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Fourth List of research and innovation needs requiring medium- or long-term approach and related Task Forces

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1. Objectives and methodology

The goal of the D2.19 “Fourth List of research and innovation needs requiring medium- or long-term approach and related Task Forces” differs from the preceding deliverable D2.17.

The aim of deliverable D2.17 “Fourth List of research and innovation needs requiring medium- or long-term approach and related Task Forces” was to provide guidance only for the research and innovation needs that require action in the medium (2021-2023) and long term (next phase of the EJP RD - beyond 2023) and which could be transformed into future task forces.

This deliverable 2.19 is focused on the development process of IRDiRC's Roadmap 2022: starting from the inception of Task Force proposals, through their selection, and finally their outputs. The aim is to retrospectively map out IRDiRC's achievements in the year 2022. Moreover, this deliverable presents the Task Force selection process implemented by IRDiRC for their Roadmap 2023, that took place in the fall of 2022.

2. Background

The management of the medium and long-term research strategy questions and their dedicated linkage with Task Forces of the International Rare Diseases Research Consortium (IRDiRC) is part of the WP2 – Strategy, Task 2.4 in EJP RD.

IRDiRC unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organizations, and researchers from all over the world to drive and promote international collaboration and advance rare diseases research strategy worldwide. It's overarching vision for 2027 is 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**”. Many of the EJP RD organizations, including the European Commission are also members of IRDiRC and participate actively in different committees. Furthermore, the Chair and Vice-Chair of IRDiRC are members of EJP RD Policy Board. Finally, the Scientific Secretariat (SciSec) of IRDiRC is ensured by the coordination team of the EJP RD. Such strong connection is a mutual advantage and prevents duplication of efforts.

It is important to underline that EJP RD agreed that close collaboration and follow up of the IRDiRC goals and strategic recommendation is central to all EJP RD actions and thus no specific Scientific Board have been established within EJP RD. However, the EJP RD consortium has the possibility to analyse the RD landscape and propose relevant complementary actions that are of benefit for all RD community. This is being done in collaboration with EJP RD Policy and Governing Boards.

It was agreed that any research strategic question or need identified by the EJP RD Policy Board as requiring medium or longer-term approach will be studied in relation to the ongoing or future Task Forces planned within IRDiRC activities.

At present, each of the IRDiRC Scientific (Diagnostics, Interdisciplinary, Therapies, Regulatory) or Constituent (Fundors, Patients Advocacy, Companies) Committees has

the possibility to seize upon specific RD research need or bottleneck and propose a Task Force aiming at issuing recommendations to overcome the identified obstacle. These proposals are evaluated, prioritized, and submitted for final validation through unanimous vote by members of the IRDiRC Consortium Assembly (CA).

The setting up of a Task Force (TF) follows a well-established scheme in accordance with IRDiRC procedures, composed of the following steps:

- i. From January to September of each year, IRDiRC Constituent and Scientific Committees identify actionable topics that can advance RD research and subsequently write an activity proposal following the IRDiRC activity proposal template, which includes the following elements: background of the topic, objectives of the activity, foreseen impact on the RD community, project plan and timeline, expected output/deliverable, required members expertise, planned potential collaboration with other organizations, and sustainability plan;
- ii. The Scientific Secretariat provides support to the different Constituent and Scientific Committees in preparing their activity proposal document. In October of the same year, all activity proposals are submitted to the IRDiRC Operating Committee (OpComm) for preliminary review and provision of recommendations, including identification of potential synergies between proposals. In November of the same year, the Scientific Secretariat sends all the activity proposals to the Consortium Assembly for review, indicating which proposals are recommended by the OpComm. The Consortium Assembly is given three to four weeks to review all the submitted proposals. The OpComm-recommended activity proposals are presented during the December Consortium Assembly meeting, wherein, members of the Consortium can challenge the activity proposers and raise questions. An online vote is launched by the Scientific Secretariat for two weeks to the Consortium Assembly after the proposals are presented. Result of the online vote is released before the end December;
- iii. Preparation and launch of Call for experts to constitute the Task Force are done by the Scientific Secretariat with the respective activity proposers during Q1 of the following year;
- iv. Establishment of the Task Force is commenced in Q2;
- v. Each Task Force has 12 to 18 months of work including regular conference calls, and an optional in-person workshop ;
- vi. Each Task Force produces their final recommendations and/or roadmap to be followed by the engaged stakeholders, generally through publications or toolkits (enquirers);
- vii. The Scientific Secretariat, together with IRDiRC members and the Task Force members, continuously disseminate all IRDiRC activity outputs.

