between ERNs and EJP RD experts.
The FAIRification stewards group is currently composed of six members, each assigned to four ERNs. For each ERN a team is formed of at least one ERN registry data manager, one registry software provider or ERN developer, and one FAIRification steward. The group also acts as a communication hub between EJP RD experts and ERNs, helping to exchange information regarding FAIR implementation needs, and the matching solutions provided by both experts and ERNs.
To oversee the FAIRification status of ERN registries, the FAIRification stewards and FAIR experts initiated an implementation inventory matrix, which includes standards and tools (coined as FAIRification artefacts) that can ease the FAIRification process. The matrix catalyzes convergence and possibly defines a common FAIR implementation profile for RD registries. Together, ERNs and stewards completed the matrix by determining the implementation status of each FAIR artefact. ERNs' FAIRification questions were recorded and grouped into five categories ("training", "community", "modelling", "implementation", and "legal") with specified start/due dates, priority, and expert assignees for efficient management. As a result, frequently asked questions were identified and answered by EJP RD experts. ERNs' practical needs will be covered in workshops throughout 2021. Additionally, ERNs' domain-specific variables will be identified and curated by ERN clinical experts. We expect that by the end of 2021 each ERN will have realized a first version of a FAIRer registry. The FAIRification stewards play an important role in building and monitoring connections among ERNs and the EJP RD and continue seeking confluences in FAIRification procedures.

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TELETHON UNDIAGNOSED DISEASES PROGRAM: OUTCOME OF 4 YEARS PILOT PROJECT TO SOLVE UNDIAGNOSED DISEASES

ABSTRACT N° C009_2021 / DIAGNOSTIC, WGS, ARTIFICIAL INTELLIGENCE, NEW TECHNOLOGIES

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Mendelian genetic conditions affect millions of individuals worldwide, and, despite extensive medical and genetic test evaluation, many patients never arrive at a diagnosis. Whole-exome sequencing (WES) resulted in significant increased detection of genes associated with rare diseases. The Telethon Undiagnosed Diseases Program (TUDP) is the first Italian national program with the objective of identifying genes associated with a wide spectrum of rare pediatric-onset single-gene disorders, characterized by severe multisystem manifestations, neurological involvement, and dysmorphic features, that do not yet have a clinical recognition and remain undiagnosed. In the 4 years pilot project, TUDP benefited from a well-orchestrated high selective and stringent clinical evaluation, the careful review of cases and interactions across academia, 14 Italian pediatric centers, and patient families. Through WES applied to probands and their close relatives, and the cooperative efforts of bioinformaticians and biologists, and with the use of emerging strategies such as matchmaking programs, the TUDP succeeds >45 percent of these unsolved cases (a total of 573 families) to reach genetic diagnosis. In particular, for 79% of cases mutations in established known disease genes were identified, while for the remaining 21% of families disease-causing variants were identified in novel gene-disease, discovered while the TUDP study was underway. Most of the findings of TUDP pilot project expanded the phenotype beyond that originally recognized, since the genetic heterogeneity and the phenotypes variability can make the clinical interpretation difficult. On most occasions (81% of families), mutations in different genes were found to be causal in affected individuals with overlapping phenotypes and, conversely, the same causative genes were found to be mutated in 19% of families. Compound-heterozygous (12%) or homozygous (10%), de novo (68%), and X-linked (7% maternally inherited and 3% de novo X-linked) mutations were all identified. The greater frequency of de novo causative variants reflects the trend to delay parenthood which increasingly and dramatically widespread in the Italian population.

Furthermore, a significative portion of TUDP patients have putative pathogenic mutations in genes that have never been previously associated with mendelian diseases. For these patients, the TUDP mission is being implemented with novel disease gene discovery and functional validation.

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EPIDEMIOLOGIC STUDY OF PORPHYRIA IN ISTANBUL TURKEY: A DESCRIPTIVE EVALUATION

ABSTRACT N° D001_2020 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Porphyria is a rare disease hardly known by clinicians resulting in misdiagnosis, if diagnosed,delay in proper treatment resulting disability, decrease in the quality of life even early death. The reported frequency of disease in North Europeen countries is changeble, in our country the prevalence is unknown. Thus a study to determine the burden of Porphyria,we collected data from clinicians. Questions on: Diagnostic methods used for PD,the names of eliminated diseases during diagnostic evaluation process, whether any PD patient treated and treatment modalities used are also included. Questionnaire was distributed to the 213 clinicians in Internal medicine, respiratory , Emergency,General practitioners and etc. before the seminar on PD given at the several university and private hospitals in Istanbul,Turkey. The data edited and analyzed by the Standard Statistical Package of SPSS version 21. Data summarized as percentages and cross classified tables are obtained for the multiple class variables. The Chi-Squared test is used for the significance of difference and/or relationship and at the significant level of 0.05. Of 213 clinicians, 80% of clinicians defined his specialty as internal Medicine, 25% stated he or she had some suspected PFD patients, the frequency of observed symptoms; U severe abdominal pain 20% and in combination with symptoms; red/brown colored urine %11.7, mental disorder 41%, and others symptoms with several combinations 22%. The 15% claimed had a patients diagnosed as PD , is most frequently as the acute intermittent porphyria 50%, Porphyria cutanae Tarda 9.5% , the acute porphyria together with cutaneous %12.5 and the rest 28%. Diagnosis is based on mostly porphyrin level in urine 70% and 30% the rest, eliminated diseases from PD during diagnosis is mostly FMF and/or Appendicitis 89% and the rest of the diseases 11%. The 4% stated to have treated patients with PD, of which 80% by clinicians in Internal Medicine and 20% in Emergency medicine. In the treatment, most clinicians used Hemargining or Hemin ,75% of the clinicians in internal Medicine and 100% of the clinicians in Emergency . Awareness among clinicians on the existent symptoms, modes of diagnostic methods, as this rare disease are lacking. For this reason, this study is extended to include the seminar to increase awareness among clinicians expected to diagnose, treat Porphyria patients in Turkey.

