INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Minutes of the Joint Consortium Assembly and Scientific Committees Meeting

01-02 June 2022

IRDiRC

EXECUTIVE SUMMARY

The International Rare Diseases Research Consortium (IRDiRC) held a two-days hybrid meeting for the Joint IRDiRC Consortium Assembly (CA) and Scientific Committees (SC) last 01-02 June 2022, via web/teleconference and Face-to-Face (F2F) in Paris, France. It was attended online by 33 participants representing 22 members of the CA and 11 members of the SC. On-site in Paris, it was attended by 37 participants representing 19 members of the CA, 6 members of the DSC, 2 members of the ISC, 4 members of the TSC, and 6 members of the Scientific Secretariat (Sci Sec).

01 June 2022:

1. **Open Meeting Rooms and Exchange**
   - Exchange 1:
     - Between Diagnostics Scientific Committee (DSC), Funders Constituent Committee (FCC), and the Companies Constituent Committee (CCC).
     - Between Therapies Scientific Committee (TSC), Interdisciplinary Scientific Committee (ISC), and Patient Advocates Constituent Committee (PACC).
   - Exchange 2:
     - Between TSC, FCC, and the CCC.
     - Between DSC, ISC, and PACC.
   - Exchange 3:
     - Between ISC, FCC, and the CCC.
     - Between DSC and TSC.

2. **Parallel Sessions**
   - FCC members used this session to discuss and prepare the FCC Task Force proposals that are planned to be submitted in September 2022.
   - CCC members participated in different parallel sessions of other Scientific Committees.
   - PACC members discussed patient engagement in research and research on facilitating impact.
   - DSC members used this session to discuss and prepare the DSC Task Force proposals that are planned to be submitted in September 2022.
   - ISC members participated in DSC parallel session.
   - TSC members used this session to focus on future Task Force work and publication strategy.

3. **Summary from Committees**
   - FCC:
     - New Task Force (planned): (1) Understanding how RD funding is approached across the funding spectrum, from initial stages of an idea through commercialization and understanding and solving bottlenecks between Public-Private Partnership; (2) Models for support of data and/or registries within regular funding mechanisms; (3) IRDiRC to mediate funding activities and priorities among the different countries/continents where possible.

- An FCC members roundtable is planned for 20 October 2022 to share regional/national funding strategies, opportunities, and challenges.

- CCC
  - Emphasized increasing membership engagement and inclusion.
- PACC
  - Presented their discussions on patient engagement in research and research on facilitating impact
- RSC
  - Update on the Structure, Objectives, Member Composition, and Mandate
- DSC
  - New Task Force (planned): (1) Phenotyping; (2) Functional Analysis
- ISC
  - Complex innovation designs of clinical trials and shared molecular etiologies underlying multiple rare diseases
- TSC
  - Update on current TSC members, TSC activities (Task Forces and Working Groups), and planned publications
  - New Task Force (planned): N-of-few Therapies

4. Plenary Presentation

- Dr. Philip John (PJ) Brooks, a member of the FCC, presented the BeSpoke Gene Therapy Consortium.

02 June 2022:

5. Update from IRDiRC Members & Scientific Experts

- In-person attendees and some online participants provided updates on their current rare disease projects and initiatives, including challenges and upcoming projects.

6. IRDiRC Task Forces and Working Groups

- Rare Diseases Treatment Access Working Group (in collaboration with RDI)
- Machine Readable Consent and Use Conditions (led by the ISC and ULEIC)
- Shared Molecular Etiologies Underlying Multiple Rare Diseases (led by the ISC)
- Integrating New Technologies for Rare Diseases Diagnosis (led by the DSC)
- Primary Care (a collaboration between FCC, ISC, and DSC)
- Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (led by the FCC)
- Working Group MedTech for Rare Diseases (led by the University of Twente)
- Pluto Project (led by the CCC and TSC)
- Drug Repurposing Guidebook (led by the TSC)

7. IRDiRC Priorities and Strategies

- Task Forces and Working Group
  - Submission Process and Timeline

- Upcoming CA Meetings in the Year 2022
  - 21-22 September 2022 (Online)
  - 30 November to 01 December 2022 (Hybrid) in Paris, France
- Upcoming IRDiRC Events
  - Clinical Research Network (CRN) Conference on 30 November to 01 December 2022 in Paris, France.
  - IRDiRC-EJPRD-RE(ACT) Congress on 15-18 March 2023 in Berlin, Germany.

8. Actions and Deliverables

- Monthly reporting by CA Members of their activities, events, and publications

REPORT

1. Open Meeting Rooms and Exchange

- **Exchange 1:**
  - DSC, FCC, and the CCC discussed topics on:
    (1) Mental health, including effects on care initiation and compliance.
    (2) To focus research on the best support for impact and outcomes aligned to the UN resolution on "Addressing the Challenges of Persons Living with Rare Diseases and Their Families".
  - TSC, ISC, and PACC discussed "Embedding patient interactions in therapeutic developments".
- **Exchange 2:**
  - TSC, FCC, and the CCC discussed "How to move forward on pre-competitive space working". CCC will take the lead in further developing this topic.
  - DSC, ISC, and PACC discussed topics on:
    (1) Methods, standards, and care pathways to link from diagnosis to care for diagnosed rare disorder, or undiagnosed phenotypes.
    (2) Mental health, including effects on care initiation and compliance.
    (3) Integrated care and access to therapies.
    (4) How to focus research on the best support for impact and outcomes aligned to the UN resolution on Addressing the Challenges of Persons Living with Rare Diseases and Their Families.
    (5) Education in RD among general physicians and other health professionals.
    (6) Application of AI tools to better identify RD patients among the general population or populations at risk.
- **Exchange 3:**
  - ISC, FCC, and the CCC discussed "Complex innovation designs of clinical trials".
  - DSC and TSC discussed topics on:
    (1) Consideration of therapeutics in the preventative space and connecting to the topic proposed by the DSC on the continuum of care.
    (2) Linking diagnosis through the full spectrum of care (e.g. Drug and non-drug, health and other sectors).
    (3) Methods, standards, and care pathways to link from diagnosis to care for diagnosed rare disorder, or undiagnosed.
    (4) Integrated Care
    (5) Functional Analysis