Usually, the IRDiRC SciSec is responsible for managing and overseeing the selected Task Forces. However, in case of actions or activities proposed that are considered of high importance, the involvement of additional partners on both EJP RD and IRDiRC side would be expected.

The establishment of an IRDiRC Task Force involves a significant emphasis on collaboration with the EJP RD program. Notably, a considerable number of individuals holding pivotal strategic roles within the EJP RD program, including Task Leaders, Work Package Leaders, and even Pillar Leaders, also hold membership in IRDiRC Task Forces, as delineated in subsequent sections of document D2.19. This interdependence underscores the robust partnership between EJP RD and IRDiRC, aligning with the overarching, enduring strategy of the EJP RD initiative and the IRDiRC consortium.

Due to considerable delays caused by the unprecedented impact of the COVID-19 pandemic, the planned publication of a new roadmap in 2022 did not take place. In consequence, the year 2022 focused on the deployment and management of activities initially launched in 2020 and 2021.

3. List of IRDiRC Task Forces, Working groups and Initiatives in 2022

3.1. IRDiRC-RDI Global Access Working Group

a. Introduction

Treatments are often 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. The goal of this Working Group, leaving no one behind, requires that access to treatments be available for rare disease patients.

b. Objectives

The goal is to improve standards of care for RD patients by promoting access to approved medicines, to initiate research into barriers to accessing RD medicines and to define opportunities to address those barriers. The Phase 1 of this WG was concluded through the publication of a paper in July 2021 entitled "Essential list of medicinal products for rare diseases: recommendations from the IRDiRC Rare Disease Treatment Access Working Group". Phase 2 is using a bottom-up approach to identify common themes and challenges, and approaches on how the problems were addressed in different countries by gathering real experiences and case studies (cystinosis, cystic fibrosis) regarding the accessibility to medicines and by analyzing the approaches taken by different stakeholders to source medicines and promote the changes in a systemic way.

c. Output

Outputs will be presented in an article (the article is being prepared at the moment of the writing of this deliverable).

3.2. Chrysalis Project

a. Introduction

This project will identify key criteria that would make rare disease research more attractive to industry for research and development. In order for industry to initiate or continue research into rare diseases, it must overcome barriers specific to the nature of rare disease research. We expect that certain minimum conditions must be fulfilled and that these will be both financial and non-financial.

Funders of rare disease research have a double effect of meeting their own goals as well as reducing the barriers to further research. This may be via natural history studies, patient registries, epidemiology studies or by reducing the risks of investment.

The Chrysalis project seeks to explore these barriers, as well as the criteria for investment into rare disease research and development, by serving as a link between industry, funders and advocates.

b. Objectives

The Chrysalis Project aims to (1) identify the key criteria that determine the attractiveness of rare disease research to industry; (2) identify gaps in the current funding opportunity landscape to develop the criteria identified in #1; and (3) identify other non-financial barriers related to the attractiveness of meeting the criteria identified in #1.

c. Output

An article entitled "The IRDiRC Chrysalis Task Force: Making Rare Disease Research Attractive to Companies" was published in Therapeutic Advances in Rare Diseases Journal: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10387802/>

3.3. Sustainable Economic Models in Drug Repurposing

a. Introduction

In recent years, new business models (e.g. patient-led R&D efforts) – alternative to the predominant pharmaceutical and academic R&D models – have emerged to address remaining patient unmet need, specifically in under-researched and/or low prevalence rare conditions. The main aim of the project is to identify key take-aways and potential recommendations to IRDiRC stakeholders regarding the suitability and key recurring elements on sustainable economic models for development and commercialization of orphan drugs.