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EXPRESSION OF CIRCADIAN RHYTHM GENES IN PATIENTS WITH NEURODEVELOPMENTAL SYNDROMES DISPLAYING SLEEP DISTURBANCE

ABSTRACT N° D002_2021 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Patients with neurodevelopmental disorders (NDDs) show a higher rate of sleep disturbances as compared to the general population. Sleep anomalies are heterogeneous disturbances characterized by difficulties with initiating or maintaining sleep, excessive daytime sleepiness, and parasomnias. The relationship between abnormal sleep patterns and NDDs is complex and impacts an already compromised neurobehavioral phenotype. Smith-Magenis Syndrome (SMS) [MIM:182290], caused by haploinsufficiency of RAI1 gene, is a disorder of the epigenetic machinery often presenting with sleep disturbances, which in 95% of the patients result from disruption of circadian rhythm, with an inverted melatonin secretion. As circadian rhythms are governed by a molecular clock system based on transcription-translation feedback loops we investigated through RT-qPCR the expression of circadian genes in peripheral blood of 18 clinically suspected SMS/SMS-like patients manifesting sleep disturbance except three, including 3 SMS molecularly confirmed patients. Out of the 6 tested genes CLOCK and BMAL2, encoding transcription factors activating clock-controlled genes, and PER2 and NR1D1 encoding clock protein repressors, were found deregulated in at least one patient with sleep problems: gene expression alterations were observed in 9 out 15 patients, whereas no dysregulation was detected in the 3 patients without sleep disturbance. Our data confirms the occurrence of sleep disturbance in molecularly defined NDDs and expands it to patients with sleep disturbance who are molecularly unsolved. We pursue to validate our study on a larger cohort and to test the investigated patients the for melatonin receptor genes, which due to their lack of expression in blood, need an alternative tissue or in vitro model.

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FROM DIAGNOSIS TO THERAPY: NOVEL APPROACH REVEALS CELIPROLOL BUT NOT LOSARTAN AND BISOPROLOL AS MEDICAL THERAPY OF CHOICE FOR VASCULAR EHLERS-DANLOS SYNDROME

ABSTRACT N° D003_2021 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Background: Patients with the rare connective tissue disorder vascular Ehlers-Danlos syndrome (vEDS) are at increased risk for fatal aortic ruptures. Using a mouse vEDS model, we established an objective, read-out system for the assessment of the clinically highly relevant biomechanical integrity of the thoracic aorta.
Objective: By means of our novel read-out system, we aimed to assess the effects of antihypertensive drugs on the biomechanical integrity of the weakened murine vEDS thoracic aorta as potential medical therapy in vEDS.
Method: Mice modelling vEDS were treated with the beta-blockers celiprolol (Selectol®) or bisoprolol (Bilol®) or the ARB losartan (losartan Actavis®) for 4 weeks. 1.5-mm-long sections of the ascending and descending murine thoracic aorta were mounted on a tissue puller and uniaxially stretched until rupture while recording the tensile force (in mN).
Results: The rupture force was significantly lower in untreated heterozygous compared to wild-type mice and decreased with increasing distance from the heart for both heterozygotes and wild-types. We showed that celiprolol but neither bisoprolol nor losartan increased the rupture force of the thoracic aorta in heterozygous mice (PMID: 31056650 and 31693161), explaining the added value of celiprolol observed in a clinical trial and a long-term observational study (PMID: 20825986 and 30999998).
Conclusions: Our novel and objective read-out system is suitable for detecting significant differences in the rupture force of the murine thoracic aorta and allows the assessment of the effect of candidate drugs on the biomechanical integrity of the aorta. Although the added value of other antihypertensive drugs in vEDS, if any, is unknown, celiprolol, but not losartan and bisoprolol, is currently the medical therapy of choice for vEDS, until further evidence emerges.

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A MOUSE MODEL CARRYING THE R406H MUTATION IN THE STXBP1 GENE SHOWS RETARDED DEVELOPMENT AND SUSCEPTIBILITY TO EPILEPSY; A POTENTIAL TOOL IN MODELING INFANTILE EPILEPTIC ENCEPHALOPATHY