2. Parallel Sessions

- **FCC Parallel Session:** The Vice Chair of the FCC presented the survey results and the three FCC task force topics selected to be prioritized, including the list of FCC members who volunteered to

draft the Task Force proposals. The FCC Chairs requested the FCC members to provide their suggestions and comments directly on the SharePoint document or sent by email.

- Proposal 1: Funding models/schemes to support the whole spectrum of RD research and development, from the initial stages of an idea through commercialization, including understanding and solving bottlenecks between public and private partnership.
- Proposal 2: Models for support of data and/or registries within regular funding mechanisms.
- Proposal 3: IRDiRC to mediate and coordinate funding activities and initiatives among the different countries/continents (maybe a strategic group to identify research priorities and align timeline with other funders globally).

➢ **PACC Parallel Session:**

- Patient Engagement in Research
- Research on Facilitating Impact

➢ **DSC Parallel Session:** DSC members used this session to discuss and draft the two Task Force Proposals they plan to submit in September 2022 for IRDiRC Roadmap 2023 and discussed a few additional topics.

- Task Force Proposals
  (1) Phenotyping
  (2) Functional Analysis
- Additional Topics Discussed:
  (1) Linking Diagnosis and Therapy
  (2) Revisiting Phenotyping
  (3) Improving Diagnostic Partnerships with Other Organisations and Consortia
  (4) Standards and Standardization of Data in Rare Diseases in Different Languages

➢ **TSC Parallel Session:** TSC members discussed publication strategies and plans for future Task Forces.

- Task Force proposal on N-of-few therapies
- Publication on personalized medicine and rare diseases
- Drug counter development

3. Summary from Committees (Plenary Session)

➢ **FCC Summary**

- The Vice Chair of the FCC presented the list of FCC planned Task Force proposals:
  (1) FCC Task Force Proposal 1: Understanding how RD funding is approached across the funding spectrum, from the initial stages of an idea through commercialization, including understanding & solving bottlenecks between Public-Private Partnerships.
  (2) FCC Task Force Proposal 2: Models for support of data and/or registries within regular funding mechanisms.
  (3) FCC Task Force Proposal 3: Maybe IRDiRC can mediate and coordinate funding activities among different countries/continents where possible (currently considering whether it could be a Working Group).
- The FCC Vice Chair also presented the plan for the FCC October meeting, which is a roundtable sharing of current funding strategies and challenges in different regions.

(1) What is the current funding scene/strategies in your region/country?
(2) What are some of the challenges or difficulties you are going through or have experienced?
(3) What is currently working well in your region/country, and what can you advise the other funders in this call?
(4) What kind of support do you wish to have from IRDiRC for your region/country?

- **CCC Summary**
  - The Chair of the CCC shared how the Covid-19 pandemic resulted in multiple challenges for companies and the CCC members. During the pandemic, some challenges within the CCC were identified, such as member engagement. The next steps are to share these identified challenges and learnings with the larger group and find solutions to increase CCC member engagement within IRDiRC and its Task Forces.
  - CCC members shared that various companies that are not CCC members yet are currently members of different IRDiRC Task Forces and Working Groups and will be simultaneously invited to participate in the CCC (ensuring that they meet the IRDiRC membership requirement) to broaden the membership. A list of potential companies to be recruited will be prepared. The next step is to gather CCC members for a meeting and identify IRDiRC activities where CCC members can participate in improving companies' engagement and potentially expanding the CCC membership to AI/data/technology companies working on rare disease research.
- **PACC Summary**
  - The Chair of the PACC shared their discussions about patient engagement in research and understanding of the future direction of clinical research. To tackle this topic, the PACC plans to propose a Working Group or Task Force on "Patient Collaboration and Engagement into Transformative Clinical Research" with a recommendation or guideline for patient engagement in research as its outcome. Current existing models will be acknowledged and taken as a basis of the paper and will be expanded more broadly.
  - The PACC members also discussed research on facilitating impact. A systematic review of studies measuring impact worldwide will be done, including a survey to build on previous work. A review paper on "Identifying the resources and training necessary to measure and improve impact" is planned as a deliverable.
- **Regulatory Scientific Committee (RSC) Update**
  - The Vice Chair of IRDiRC provided a brief update on the progress and development of the RSC. The RSC is a new Scientific Committee of IRDiRC alongside the Diagnostics, Interdisciplinary, and Therapies Scientific Committees. It will focus on identifying regulatory and scientific issues common to many or all members that limit achieving IRDiRC goals. It will contribute to Task Forces and Working Groups, including creating pathways for regulatory harmonization and potentially answering regulatory questions. The RSC will include multiple stakeholders (regulatory bodies, patient groups, industry, public and not-for-profit funders, clinicians, and scientists) having regulatory background or experience as a priority.
  - The RSC will be composed of 15 members with balanced geographic and expertise representation. Members of the IRDiRC CA and SCs can nominate candidates until 10 June 2022 and must be sent to the SciSec. The final RSC members will be approved by the CA. The

future RSC Chair and Vice Chair will be elected internally by the RSC members and approved by the IRDiRC Operating Committee. The RSC members will have a minimum of quarterly meetings (by teleconference and once a year in-person) to be coordinated and organized by the SciSec.