b. Objectives

- Review successful case of academic and industrial drug repurposing;
- Identify their characteristics and similarities;

- Characterize the specificity of their economic models and their long-term outcomes;
- Develop recommendations to IRDiRC stakeholders and the RD community.

c. Output

An article entitled “Sustainable approaches for drug repurposing in rare diseases: recommendations from the IRDiRC Task Force” was published <http://dx.doi.org/10.20517/rdodj.2023.04>

3.4. Machine Readable Consent and Use Conditions

a. Introduction

IRDiRC has previously invested a lot of effort towards defining better data structures (ADA-M Task Force) and improved harmonization of consent clauses (Generalized consent clauses Task Force), in order to improve the access to patient data in RD registries and biological samples in RD biobanks. With the publication of the FAIR Guiding Principles for Scientific Data Management and Stewardship (Wilkinson et.al. 2016) and adoption of the FAIR principles in the guidelines for RD registries (Kodra et.al. 2018), it is important that this work is adapted to incorporate the FAIR principles.

b. Objectives

The main objective of this Task Force is to explore and understand the current range of needs, activities and gaps around data tools and standards for digital management of consent and use conditions. Enabling machine readable representation of the consent of patient data in the biobanks and registries will contribute towards:

- More regularised consent forms and statements;
- Easier storage and less ambiguous exchange/communication of consent and use conditions; A basis for federated incorporation of such information into such things as discovery networks;
- Computer-readable/actionable semantic representation of consent and use conditions, towards enabling automated data sharing decisions.

c. Output

Two articles are currently under review will be published in Q3 2023.

3.5. Shared Molecular Etiologies Underlying Multiple Rare Diseases

a. Introduction

While there are several thousand rare diseases, the number of underlying molecular etiologies is far fewer. Moreover, there are ongoing research efforts and drug development efforts to target these shared molecular etiologies.

Grouping rare disease patients based on the underlying molecular etiology, rather than the traditional, symptom-based definition of disease, has the potential to in effect reduce the numbers of disease, while greatly increasing the number of patients gaining access to clinical trials. Importantly, the basic approach of enrolling patients in “basket” clinical trials based on a molecular marker, rather than clinical features or organ system, is becoming common in the field of oncology, and has been accepted by the US FDA, resulting in drug approvals.

Therefore, the focus of this activity is to adapt the molecular targeted basket trials approach from oncology and apply it to drugs that target shared molecular etiologies underlying multiple rare diseases.

This Task Force will address and document the existing challenges in adapting the basket trial approach used in molecularly targeted oncology clinical trials to drugs targeting shared molecular etiologies underlying multiple rare diseases. Activities include to identify how previous, ongoing, and planned initiatives will address these challenges, provide to potential funders recommendations for how they might help accelerate this process, and thereby greatly expanding the number of rare disease patients in clinical trials.

b. Objectives

- To assess the global landscape for development of drugs targeting same molecular etiologies.
- To develop a framework for basket trials of drugs targeting shared molecular etiologies underlying multiple rare diseases, based on the success of tissue agnostic basket trials in oncology.
- To identify potential regulatory roadblocks to such rare disease basket trials, and solutions to overcome them.
- To explore strategies to identify patients that would be eligible to participate in same molecular etiologies clinical trials.

c. Output

An article entitled “Targeting shared molecular etiologies to accelerate drug development for rare diseases” was published <https://doi.org/10.15252/emmm.202217159>

3.6. Integrating New Technologies for Rare Diseases Diagnosis

a. Introduction

Technological advances in the areas of metabolomics, large scale genomic sequencing, and machine learning algorithms are being combined in research settings to increase the diagnostic yield in rare diseases. When combined with a rapid technological pace of change, it is likely that the widespread adoption of combined metabolomics and genomic technologies will be relatively slow, due to high costs and the lack of a standardized diagnostic framework. However, as has been demonstrated with the clinical adoption of whole exome sequencing, it is possible to

move new technologies into mainstream diagnostic laboratories once the benefits have been clearly proven in the research setting.

b. Objectives

The New Tech Task Force aims to (1) to identify new technologies in development or in experimental use which are likely to increase the diagnostic rate for patients with rare diseases, (2) identify opportunities to enable the safe, widespread clinical adoption of the most elective technologies in a meaningful timeline, and (3) develop a clinical framework/guideline for implementation of the combined diagnostic approach of metabolomics/genomic/AI.

c. Output

An article under review will be published.