ABSTRACT N° D004_2021 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Mutations in STXBP1 are linked to severe early epileptic encephalopathies and related neurodevelopmental disorders. The STXBP1 gene (also referred to as Munc-18) codes for an essential subunit of the synaptic fusion machinery that enables synaptic transmission.
De novo germline missense mutations and truncating mutations or deletions can lead to early infantile epileptic encephalopathy probably through haploinsufficiency1. Over 250 mutations have been identified to date2 including nonsense, splice site and frameshift mutations, partial and whole gene deletions, and larger microdeletions. No correlation has been found between mutation type and the presence of seizures, age at seizure onset, or cognitive outcome2.
Knockout mouse models3, indicate that homozygous Munc-18 null mutants have normal brain assembly in spite of complete and permanent loss of synaptic transmission. Null mutant embryos are completely paralyzed, and although vital at birth, they die immediately probably since they are unable to breathe.
In order to better understand the mechanisms that underlie STXBP1 related intellectual disabilities and epilepsies we utilized CRISPR/Cas9 technology to generate a mouse model carrying a frequent human missense in the STXBP1 gene, a G>A substitution; R406H, which has been implicated in a variety of epileptic and developmental pathologies4.
Heterozygotes of the mutated Stxbp1 gene (HETs, hereafter) and wild-type (non-mutated, WT hereafter) littermates underwent early developmental assessments and in adulthood their muscle strength and seizures responses to Pentylenetetrazole (PTZ) were assessed.
The developmental assessments indicated significant slower growth between the ages of 1 to 3 weeks, and a significant delay in walking at the age of 1 week among HET mice. In adulthood, at 14 weeks, HETs exhibited significantly reduced muscle strength (inverted grid test). In addition, at 22 weeks HETs showed a significant increased seizure response to PTZ and significantly reduced body weight.
Together, our data suggest that this novel line may be used a mouse model to study STXBP1 deficiency related infantile epileptic encephalopathy and may be used for exploring the disrupted neuronal mechanisms and therapeutic approaches.

1 Kovacevic et al, 2018. Brain, 141:1350–1374. 2 Abramov et al, 2020. J Neurochem, 00: 1–14. 3 Verhage et al, 2000. Science, 287:864-9. 4 Stamberger et al, 2016. Neurology, 86: 954-962.

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SIMVASTATIN TREATMENT DOES NOT AMELIORATE MUSCLE PATHOPHYSIOLOGY IN A MOUSE MODEL FOR DUCHENNE MUSCULAR DYSTROPHY

ABSTRACT N° D005_2021 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Background
Duchenne muscular dystrophy is an X-linked, muscular dystrophy where the absence of dystrophin protein leads to fibrosis, inflammation and oxidative stress, resulting in loss of muscle tissue. Currently there is no cure. Up to now, the only available treatment is corticosteroids, to counteract inflammatory response. One big effort is drug repurposing, i.e.using drugs already approved for other disorders, aiming to ameliorate patients' life quality. Drug repurposing is attractive as it decreases drugs development time and animal use, thus decreasing the overall cost of research.
Methods
Recent studies suggested that Simvastatin, a cholesterol lowering drug, has beneficial effects on several parameters in mdxmice, the mouse model for DMD. To validate the effectiveness of simvastatin, we tested the effects of 12 weeks simvastatin oral treatment in adult mdx mice. In this study, no remarkable benefits of simvastatin treatment were observed.
Results
The dose administrated was similar to the one published previously, 7 10 mg/kg/day. The outcome of the treatment was evaluated on several parameters, such as muscle function, histology or expression of genes involved in fibrosis, regeneration, oxidative stress and autophagy, mostly on diaphragm since is the most severely affected muscle. Functional performance, assessed after 4 and 8 weeks of treatment, using a four limb hanging test showed no differences between control and treated mice. Then, at the endpoint, force frequency relationship, a measure of muscle strength, and response to eccentric, lengthening, contractions, a measure of membrane integrity, were determined in the tibialis anterior by stimulation of the sciatic nerve and in the diaphragm by direct muscle stimulation. Both measure didn't show any improvement from simvastatin treatment. Markers of fibrosis and inflammation assessed both by qPCR and at histological level didn't show any amelioration.
Although the treatment protocol was similar to the one suggested by previous publications, simvastatin plasma levels were found be much lower than the ones observed in a previous study.
Conclusions
Results showed that simvastatin did not ameliorate disease pathology in mdx mice, which could be due to the ineffectiveness of simvastatin itself or to the low plasma levels following oral administration in the feed. Further studies are needed to assess whether a different administration route could give a better result for this drug.

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METABOLIC COMA: GENES OR METABOLITES?

ABSTRACT N° D006_2021 / MOLECULAR ETIOLOGY OF RD, INNOVATIVE CLINICAL TRIALS, PRECISION MEDICINE

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Introduction: Significant proportion of coma in early infancy may be caused by inborn errors of metabolism (IEMs), especially if infection and injury have been excluded. Identifying the cause of coma may be life-saving for the patient and should direct clinicians to take prompt actions to identify treatable IEMs.

Case report: We describe a 1 months old boy born from consanguineous parents, who developed progressive paroxysmal movements, spasticity, lethargy and was hospitalized in ICU. He developed coma in 4 days after admission. His ammonia, glucose, lactate, and liver transaminases were normal. Brain MRI showed cortical ischemia involving basal ganglia, brainstem and cerebellum. His newborn screening (NBS) results were normal as well. There was a family history of older sister how died of unexplained coma at 3 months of age. Metabolic gene panel (including 188 genes) was performed within the BioMetabol clinical trial project (ID: NCT04098198), which revealed two heterozygous variants in ATP7B gene, both classified as VUS and a hemizygous variant in ATP7A gene, also classified as VUS. Wilson diseases seemed unlikely because copper accumulation needs time; Menkes diseases was also doubtful, because assuming the deceased sister also had the same disease, it would have been unlikely that X-linked Menkes disease could have caused severe metabolic abnormality in a female infant. After investigating ceruloplasmin, copper and dopamine to norepinephrine ratio (which were all normal) whole exome sequencing (WES) was performed and homozygous pathogenic frameshift variant in SLC19A3 gene was detected. Treatment with high doses of IV thiamine and oral biotin was started but there was no improvement, which most likely is attributed to the fact that null mutations of SLC19A3 produce severe phenotype, whereas mutations with some residual function produce treatment-responsive phenotype. Treatment was ceased after 3 months.