- **DSC Summary**
  - The Chairs of the DSC presented the two DSC Task Force proposals planned to be submitted in September 2022:
    (1) DSC Task Force Proposal 1: Phenotyping
    DSC has been discussing its potential scope and how it can be integrated with other technologies.
    (2) DSC Task Force Proposal 2: Functional Analysis
    DSC is considering producing a guideline on how to implement it both in clinical practice and research.
  - The Vice Chair of the DSC shared their discussions about linking diagnosis and therapy and its potential inclusion in care pathways, some of which are currently being tackled by the IRDiRC's Primary Care Task Force. Also, DSC discussed how to expand collaborations with other organizations and different regions. The DSC Vice Chair also mentioned that it is important to incentivize countries/institutions that apply the linkage. The DSC Chair raised how IRDiRC can do strategic and targeted partnerships with other external organizations and improve collaborations.
- **ISC Summary**
  - The Vice Chair of the ISC presented the concept of shared molecular etiologies and basket trials of rare diseases. Autoimmune diseases are usually classified wrongly. There is a working group in Europe for autoimmune disease who are working on re-classifying autoimmune diseases. This could potentially be considered for basket trials. On the contrary, umbrella trials take a longer time than basket trials.
- **TSC Summary**
  - The Vice Chair of the TSC presented an update on the current members of the TSC and its composition in terms of geographical coverage and type of stakeholder. An open call for new members is planned to be launched in Q3 2022, targeting experts from Africa, the Americas, Asia, and Australia. TSC is currently leading four ongoing Task Forces and Working Groups and is participating in four other Task Forces led by other IRDiRC Committees. The TSC Vice Chair also inquired the methodology for counting therapies and how to measure IRDiRC's Goal 2 on 1000 new therapies approved for rare diseases.
  - The Chair of the TSC presented the concept of the new Task Force entitled "N-of-few Therapies. The activity is a build upon work from the Dutch Centre for RNA Therapeutics, 1 Mutation 1 Medicine Europe, and N=1 collaborative. It could be a follow-up chapter from the IRDiRC's Orphan Drug Development Guidebook. TSC also plans to write an article on "Rare Diseases in a Time of Personalized Medicine" and continue working on the Drug Counter. The TSC Chair also presented their discussions and questions on how to incorporate the increasingly divergent views of the FDA and EU in defining conditions and the definition of a "rare condition or disease". The TSC would like to develop a position or white paper on the

role of personalized medicine and evolving classification systems in the context of the "rare" definition.

- The Chair of PACC raised questions on how to make the treatments under research available and accessible to rare disease patients. The DSC Chair mentioned to the PACC Chair that some developing countries get treatment access through partnering with developed countries. An FCC member raised the question on how to find all the rare disease patients and advised to consider including Whole Genome Sequencing with Newborn Screening. Another FCC member mentioned that a trend had been observed in some consortia trying to build the N-of-1, which is an optimized and individualized clinical model for specific patients. It is cost-efficient, innovative, and patient-specific.
- The PACC Chair shared that the WHO and RDI are working together to produce a definition of rare disease (number base), but they acknowledge the continuous change of rare disease definition.

4. Updates from IRDiRC Members and Scientific Experts

- **French National Institute of Health and Medical Research (INSERM, France)** representative presented the achievements of the institution, such as participating in the celebration of Rare Disease Day and organizing a "Scientific Symposium on Rare Diseases", which is supported by the French Presidency of the Council of the European Union (PFUE 2022). Among other achievements was creating a mapping of the research structure in France that is working on rare diseases. There are 330 individual researchers in 23 national structures. A Rare Disease Congress is planned together with Agence National Recherche (ANR), presenting the ten years of funding of ANR on rare diseases. A bi-annual genomics school/workshop will be organized this year in bioinformatics focused on data analysis and processing related to genomics. INSERM is also largely involved in personalized medicine research.
- **AFM-Téléthon (France)** representative highlighted that the Généthon laboratory launched at least five clinical trials, including one focused on Duchenne Muscular Dystrophy. A workshop will be organized with companies that are working on Duchenne to identify causes and types of adverse events. Their stem cell laboratory recently launched two trials, one focused on rebuilding the skin after severe diseases and/or rebuilding burned skin. Généthon can host academic researchers working on vector or stem cell research in their laboratories. Généthon also has the production capacity for stem cell/vector type treatments. The stem cells at Généthon laboratory are stem cells affected by various skin and neuromuscular diseases. The Myology & MitoNICE 2022 Congress will be held on 15-17 September 2022 in Nice, France.
- **University Hospitals Leuven (Belgium)** representative spoke about the lack of orphan drug regulations in Europe, compared with the US and Japan, and the need to constitute a working group with a focus on this topic.
- **National Center for Advancing Translational Sciences (NCATS, US)** representative shared updates on a recent funding opportunity for diagnostics to find novel ways to diagnose rare diseases, including genomics approaches and Artificial Intelligence (three projects). Several of them include a focus on underserved or minority communities. Several efforts have been in place to estimate the cost of undiagnosed and untreated rare diseases (up to 400 billion dollars

annually). The NCATS representative highlighted the cost of gene therapies and genome sequencing compared to the cost of undiagnosed diseases and raised the question of the economic impact of this aspect in the US.