3.7. Primary Care

a. Introduction

Individuals living with rare diseases typically present first, and often recurrently, to their primary care providers (PCPs). PCPs are therefore central to all aspects of patients

b. Objectives

This Task Force aims to (1) bring together representatives from the stakeholders required to identify the priority research areas in primary care that need to be addressed to deliver against the IRDiRC goals, (2) identify current state of play, and (3) identify challenges and opportunities in rare diseases research in primary care. This may include the following areas: diagnosis, therapies, ELSI, and patient engagement.

c. Output

An article under review will be published.

3.8. Enabling and Enhancing Telehealth for Rare Diseases Across the Globe

a. Introduction

Telehealth, whose value has been enhanced by the recent COVID-19 pandemic, has the tremendous potential to revolutionize medical care for rare disease patients. Due to multiple factors limiting access to expert care for individuals with more than 700 rare disease conditions, telemedicine has the unique capacity to increase access effectively and efficiently to expert care and information for those who would otherwise have no or limited access. While the demand and use of telehealth have decreased with the pandemic gradually under control, the value and effectiveness of telehealth need to be evaluated and demonstrated for its continued uptake. The undeniable potential of telehealth also needs to be maximized to be most "fit for purpose", and factors leading to the optimal use cases need to be better understood, as do barriers responsible for suboptimal uptake and use which can serve as opportunities for improvement. In this way, best practice telehealth can be delivered

to establish, or enhance and augment efforts to expand local capacity when resources exist to do so.

b. Objectives

The Telehealth Task Force aims to (1) conduct survey and systematic review of existing models of telehealth, their uptake and usage by the rare disease community, and their specific value and effectiveness, to identify the factors that enhance or limit their adoptability, sustained use, efficiency/ease of access, and effectiveness in the rare disease community; (2) identify barriers to and opportunities for the use of telehealth to improve access to diagnosis, care, and research experiences for rare disease patients—including technological, legal, cultural, linguistic, healthcare system, and patient/provider factors; and (3) develop “best practices” for introducing telehealth services into communities where they would be most beneficial using realistic and culturally-sensitive approaches, in partnership with local providers.

c. Output

An article under review will be published.

3.9. **MedTech Working Group**

a. Introduction

The Therapies Scientific Committee, the Interdisciplinary Scientific Committee and the University of Twente, the Netherlands, are jointly establishing a Working Group to explore the role and value of medical devices in rare diseases. The Working Group will primarily focus on devices used for either the treatment of rare diseases, such as implants, or devices used to support physical activities of patients, such as exoskeletons.

The development of ‘orphan’ devices faces scientific and technological challenges, next to the need for an improved clarity regarding the requirements for specific technical and functional needs for each device (development, clinical trial, regulatory aspects). As such, the Working Group aims to create a better understanding and enhanced awareness of device developer’s needs, the standardized outcomes to define user needs for devices, and to offer a groundwork for developing solutions to improve the (regulatory) landscape of MedTech use for rare disease patients. To truly focus on these aspects, the Working Group will not focus on the reimbursement of medical devices.

b. Objectives

Understand and map out the current incentives and supportive frameworks for the development of medical devices in rare disease and the need for harmonization of approaches, in different geographical contexts. This will also provide a clearer image of what is needed to gain approval for an orphan device in different geographies.

Understand and identify unmet technical and functional needs. While there is a considerable variety between different devices, few studies have investigated user requirements, specifically for clusters of medical devices. This should also focus on how patients interact with medical devices.

Understand and identify the possibilities for patient involvement in the medical device design process. Patient involvement in medical technology development is essential, among others, in recognizing unmet needs, setting up collaborations, providing guidance on functional needs, in stimulating regulatory approval and gaining access to technologies.

c. Output

An article under review will be published.