Conclusion: IEMs should be suspected in any infant with unexplained coma and basic metabolic investigations should be initiated promptly in order not to miss treatable conditions. Genetic investigations (panels or WES) have high diagnostic yield for severe and early onset phenotypes, but their major drawback is interpretation of VUSs and the longer turnaround time compared to metabolic investigations. Thus, basic and targeted metabolic investigations may save time and give accurate diagnosis for infants and neonates presenting with coma.

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CERULOPLASMIN REPLACEMENT THERAPY AMELIORATES LIVER IRON DEPOSITION AND STEATOSIS IN A PRECLINICAL MODEL OF ACERULOPLASMINEMIA

ABSTRACT N° E001_2020 / ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

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Purposes Aceruloplasminemia (Acp) is a rare disease caused by mutations in ceruloplasmin (Cp) gene resulting in loss of Cp ferroxidase activity, fostering iron deposition in liver and brain. Cp has a role in iron homeostasis, mobilizing iron from stores and promoting incorporation into transferrin. Cp is mainly expressed in liver and brain as form secreted in blood and liquor, respectively. In Acp patients, iron accumulation induces neurodegeneration preceded by diabetes and anemia. No therapy for Acp is nowadays available. In the CpKO mouse model of Acp, we showed the therapeutic potential of peripheral-administered Cp replacement that ameliorates neurological symptoms. Interestingly, 4 out of 7 Acp patients we described show lipidosis; and a connection of iron dysregulation and dyslipidemia has been reported in nonalcoholic fatty liver disease and metabolic syndrome in association with reduction of serum Cp. Liver is the primary organ regulating iron metabolism, mainly through hepcidin and Cp release, but these proteins are also synthesized by adipocytes. The project is aimed to study the efficacy of Cp replacement therapy (Cp-RT) at systemic level in particular on liver and adipose tissue to highlight iron/lipid dysmetabolism association in Acp. Methods CpKO and Wild Type (WT) mice have been treated for 2 months with purified Cp, then liver and visceral adipose tissue (VAT) were investigated for Cp expression and activity replacement, for histological appearance, and for lipids and iron accumulation. Results CpKO mice were overweight compared to WT, showing VAT accumulation and small increase of adipocyte size. CpKO mice displayed liver steatosis with ballooned hepatocytes, and iron accumulation in liver but not in adipocytes. Intraperitoneal administration allows Cp to enter and accumulate in the tissues with ferroxidase activity rescue. In CpKO mice, Cp-RT limited liver steatosis reducing lipids accumulation and hepatocytes balooning, and prevented iron accumulation. Cp treatment was less effective on VAT metabolism, being not able to prevent body weight increase. Conclusions The results underline the link of iron dysmetabolism and lipidosis in Acp, and indicated that Cp-RT is effective at systemic level, reducing at least liver symptoms. Lack of Cp-RT efficacy on VAT might depends on either the short treatment duration, not sufficient to affect VAT metabolims, or the presence of tissue specific compensatory molecules/mechanisms.

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PRECLINICAL MODELS FOR NONINVASIVE TREATMENTS FOR NONSYNDROMIC CRANIOSYNOSTOSIS: COUPLING STIMULI RESPONSE DRUG DELIVERY IN CALVARIAL SUTURE CELLS

ABSTRACT N° E002_2020 / ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

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Craniosynostosis (CS) is a rare craniofacial malformation that causes the premature fusion of one or more cranial sutures. There is still lack of understanding of the dysregulation of multiple signalling pathways ruling the osteogenic stem cell fate in the fused suture. The treatment of CS is exclusively based on surgery, with associated increased morbidity and lethality. Post-surgical relapses occur in about 10% cases and require re-interventions, with increasing morbidity and mortality. A multidisciplinary team within the ERN CRANIO network (European Reference Network for rare and/or complex craniofacial anomalies and ENT disorders; https://ern-cranio.eu/) is developing novel strategies to design and test pharmacological approaches to dampen suture ossification and therefore decrease the need of invasive treatments. To this aim, we characterized the molecular mechanisms underlying the aberrant osteogenic properties of calvarial-derived mesenchymal stromal cells (CMSCs) within the fused suture. This information is expected to reveal novel endogenous biomolecules to be exploited in the development of nanotechnologies for targeted therapies. In our model, recombinant human ferritin (hFT) was tested as a suitable nanocarrier for intracellular delivery upon binding to the its cognate receptor CD71, which is expressed in CMSCs. A hFT construct functionalized with the N-terminus of each hFT subunit fused to a target domain for proteolytic cleavage by metalloproteases (MMPs) followed by an outer shielding polypeptide sequence. In the hFT carrier the interaction between hFT and the receptor is masked, being favored in the presence of MMP-enriched environment. Our preliminary results show that, upon osteogenic induction, the expression of MMP-9, -13 and -14 is higher in CMSCs isolated from fused suture compared with unfused ones. Optimization of hFT nanocarrier using a sequence cleaved by the identified MMPs represents an innovative strategy to specifically target cells in the pathological skull suture using stimuli-responsive delivery. In addition, to mimic the complex tissue microenvironment, a dynamic 3D culture system ("bone-on-chip") is being developed and will be tested to evaluate new drugs in a more realistic scenario. Future studies will address the upload of selected compounds able to reprogram the cell fate in the skull suture niche.