- **National Human Genome Research Institute (NHGRI, US)** representative shared the project of the Undiagnosed Diseases Program, which has ten-year funding. The components of the network are currently working on models for sustainability. One initiative in the Undiagnosed Diseases Network (UDN) is the therapeutic matching committee, which uses the clinical records from different sources/clinical teams, machine learning, and other technologies that might work for rare diseases, especially new and ultra-rare diseases, and then to bring together a group of stakeholders to try to transition families into being able to participate in research around those therapies and work with companies that need participants for developing novel therapies. Another ongoing project is the Diagnostics Working Group, where families submit undiagnosed cases. There will be an international collaborative effort to consult around that case, do bioinformatics analysis, and provide recommendations.
- **Congenica (UK)** representative expressed interest in gene variants, their contribution to phenotyping, and the onset of some observable traits. The second challenge is related to the reference genome and genomic data. An example of collective public datasets is ClinVar, which collects the variants and associated diseases. The disadvantage of ClinVar is that it only represents specific populations. The Machine Learning Group previously developed an algorithm to reclassify variants, a step to understand the diseases' biology and develop the therapies. The Congenica representative mentioned that the work of the Machine Learning Group was combined with the genomics insights and solutions programme and going into one gene and predicting the pathogenic variants in that gene.
- **Vall d'Hebron Research Institute (Spain)** representative shared that in Spain, they are advancing in collaboration with the pediatricians and the adult professionals involved in rare diseases by creating a common association to tackle some of the rare disease topics work on registries. At the Spanish hospital level, some progress in nanomedicine, nanoparticles, and extracellular vesicles research for cancer and lysosomal disorders in the central nervous system were observed.
- **Sheba Medical Center (Israel)** representative shared the recent discovery of 50 genes with a variable of unsignificant changes in paediatric cancer patients during regular diagnostic, but it turned out that these genes are significant to be verified.
- **Asia Pacific Alliance of Rare Disease Organisations (APARDO, Singapore)** representative mentioned submitting nominations for future IRDiRC Task Forces.
- **James Cook University (Australia)** representative emphasized his support for the expansion of IRDiRC to other emerging countries and advised including experts from emerging countries in the different IRDiRC Scientific Committees. He also stressed the importance of increasing collaboration with other organizations working on rare diseases.
- **Fondazione Telethon (Italy)** representative announced the recent launch of 24 research projects with a total investment of around €5.7 million within an initiative co-funded by Fondazione Cariplo (Bank Foundation) on Tdark as defined by the NIH Pharos initiative. Fondazione Telethon revised its investment strategy, changing the structure of its for projects to make them more focused and open on a continuous base with multiple cut-off dates in the

next three years. The aim is to reduce the project length and ask researchers to focus either on targeted identification and target validation or on preclinical/proof of concept to better monitor how the projects evolve along the pipeline. Another news from Telethon research is the launch of a start-up called Iama Therapeutics for neurodevelopmental disorders. The first clinical trial will be launched in 24 months.

- **Dutch Medicines Evaluation Board (The Netherlands)** representative shared the ongoing projects by 16 PhDs working in the agency, and their different publications focused on eight selected themes. She shared the new European Database for Pharmaceutical Policy & Regulation created by the agency currently being developed.
- **EURORDIS (Europe)** shared nine Innovative Medicines Initiative (IMI) projects (public-private projects) on newborn screening and Artificial Intelligence. EURORDIS has a server from their method program, which gathered thousands of voices of patients living with a rare disease and get their experience, needs on the diagnosis journey, issues, challenges, and what could be improved. They are highly involved in the European Joint Programme on Rare Disease. One of the projects of EURORDIS is to build a platform to help developers to perform drug repurposing. They will select and support project leads from academicians with a repurposing initiative. They will help develop the regulatory case and all the steps leading to market access. They aim to create collaboration between the clinician, the researcher, and the patient in the rare disease community to ensure concrete collaboration throughout the whole step of the therapeutic development. It is a real patient-centric approach.
- **Illumina (EMEA)** representative shared their projects on rapid Whole Genome Sequencing (WGS) for critically ill infants. One was a multicentric randomized clinical trial in the US with five different centres, looking at the effect of WGS versus Standard of Care for different genetic test panel with exome sequencing, including the clinical utility but measured by the changing clinical management (already published). A recent publication using rapid whole genome in NICU patient population done in Children's Hospital in Dubai was released. A collaboration with Hanover Medical school was recently established. In collaboration with the Ministry of Health, a national program in Israel was launched with different neonatal units using WGS to identify the benefits of using the whole genome for their patient population. Another project is the iHope project, a project with Genetic Alliance, a global initiative to increase equity and access to whole-genome sequencing for low- and middle-income countries, with specific allocation dedicated to patients in Africa.
- **Rare Disease International (RDI, Global)** shared the success of the recent United Nations (UN) Resolution on Persons Living with a Rare Disease which includes not only a focus on the clinical aspects of rare diseases but also expands considerations with social, economic, educational, and certainly gender disparities. In addition, RDI is working with the World Health Organization (WHO) of the global definition of rare diseases. A Memorandum of Understanding (MOU) with the WHO on the collaborative Global Rare Disease Network was signed with the vision to create a network of rare disease centres of excellence globally. RDI also shared that Canada will be using rare disease drug strategy to develop an infrastructure for rare diseases that would be working with a network of centres of excellence to cover everything from diagnosis to management and monitoring of the use of therapies.

- **University of Twente (The Netherlands)** representative shared details about the Super Phantom Imaging facility, which can help optimize imaging equipment and can help see the actual growth or regression of rare cancers easily.
- **Medicines and Healthcare Products Regulatory Agency (MHRA, UK)** representative shared the work on the UK rare disease framework. Another work is with IMI on a project to create consistency in patient-reported outcomes and to create some guidelines. It includes regulators, US Food and Drugs Administration (FDA), European Medicines Agency (EMA), different companies, and groups. The initial focus is on randomized control trials, and there will be a focus on collecting patient-reported outcome data from single-arm studies.
- **Western Australia Department of Health (Australia)** representative shared about the new Rare Care Centre for Rare Disease, Power of 1 Project, and Lyfe Languages. he Lyfe Languages has now expanded to cover several languages across Australia, Malaysia, New Zealand, Ghana, and North America. It is a web-based platform where indigenous youth can partner with the community and elders to do the translations, both for intergenerational knowledge transfer and cultural well-being, as well as improve healthcare delivery equity. In partnership with SingHealth, 3D facial technology is now applied to monitoring clinical trials and diseases in Singapore. A "Parliamentary Friends Group for Rare and Undiagnosed Diseases" was created to build a birth defects registry using existing infrastructures. They will soon publish extensive genome studies of a few regions of Australia's Aboriginal populations on genomic reference data. 25% of the variance in that set is completely novel (not just the allele frequency data), and the generic genomic architecture is different.
- **ZonMw (The Netherlands)** representative shared about the European Joint Programme on Rare Disease (EJPRD), which they are a co-pillar of the funding part. Three joint transnational calls were launched with 23 participating countries and funded 52 projects with about €66.5 million in collaborative funding, which two of the joint transnational calls are co-funded by the European Commission. Australia is a new partner in the current fourth Call. ZonMw is the acting secretariat of the networking support scheme as part of the EJPRD. The draft of the Rare Disease Partnership (the successor of EJP RD) has been published, and the next step is to develop the Strategic Research and Innovation Agenda (SRIA) as part of the whole process.
- **Agence National Recherche (ANR, France)** representative shared their involvement in the EJPRD like ZonMw. Funding calls on priorities on rare diseases are ongoing on the national level in France on transnational diseases. A congress, co-organized with INSERM, about the 10-years funding activities of ANR on rare diseases will be organized in Paris on 21 November 2022.
- **Vilnius University Hospital Santaros Clinic (Lithuania)** representative raised the topic of care organization and Universal Health Coverage (UHC) for rare diseases. She mentioned that maybe there is a lack of research for evidence-based policy making for rare diseases and that it would be great to collaborate with IRDIRC for that evidence-based part of the research on health care organizations. Another topic she raised is education and capacity building. Without education, we will not have a workforce to research and a healthcare workforce who knows the diseases well, recognizes them, and refers to highly specialized services. Education should be incorporated into the whole ecosystem, as there is no current alignment of national and international policies in education.

- **European Commission (EC, Europe)** representatives shared their recent exchange with the European Federation of Pharmaceutical Industries and Associations (EFPIA) on how the industry can contribute to the different EU policies and contact IRDiRC leadership to create synergies. The European Rare Disease Partnership (RDP) concept paper was recently published in February 2022. It will be built on the results and the lessons learned from the EJP RD. The RDP is a co-funded partnership with European and associated countries that will be open to foundations, international partners (such as the US and Canada), and the industry. It is directed strategically by the research funders but with the alliance to build together a strategic agenda. There is a current process of building a Strategic Research and Innovation Agenda (SRIA) for its roadmap and activities prioritization, where all the partners will commit. The European Commission will commit €100 million in 2023 with the Member States for the RDP. Concerning acceleration of new therapeutic development, approximately €60 million in 2023 for seven to eight new projects, with around €8 million each, will be committed. The projects will work in different levels of the innovation path from preclinical proof of concept to clinical trials, proof of the clinical validity or efficiency of the orphan designated product, with applied modern technologies, data-driven approaches in silico approaches such as AI algorithmic, big data analytics, novel clinical trials design. Regarding the European Research Networks (ERNs), it has expanded to include more than 860 specialized clinical units, and since January 2022, it has involved more than 1500 interested units in Europe. Now, all the 24 ERNs have one type of funding with one model financial instrument, with a bridge ground that will be launched or has been launched in March 2022 until mid of 2023. In addition, a Super Computing Center in Barcelona, in alliance with several ERNs and clinical centers in Europe (in the Solve-RD project), was established to work on "solving the unsolved" rare diseases in Europe. It was initiated in 2018 and will run for five years until 2023. The Center did a massive reanalysis of genomic and exome sequences from different cases, which were not solved by different healthcare. They have inconclusive results about the pathological mechanism or the mutations involved. At the end of 2021, a reanalysis using machine learning, and big data analytics of more than 5000 cases, out of which 500 cases were solved (approximately 10% increase rate in diagnostic accuracy). 1 Million Genomes Initiative, which involves the several Member States, bringing together 22 EU countries, the UK, and Norway, with a goal in 2022 to have at least access to 1 million sequenced genomes across Europe in a federated type of infrastructure, which an IRDiRC DSC member is very much involved. Remedy for All project is a new large-scale project for drug repurposing for a common platform in Europe wherein three or four demonstrators are on rare diseases. It will start on 01 September 2022 with €15-20 million.
- **Indian Organization for Rare Diseases (IORD, India)** shared about Asha workers. The central government appoints Asha workers to work with the rural population in India. The Asha workers, together with villagers, oversee the child immunization, nutritional requirements, and ideal needs of adults and children. Asha workers see all patients, rare, along with healthy people. Therefore, Asha workers are a great source to collect information and data at a fraction of the cost. India has 29 states, ten union territories, and more than 1.3 billion people. The central government currently employs 1 million Asha workers. On 23 May 2022, at the 75th World Assembly, Asha workers were honored for their crucial role in connecting the community with the health system to ensure Primary Health care services. Through the established network with