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DMPK PROMOTER SILENCING BY TRANSCRIPTOME EDITING AS A NEW THERAPEUTIC STRATEGY IN MYOTONIC DYSTROPHY TYPE 1

ABSTRACT N° E003_2020 / ADVANCED THERAPIES: GENE EDITING, CELL THERAPY

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a. Introduction Type 1 myotonic dystrophy (DM1) is one of the most prevalent muscular dystrophies. DM1 is also a life threatening disease and causes severe multisystem symptoms. Specifically, this disease originates from an increase of CTG triplet localized in the DMPK gene. Its transcription leads to a pathologic mRNA, inducing a general dysregulation of gene expression. Unfortunately, there are currently only symptomatic treatments. In addition, various therapeutic strategies have already been tested in order to neutralize the pathologic DMPK mRNA or its consequences. Nevertheless, they all have at least one serious drawback that limits their clinical applicability. Therefore, our team aims at elaborating a new curative approach which consists in the DMPK promoter silencing by the CRISPRi transcriptome editing.

b. Methods The ability of our CRISPRi transcriptome editing to inhibit DMPK promoter was tested in immortalized myoblasts from a DM1 patient (myoDM1) or cells from a healthy donor (myoWT). 13 sgRNAs against the DMPK promoter (sgDMPK) and 3 scrambled sgRNAs (sgNT) were individually cloned into different CRISPRi plasmids used to produce respective lentiviral vectors. Next, the myoblasts were transduced and selected with blasticidin to produce stable cell lines. From these cell lines, the myoblasts were differentiated during 3-5 days. Next, their cellular and molecular characteristics were assessed by FISH, RT-qPCR and RT-PCR.

c. Results The density of nuclear DMPK RNA foci determined by FISH was used to screen the sgDMPK. Three out of the 13 sgDMPK candidates sharply reduced by up to 80% the density of foci in the nuclei. Next, the DMPK promoter silencing was evaluated by quantifying the amounts of DMPK RNA using RT-qPCR. The DMPK expression was inhibited by up to 80% in both myoDM1 and myoWT myocytes. Finally, RNA splicing of genes involved in muscle physiology was studied using RT-PCR. Indeed, these genes have been shown to undergo aberrant splicing in DM1 patients. The CRISPRi treatment leads to a strong correction of the splicing for these studied genes.

d. Conclusions Our CRISPRi transcriptome editing system is able to efficiently inhibit the formation of foci by preventing the production of DMPK mRNA in a relevant cell model. As a consequence, it is also able to correct the splicing defects of important genes.

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PAEDIATRIC ORAL LIQUID FORMULATIONS OF SODIUM DICHLOROACETATE FOR THE ACUTE AND CHRONIC TREATMENT OF ACQUIRED OR CONGENITAL LACTIC ACIDOSIS

ABSTRACT N° G001_2021 / ACCESS TO DIAGNOSTIC AND DRUGS FOR ALL

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Background and contest
Sodium dichloroacetate (DCA) has been administered for decades as an investigational drug for the treatment of several cardiovascular and metabolic disorders and has been widely used for the acute and chronic treatment of acquired or congenital lactic acidosis (CLA). DCA is rapidly absorbed following oral administration, crosses the blood-brain barrier and activates pyruvate dehydrogenase complex (PDC) within few minutes. Indeed, open-label studies have revealed its effectiveness in reducing blood or brain lactate concentrations so as to improve the morbidity in some patients with defects in the PDC or the respiratory chain and their neurological status.
To date, there is no univocal consensus on the therapeutic treatment of lactic acidosis because of the absence of a definite therapy. Even though the therapy with sodium DCA is the only one that showed some significant clinical improvements, today this active molecule is used exclusively as a lifesaver for the treatment of acidosis in which lactate concentration reach critical values. DCA was designated as orphan drug by the FDA.
Recent randomized controlled trials followed by other open-label studies have shown that oral DCA is generally well-tolerated by the majority of young children exposed to a continuous treatment for several months or years, without any significant side effects. However, the available DCA forms are not adapted to be used in the paediatric populations, mainly considering neonates and young patients and in many countries of the European Union, DCA based extemporaneous formulations are usually made by using non-pharmaceutical grade DCA solubilized in food beverages.
Aim and Methods
Our study will be based on methods and technologies provided within experienced Research Units participating to EPTRI the European Paediatric Translational Research Infrastructure, that is a new proposed distributed research infrastructure aimed to accelerate the paediatric drug development processes and that includes an ad hoc Thematic Research Platform devoted to study paediatric tailored formulations.
This study will identify stable palatable solutions containing excipients tolerated by paediatric patients and orally disintegrating mini-tablets of sodium DCA as an alternative suitable for children formulation and will therefore represent a relevant pilot case to reduce off-label use in children.