different funding agencies, a mechanism was created in which discoveries get translated into therapies and diagnostic tools. In addition, a dedicated office for orphan product development (similar to US-FDA) was requested by the Indian Ministry of Health and is currently being reviewed.

- **Innoskel (France)** representative shared their overall progress. With now 40 FTE in 1000 square meters in the French Riviera (close to Nice). Innoskel is highly focused on rare bones. Using novel technologies, their lead product is lentiviral for skeletal dysplasia, such as type 2 collagen disorder. All proof of concept is done internally, with access to models and testing in large animals in their laboratories, including a site for manufacturing. In addition, a big natural history international study in skeleton space was launched. Also shared was the effect of the COVID pandemic on their regulatory activities and challenges with regards to epidemiology for various diseases and the existing information siloes and questions of nomenclature and coding that makes it difficult to get good and robust data.
- The current IRDiRC Chair, also the **Sanford Health (US)** representative, shared the challenges encountered in building some infrastructure in New Zealand, Costa Rica, and Ghana (countries with similar primary care delivery to the US). There is a lack of diversity in science in general. Sanford Health is currently working on projects and research to identify the diversity of the human genome. The first phase is to register people, then biobank samples, and then identify the diversity of genome from different samples from Ghana (for African population), Costa Rica (Latino population), and New Zealand (Samoan population). Another project that Sanford Health would be leading is type 1 diabetes.
- **Foundation for Rare Diseases (France)** representative shared the new Rare Disease and Orphan Drugs (RDODJ) Journal, which can host a special edition for IRDiRC that could include how rare disease research and treatment in different regions are organized. In addition, Foundation for Rare Diseases has been coordinating a series of courses on rare disease topics through the online platform Massive Open Online Course (MOOC). Some topics covered are the different technology for diagnosing rare diseases, including genetic testing.
- **BGI Genomics (Europe)** representative shared their mission to democratize omics for people across the globe, reflected by their global presence in Asia, Europe, and United States.
- **Istituto Superiore di Sanità (ISS, Italy)** representative shared the new Italian law on rare diseases following the recent UN resolution to include the different European Reference Networks located in Italy to be embedded in the national network for rare diseases. The general framework includes education, equity, and social factors. In Italy, since a few years ago, there has been a law on Newborn Screening, which is a system that allows newborns to be screened for more than 40 rare metabolic diseases. The second national plan on rare diseases will soon be published to discuss increased research, diagnosis, and treatment. The Ministry of Health and ISS has organized Webinars. In addition, the Ministry of Health committed €50 million to rare disease research projects. ISS hosts the website of Undiagnosed Diseases Network International (UDNI). A new rare disease law was implemented that the national rare disease center is located permanently in ISS.
- **National Institute of Health Carlos III (ISCIII, Spain)** representative shared the ongoing collaboration with UDNI and the National Center for Genomic Analysis. In addition, a national program for personalized medicine with a significant investment in genomic analysis and data

science, including the Super Computing Center in Barcelona. ISCIII has been continuously collaborating with EJPRD and for the future RDP with the EC. Regarding therapeutics, ISCIII is planning and will soon approve the inclusion in the national strategy of creating a new Center for Advanced Therapies. ISCIII also mentioned the role of The Spanish Federation of Rare Diseases (FEDER) in the recent UN resolution on rare diseases with RDI. ISCIII recently submitted to IRDiRC their list of funded projects (with €18 million investment) and emphasized the value of collaborative efforts of the different IRDiRC funders to submit their list of funded projects to be an example for others the list of projects that the different funders have been funding.

5. IRDiRC Task Forces and Working Groups

- Updates on ongoing and foreseen activities were presented by Task Force/Working Group leaders.

- **Nine Activities are Ongoing for the Year 2022 (Task Forces and Working Groups):**
  - IRDiRC-RDI Global Access Working Group (in collaboration with RDI)
  - Machine Readable Consent and Use Conditions (led by the ISC and ULEIC)
  - Shared Molecular Etiologies Underlying Multiple Rare Diseases (led by the ISC)
  - Integrating New Technologies for the Diagnosis of Rare Diseases (led by the DSC)
  - Primary Care (in collaboration between FCC, ISC, and DSC)
  - Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (led by the FCC)
  - Working Group on MedTech for Rare Diseases (led by the University of Twente)
  - Pluto Project – Disregarded Rare Diseases (led by the CCC and TSC)
  - Drug Repurposing Guidebook (led by the TSC)

- **IRDiRC-RDI Global Access Working Group**
  - Presentation: Durhane Wong-Rieger from RDI (PACC Chair) presented the updates and summary of progress. This WG is a collaboration with RDI.
  - Objective: The goal is to improve access to rare disease medicines by creating a list of standard-of-care medicines, looking at innovative schemes, and identifying the systemic and idiosyncratic barriers to access (e.g., barriers in screening, treatment, aftercare, cost, and exclusivity expiration, etc.), especially in low-and-middle-income countries, and potentially working to include RD medicines in the WHO's Essential Medicines List and then identify how different healthcare systems can incorporate it.
  - Progress Update: This WG is currently developing a cystinosis case study i.e., identify the barriers encountered by different stakeholders to accessing cystinosis drugs in different regions and develop recommendations. The planned country case study in Ghana.
  - Expected Output: Publication based on case study approach to describe the barriers to access stratified by types of therapy, characteristics of rare disease populations, and key country parameters.