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ECRIN AS A FACILITATOR OF MULTINATIONAL CLINICAL RESEARCH FOR RARE DISEASES (RD) IN EUROPE

ABSTRACT N° H001_2020 / METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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Investigator-initiated trials are conducted mainly as single-centre or multiple-centre setting in one country. This fact might bias studies' outcomes or limit trial initiation within one country. This last constraint is especially remarkable in the case of rare diseases (RD), considering the limited number of patients per country. The main hurdle for academic investigators is due to the fragmented health and legal systems within Europe. ECRIN's unique pan-European organisation enables to successfully work across borders, coordinating Clinical Trial Units and other stakeholders from multiple countries. ECRIN can help to circumvent the challenges associated to RD clinical research by supporting European Reference Networks (ERN) investigators in design, planning and performing clinical studies: 1. Providing support to plan multinational clinical trials, through a Clinical Trials Helpdesk for Rare Diseases aiming to facilitate access to RD specific expertise, including design aspects, in the framework of the EJP RD H2020 project. 2. Providing support to perform multinational clinical trials (operational coordination), as part of ECRIN services.

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ORPHAN PAEDIATRIC MEDICINES IN EUROPE

ABSTRACT N° H002_2020 / METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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INTRODUCTION AND METHODS The impact of the Paediatric Regulation (EC) N° 1901/2006 provisions on the approval process for paediatric Orphan Medicinal Products (p-OMPs) in Europe was investigated. The number of OMPs available for children receiving a Marketing Authorisation (MA) under the conditions foreseen in a Paediatric Investigational Plan (PIP) was considered. For each drug the following items were analysed: medicinal trade name, approval date, approved indication, age specification, clinical studies and trials included in the MA dossier, designation status, date, orphan indication, approved PIP and its status at the time of the first paediatric MA. The search for p-OMPs receiving a MA in Europe from January 2007, 26th to July 2019, 31st was performed on TEDDY-EPMD (https://www.teddynetwork.net/) and on EU-Orphan Database (https://www.ncbi.nlm.nih.gov/pubmed/17637514). Moreover, the European Public Assessment Reports (EPARs) and other EMA official sources were searched. RESULTS AND CONCLUSION Since January 2007, 52 OMPs on a total of 293 paediatric medicinal products were authorised, most of them under special provisions. The 90% of OMPs was authorised for adolescents versus 8% for neonates. Among the p-OMPs, 38 (73%) granted a PIP/waiver while 14 (27%) did not (of these non-PIP group 13/14 received a paediatric MA under the Directive 2001/83/EC). A total of 331 studies were found for the 38 p-OMPs with a PIP/waiver and 64 for the 14 medicines without a PIP/waiver (less than 50%). The findings of our analysis show that the number of OMPs approved for children in Europe is still low and, among them, around 1/3 did not follow the Paediatric Regulation provisions. This group, not receiving PDCO revision and PIP approval, appears less supported in term of paediatric efficacy-safety studies. Finally, the Paediatric Regulation should be applied more in case of p-OMPs.

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THE C4C CROSS CUTTING PAEDIATRIC DATA DICTIONARY: BUILDING CONSENSUS TO IMPROVE AND INCREASE DATA HARMONIZATION AND STANDARDIZATION ACROSS PAEDIATRIC STUDIES

ABSTRACT N° H003_2021 / METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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conect4children (c4c) is an ambitious project which seeks to overcome the barriers to involving children in clinical research by creating a pan European paediatric clinical trial network. The ultimate aim of c4c is to bring better medicines to the paediatric population by creating a robust network strengthened by a range of tools and resources. c4c will be validated by both academic and industry proof of viability (PoV) studies who will use the network to conduct their paediatric trials.
One key bespoke resource is the c4c Cross Cutting Paediatric Data Dictionary (CCPDD) which will help to increase the harmonisation and standardisation of data collected in paediatric studies. The lack of guidance on how to capture common data elements in paediatric trials results in heterogeneity, reduction in efficiency, and difficulties in aggregating or sharing data post-study. Many paediatric diseases are classed as rare, meaning data tends to be scarce and is consequently extremely precious. The CCPDD will facilitate the harmonisation of data terminology, enhancing comparability and complimenting the move in the health research field towards re-usability of data. For each of these goals, having data standards is becoming increasingly important.

This poster details the steps taken to create the first version of the c4c data dictionary including:

- A consortium wide survey to ascertain opinions and experiences around clinical trial data
- Establish of the 'State of the Art' data initiatives relevant to rare and paediatric diseases
- Modified Delphi process to identify 'cross cutting' items
- Learning from, and results of a consensus building workshop
- Work with Clinical Data Interchange Standards Consortium (CDISC) to apply standards
- Launch of version 1 of the Data Dictionary

Initial research shows that there is a need and desire to harmonise and share precious and scarce data from paediatric clinical studies. This is coupled (especially in the academic community) with a lack of understanding and knowledge of the use of data standards. Working closely with paediatricians, and data experts, c4c has created a data dictionary based upon CDISC standards. This dictionary is being tested by the PoV studies of c4c, and is accompanied by a wider set of recommendations to harmonise data. Once successfully implemented, it will allow those commonly collected, paediatric data items to become interoperable across studies and potentially shareable with other data sources.

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DOWNREGULATION OF RNA-BINDING PROTEINS IN THE TRANSCRIPTOME OF RUBINSTEIN-TAYBI IPSC-NEURONS HIGHLIGHTS KEY GENES INVOLVED IN NEURAL FUNCTIONS AND CROSS-TALK WITH CHROMATIN REGULATORS

ABSTRACT N° H004_2021 / METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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This study relies on the iPSC neuronal model for Rubinstein-Taybi, a rare neurodevelopmental disorder of the epigenetic machinery caused by mutations in CREBBP or EP300 genes encoding the CBP/p300 lysine acetyltransferases.To get insights into the molecular basis of intellectual disability (ID) and the gene programs underlying the morpho-functional alterations of RSTS iNeurons we compared by RNASeq the differentially expressed genes marking the transition from iPSC neural progenitors to cortical neurons of RSTS patients with differently graded ID versus controls. Transcriptome analysis revealed a number of modulated genes lower in RSTS iNeurons than controls with pronounced decrease of downregulated genes (DRGs), suggesting that dented neuronal identity drives impaired differentiation. Analysis of RSTS-univocal DRGs, sorted into "RNA processing" and "Ribonucleoprotein complex biogenesis" GO clusters, disclosed a coherent network of RNA binding proteins (RBPs) genes with a role in alternative splicing (AS) and ribosome biogenesis. RBPs acting in pre-mRNA AS and post-transcriptional regulation of gene expression include hnRNP A1, A2B1, H1/H2, MAGOHB, mis-regulated in neurological/ID syndromes, core subunits of U snoRNPs and Ser-Arg Splicing Regulators. Interestingly, consistent with reduced expression of SR-protein SSRM4, top hit of the neural-specific microexons program upon crebbp/ep300depletion in mouse neuronal cells, several RSTS DRGs impact this network, disrupted in ~30% of patients with neurodevelopmental disorders. DRGs involved in ribonucleoprotein biogenesis encode ribosomal subunits components and nucleolar proteins that form complexes with snoRNAs with a key role in guiding post-transcriptional modifications needed for rRNA maturation. Examples are NOP58 and Fibrillarin (FBL), core partners of Box C/D snoRNAs and also performing as "dual specificity" proteins, FBL methylating histone H2 of Pol1 promoters required for epigenetic regulation of ribosomal genes and NOP58 interacting with BMAL, a transcriptional regulator of the circadian rhythm clock. Other RBPs bridged to chromatin, such as RUVBL1 and METTL1, highlight the links between chromatin and the RBPome and contribution of perturbations in their cross-talk to RSTS. This study underlines the impact of CBP/p300 deficiency on posttranscriptional regulation in RSTS iNeurons and the potential use of epidrugs in therapeutics of RBP-caused neurological disorders.

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MATERNAL UNIPARENTAL DISOMY OF CHROMOSOME 20 (UPD(20)MAT) AND ADVANCED MATERNAL AGE IN SILVER RUSSELL SYNDROME: IDENTIFICATION OF THREE NEW CASES.

ABSTRACT N° H005_2021 / METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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Silver Russell Syndrome (SRS, MIM #180860) is a rare (1:30,000-1:100,000) growth retardation disorder, whose clinical diagnosis is based on the Netchine-Harbison clinical scoring system (NH-CSS), combining six features: pre- and postnatal growth failure, relative macrocephaly, prominent forehead, body asymmetry and feeding difficulties.
The molecular mechanisms underlying SRS are highly heterogeneous, including (epi)genetic deregulation at multiple loci. Over 50% of SRS show loss of methylation (LOM) at the paternal H19/IGF2:IG-DMR (chr11p15.5), about 10% maternal uniparental disomy of chromosome 7 (UPD(7)mat), while pathogenic CNVs, 14q32 abnormalities, rare CDKN1C and IGF2 mutations, UPD(16)mat and UPD(20)mat have been reported. The screening of the most frequent (epi)mutation does not allow to achieve a diagnosis in about 40% of SRS, pointing to the need of defining the rare mechanisms underlying SRS/SRS-like presentation in such consistent fraction of unsolved patients.
Within a cohort of 176 SRS with a NH-CSS≥3, we found LoM at H19/IGF2:IG-DMR in 55 patients(31.3%), 17 UPD(7)mat (9.7%) and 4 had a deregulation in chromosome 14 DMR (2,2%). Single cases with rearrangements in 11p15.5 region or NSD1 gene were identified. Further analyses on the remaining patients allowed to detect UPD(20)mat in 3 cases(1,7%). UPD(20)mat has been described only in 21 cases, characterized by severe feeding difficulties and failure to thrive, preterm birth and intrauterine/postnatal growth retardation and may explain SRS cases. Pathophysiological mechanisms underlying the clinical manifestations of UPD(20)mat remain not understood, though a few studies have hinted the possible implication of the GNAS locus in feeding, growth and energy metabolism. The patients here described share prominent forehead, feeding difficulties and postnatal growth delay, while 1 case display relative macrocephaly, and another body asymmetry. Interestingly maternal age in these three UPD(20)mat cases > 40 years and literature survey pointed out on a total of 16 cases with a mean age of 38 years. Our study contributes to better define the characteristics of this rare imprinting disorder and facilitate the future diagnosis through specific updated molecular tests. Considering that in our cohort UPD(20)mat is the fourth most common pathogenic mechanism identified, we purpose to introduce UPD(20)mat in the SRS diagnostic flow-chart investigating imprinting loci on 11, 7, 14 and 20 chromosomes

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DRUG REPURPOSING OF NIFLUMIC ACID FOR PRECISION MEDICINE IN MYOTONIA CONGENITA