- **Machine Readable Consent and Use Conditions**
  - Presentation: Esther van Enckevort from University Medical Center Groningen (UMCG) presented the updates and summary of progress. This Task Force is led by Esther van Enckevort (from ISC) and Anthony Brookes (from the University of Leicester (ULEIC). The team comprises of approximately 40 international scientists.
  - Objectives: To create machine-readable profiles for consent and use for registries and biobanks by building on Global Alliance for Genomics and Health (GA4GH) + IRDiRC standard data structures and semantics.
  - Progress Update: Devised a Consent form template for European Reference Networks (ERN) Registries (ontologized); Devised, tested, and validated a flexible data structure (DUC) for consent and use conditions (CCE); Created and optimised a list of 19 commonly relevant, atomic CCEs as a basis for DUC content; and Mapped CCEs to existing ontologies for semantic content.
  - Expected Output: Work with ontology developers to define new classes and properties to fill gaps identified in the ontologies; Extend the CCE concepts to provide a basis for consent and use conditions at record level, in DUC format.

- **Shared Molecular Etiologies Underlying Multiple Rare Diseases (SaME)**
  - Presentation: Marc Dooms from the University Hospital of Leuven presented the updates and summary of progress. This Task Force is led by the ISC (PJ Brooks and Marc Dooms).
  - Objectives: To assess the global landscape of clinical trials of drugs with SaME, including approaches to identify and include patients, and to identify potential clusters of rare diseases that may benefit from the SaME approach. The group would also like to explore the applicability of the tissue-agnostic oncology basket trials framework for basket trials of drugs targeting SaME underlying multiple rare diseases and identify the roadblocks, potential regulatory pathways, and ethical issues for such trials.
  - Progress Update: Landscape analysis and collection of information on basket clinical trials for rare diseases (shared molecular commonalities, trial design, and analysis).
  - Expected Output: Recommendations paper on the key considerations for setting up basket clinical trials in RD.

- **Integrating New Technologies for Rare Diseases Diagnosis**
  - Presentation: Clara van Karnebeek presented the Task Force objectives, timeline, updates, and summary of progress, including the presentation of the new Co-Chairs. This Task Force is led by the DSC Clara van Karnebeek and Gareth Baynam).
  - Objectives: To identify new technologies in development or in experimental use which would likely increase the diagnostic rate of rare diseases patients and to develop a clinical framework or guideline for implementing a combined diagnostic approach of metabolomics, genomics, and AI.
  - Progress Update: Survey was distributed to ask members for suggestions on the manuscript outline and which sub-topic they will write; Result of the survey was presented last May 24th; Key questions have been identified for the manuscript; Currently, the Task Force is on writing phase and collection of literature.

- Expected Output: Publication Title "Leaving No Patient Behind! Innovative Technologies to Diagnose Rare Diseases".

➢ **Primary Care**

- Presentation: Gareth Baynam from the Western Australia Department of Health presented the updates and summary of progress. This Task Force is led by the DSC (Gareth Baynam), FCC (Adam Hartman), and Stephen Groft (from NIH/NCATS). The call for nominations was opened for one month and ended last October 29, 2021. The Sci Sec received 35 applicants from North and South America, Europe, Africa, Asia, the Middle East, and Australia.
- Objectives: To bring together representatives from different stakeholders to identify the current state of play, priority research areas, and the challenges and opportunities in rare diseases research in primary care.
- Progress Update: Survey was distributed to ask members about the top three priority topics; Manuscript outline created; Writing groups formed, and currently in the writing phase and collection of literature.
- Expected Output: Publication Title: Empowering Rare Disease Patients, Patient Advocates, and Primary Care Providers to Improve and Optimize Patient Care Pathways.

➢ **Enabling and Enhancing Telehealth for Rare Diseases Across the Globe**

- Presentation: Melissa Parisi from NIH/NICHD and Faye Chen from NIH/NIAMS presented the updates and summary of progress. This Task Force is led by the FCC.
- Objectives: To conduct a survey and systematic review of existing telehealth models and identify its barriers and opportunities to improve access to rare diseases diagnosis, care, and research, and leverage the output to develop best practices for introducing telehealth services into the rare diseases' community.
- Progress Update: World Health Organization (WHO) definition of Telehealth was selected for this Task Force; Survey on keywords for literature search was performed; Collection of related literatures was performed; Collected literature (430 literature) was categorized into three groups based on relevance (Group 1: Diagnosis, Treatment, and Prevention; Group 2: Research and Evaluation; Group 3: Continuing Education for Healthcare Providers); currently, this Task Force is reviewing abstracts. Additional members will be added to cover all the planned activities.
- Expected Output: Identify barriers, facilitators, and "best practices" for introducing Telehealth services into rare disease communities, culminating in a publication that summarizes the literature search and key stakeholder interviews.
- Comments from the Audience: Gareth Baynam shared that in Australia, on-site mental health services funding was reduced as an effect of Telehealth. Dave Pearce shared that in February 2020, Sanford Health had two video/virtual visits, and after a telehealth infrastructure was installed, it resulted in 3000 video visits in March 2020.