ABSTRACT N° H006_2021/ METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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Myotonia congenita (MC) is a rare genetic disease characterized by impaired muscle relaxation after voluntary contraction, resulting in muscle stiffness. It is caused by loss-of-function mutations in ClC-1 chloride channel, that reduce chloride currents by altering the gating of ClC-1 channel (gating defect) or by decreasing its membrane expression (trafficking defect). Based on the use of sodium channel blockers to contrast muscle hyperexcitability, MC therapy is purely symptomatic with significant pitfalls. One promising strategy to restore ClC-1 membrane expression is based on the use of pharmacological chaperones that bind and stabilize misfolded mutated proteins. To verify this hypothesis in MC, we test niflumic acid (NFA), a reversible inhibitor of ClC-1, on three myotonic hClC-1 mutations that show a reduction of chloride currents, due to an impaired channel surface expression (G411C,A531V,V947E). Wild-type (WT) or MC mutant ClC-1 channels were expressed in HEK293 cells and whole-cell chloride currents were recorded with patch-clamp technique, in control condition and after 24h incubation with NFA 50 µM. Membrane biotinylation assays and confocal imaging were performed to support electrophysiological results. Expression of A531V and V947E channel mutants yield chloride currents similar to WT but with reduced amplitude, whereas no chloride current was detected in G411C-transfected cells. About 60% of V947E and 70% of G411C channels were retained within the cell, confirming the trafficking defect. Incubation of transfected cells for 24 hours with 50 µM NFA enhanced A531V and V947E chloride current density more than two-fold, thereby restoring current amplitude similar to WT. In contrast, NFA incubation did not produce any significant effects on G411C chloride current, suggesting NFA inability to exert chaperone effect on G411C or G411C inability to conduct chloride currents. To gain more information, G411C-transfected cells were incubated with the proteasome inhibitor MG132. MG132 rescued the surface expression level of G411C mutant. However, no significant chloride current was recorded after MG132 incubation, indicating that G411C produces nonfunctional ClC-1 channels that are likely degraded before to reach the membrane. Because of the favourable safety profile of NFA, this drug might be repurposed to MC patients carrying trafficking-defective ClC-1 channel mutations, emphasizing the clinical relevance of precision medicine in the treatment of MC.

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IMPAIRED MYOGENESIS AND MITOCHONDRIAL BIOGENESIS IN A GAIN-OF-FUNCTION STIM1 MUTATION OF TUBULAR AGGREGATE MYOPATHY: TOWARDS THE IDENTIFICATION OF DRUGGABLE TARGETS

ABSTRACT N° H007_2021/ METHODOLOGIES TO ASSESS THE EFFECT OF DIAGNOSIS AND THERAPIES ON RD PATIENTS

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Tubular aggregates myopathy (TAM) is a hereditary rare muscle disorder, clinically heterogeneous, actually without a cure. Signs and symptoms typically begin in childhood and worsen over time. TAM patients mostly present elevated creatine kinase (CK) levels and slowly progressive muscle weakness, muscle pain, myalgia and cramps predominantly affecting the proximal muscles of lower limbs (Bohm et al., 2014; Hedberg et al., 2014; Walter et al., 2015). Biopsies from patients with TAM show the presence of tubular aggregates (TAs) originated from sarcoplasmic reticulum (SR) (Bohm 2018). TAs formation is triggered by functional consequences due to disruption in the SR-T-tubule junction, such as altered Ca2+ homeostasis (Lee 2016). Gain-of-function mutations in STIM1/ORAI1, proteins involved in Store-Operated-Calcium-Entry(SOCE), cause TAM. Considering the role of Ca2+homeostasis in myogenesis and mitochondrial biogenesis, we investigated, for the first time, whether TAM Ca2+alteration impacts these processes. We characterized myoblasts and myotubes derived from a TAM patient's biopsy carrying Leu96Val-STIM1 mutant using Ca2+cytofluorimetry, High-Content-Imaging technology, RealTime-PCR. By Ca2+cytofluorimetry we confirmed the increased resting Ca2+concentration and SOCE activity associated to Leu96Val-STIM1 mutation. Impaired fusion process and mitochondrial morphology were demonstrated by automated fluorescence microscopy: mononuclear Leu96Val-STIM1 myoblasts resulted in a reduced myotubes multinucleation with different morphology and mitochondrial network geometry vs controls. RealTime-PCR showed a compensatory down-regulation of genes involved in Ca2+handling (RyR1,SERCA1/Atp2a1,Trpc1) in STIM1 mutants; early differentiation markers (Myf5,Mef2D) were increased in mutated myoblasts, while late differentiation markers (Dystrophin/DMD,Troponin/Tnnt3) were reduced in mutated myoblasts and myotubes indicating an altered myogenesis in the late differentiation phase. Finally, the mitochondrial Isocitrate-Dehydrogenases/IDH3A, 2-Oxoglutarate-Dehydrogenase/OGDH genes were reduced in Leu96Val-STIM1 myoblasts, with OGDH defect persisting in mutated myotubes, suggesting impaired mitochondrial vitality. Our results give us an insight for a possible development of SOCE-inhibitor molecules and /or anti-aggregant molecules (such as Guanabentz analogues) with the aim to prevent or reduce cellular defects and symptoms towards a mutation-dependent personalized therapy.

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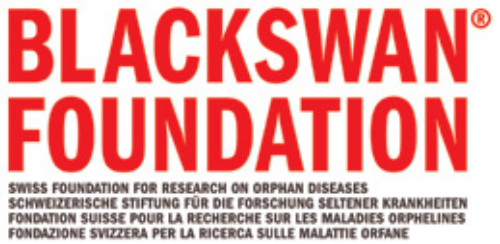
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