➢ **Working Group on MedTech for Rare Diseases**

- Presentation: Anneliene Jonker from the University of Twente presented the Working Group's updates and summary of progress, including the current Orphan MedTech industry

landscape and developments globally. This Task Force is initiated by the University of Twente (The Netherlands).

- Objectives: To understand and map the current incentives, supportive frameworks, and possibilities for harmonization. The group would also like to identify the regulatory landscape in the different regions for medical devices. Furthermore, the group wants to raise further awareness for the field of medical technology in rare diseases.
- Progress Update: Agreement on definition of medical technology has not been finalized but collected official definition from FDA, EC, and Pharmaceuticals and Medical Devices Agency (PMDA); Discussions on literature review; Exploration of the regulatory landscape of medical devices (from FDA, PMDA, and EU Notified Bodies).
- Expected Output: Publication providing a comprehensive overview of incentives and frameworks for medical devices around the world, opportunities for harmonization approaches in the regulatory space, and patient involvement in medical device development. Orphanet Journal of Rare Diseases has agreed to a special issue on this topic.

➢ **Pluto Project on Disregarded Rare Diseases**

- Presentation: Daniel O'Connor from MHRA presented the Task Force updates and summary of progress.
- Objectives: To identify those rare diseases that appear to have attracted virtually no interest from academic researchers and industrial developers; determine the characteristics they have in common; and understand roadblocks in developing effective treatments for such diseases.
- Progress Update: A new working definition of a disregarded (under-researched) rare disease has been drafted as a disease that has a "4-Zero Concept": No clinical trial activity, No scientific publication available, No regulatory authority orphan drug designation, and No approved medicine/therapy. Database incorporating data from different sources has been constructed and analysed. Based on the initial definition, there were 992 (17%) out of 5698 rare diseases
- Expected Output: Recommendation paper describing identified commonalities between disregarded RD, roadblocks for therapy development, and opportunities to overcome them and foster research and development
- Face to Face Meeting: Requested for 28-29 November 2022

➢ **Drug Repurposing Guidebook**

- Presentation: Anneliene Jonker from the University of Twente presented the Task Force updates and summary of progress.
- Objectives: To create a guidebook focused on repurposing approaches (incentives, regulatory tools, initiatives, development tools, etc.).
- Progress Update: Presentation of the methodology used for the Orphan Drug Development Guidebook (ODDG) and past IRDiRC activities on drug repurposing. The group will start identification and integration of the building blocks
- Expected Output: Create a guidebook describing the available tools and initiatives for drug repurposing and how to best use them.

- Face to Face Meeting: Requested for 13-14 October 2022

6. IRDiRC Priorities and Strategies

- **IRDiRC Members Diversity and Expansion of Geographic Coverage**
  - Increase representation from emerging countries
  - Increase involvement of industry

- **IRDiRC Increase in Publications and Output:**
  - A working group on Newborn Screening will be organized to submit a special edition to Rare Disease and Orphan Drugs Journal.

- **IRDiRC Task Force (TF) and Working Group (WG)**
  - TF/WG proposal submission deadline is September 2022.
  - TF/WG proposals review and approval from October to December 2022.
  - Selected TF/WG proposals to be announced on 16 December 2022.
  - TF/WG proposals are submitted firstly to the IRDiRC Operating Committee to review their completeness and state of the art, their linkage to the IRDiRC goals and whether it is a topic specific to rare disease, its strong translational potential and international scope, and well-defined objectives, timeline, and deliverable. It is highly advised to collaborate with other IRDiRC Committees and global organizations.
  - The SciSec will disseminate a one-pager about the TF/WG process, requirements, and responsibilities, including the TF/WG proposal template, to the CA and SC members.
  - All IRDiRC Task Forces must be completed by December 2023 to ensure budget coverage by the European Commission through the EJPRD (the end of EJPRD is December 2023).

- Upcoming IRDiRC Meetings and Events
  - Year 2022 CA Meetings (2):
    (1) 21-22 September 2022 (online)
    (2) 30 November to 01 December 2022 (F2F): This Face-to-Face meeting will be organized back-to-back with the Clinical Research Network Conference in Paris, France, which is co-organized with the European Joint Programme on Rare Disease (EJPRD).

  - Upcoming Operating Committee (OpComm) Meetings (6): Monthly

  - Upcoming IRDiRC Events (2):
    (1) Clinical Research Network (CRN) Conference on 01-02 December 2022 in Paris, France, in collaboration with the European Joint Programme on Rare Disease.
    (2) RE(ACT) Congress on 15-18 March 2023 in Berlin, Germany, in collaboration with BlackSwan Foundation and the European Joint Programme on Rare Disease.

- Interdisciplinary Constituent Committee (ISC) Open Call for Nominations to be launched in July 2022.

- Communication Activities
  - New IRDiRC website launched
  - New IRDiRC Animated Introduction Video
  - New IRDiRC YouTube Account
  - New IRDiRC State of Play of Rare Diseases Research Initiatives 2019-2021

7. Actions and Deliverables

- Monthly Reporting by CA Members
  - The Sci Sec has been collecting a monthly update/report from the CA members on their key activities, events, and publications for dissemination with all IRDiRC networks and publishing them on IRDiRC media platforms (website and social media).