3.10. **Drug Repurposing Guidebook**

a. Introduction

Developers in the rare diseases field, particularly those engaged in repurposing approaches, include diverse stakeholders ranging from big pharma, but increasingly and more often to clinicians and not for profit organisation including patients-led initiatives. Hence the whole Rare Disease Community and in particular the patients would benefit from a guide helping developers to navigate the regulatory & development tools and resources, efficiently and effectively repurposing medicines in new rare disease indications.

b. Objectives

The objective of the Drug Repurposing Guidebook is to help developers (of all kinds) navigating the rare disease landscape and identifying specific tools and practices of relevance for repurposing projects. The creation of the Development Guidebook will focus on repurposing approaches, following the same successful methodology used for the Orphan Drug Development Guidebook, i.e. explore incentives, regulatory tools, initiatives, development tools ('building blocks') that exists or are missing for drug repurposing.

c. Output

An article under review will be published. Addition of the materials (building blocks, checklist, use cases) to the Orphan Drug Development Guidebook.

3.11. **Pluto Project on Disregarded Rare Diseases**

a. Introduction

As of today, less of 6% of rare diseases have approved treatments and most of the drug development efforts are actually concentrated on a limited number of conditions. Therefore, there are many rare diseases with little or no research activity, the so-called "disregarded rare diseases". Many technical and social reasons may account for this: lack of disease knowledge and academic interest, the pathophysiological complexity of many diseases, cellular localization of the defective protein (for genetic diseases), diagnostic complexity, and – possibly above all – extreme rarity. Although the existence of a large group of "disregarded" rare diseases is unanimously acknowledged by the rare disease research, patient and development

communities, no specific analysis has been conducted so far to characterize specific commonalities amongst these diseases, with the potential secondary aims to identify removable roadblocks that may foster future research and development.

b. Objectives

The PLUTO project aims at using an integrated database search approach to: (1) identify and classify the groups of rare diseases that are currently under-represented by academic research and industrial development alike, (2) determine what characteristics they have in common, and – through this analysis – (3) to understand what are the roadblocks that are preventing the chances of seeing effective treatments being developed in the near future.

Based on the results of this analysis, the working group also aims at providing potential recommendations to policy makers, funders and developers to overcome existing limitations and roadblocks for research and development for these “disregarded” diseases.

c. Output

Outputs will be presented in an article (the article is being prepared at the moment of the writing of this deliverable).

3.12. Newborn Screening Initiative

a. Introduction

The necessity of having a dedicated group on Newborn Screening (NBS) was initially expressed during the Consortium Assembly – Scientific Committee (CA-SC) meeting (Paris, France, June 1-2, 2022), when the IRDiRC chair highlighted that different parts of the world view NBS in different ways, and there are different platforms or targeted ways to look at specific genes. In consequence, putting together different papers based on the expertise and processes in different parts of the world would showcase the current state of the newborn screening in different regions and identify and evaluate the gaps in terms of government policies, practical capabilities and technologies available, social and ethical aspects. The first mission was to obtain an inventory of emerging topics and areas that will be covered. The kick-off meeting took place in August 2022, after SciSec launched an open call to the IRDiRC members to inquire about the interest in joining such initiative. Two working groups were formed in September 2022, composed of IRDiRC members along with identified external contributors. The two working groups have two different thematic focus areas:

1. Real World Applications and Technologies
2. Policy, Ethics, and Patient Perspectives

For each group an associate editor (IRDiRC member) was designated to help the groups on operational directions. This initiative runs under minimal supervision from SciSec.

b. Objectives

Given IRDiRC's goal of shortening the diagnostic odyssey for RD patients, we have brought together international experts to provide insight into the current state of NBS

worldwide, highlighting technological advances, as well as the many challenges, to implementing comprehensive screening programs.

c. Output

The output of this working group will be a set of papers that will be published in two special editions in the Rare Disease and Orphan Drugs Journal (RDODJ), planned for Q2 and Q3 of 2023. Multiple articles are currently in preparation.

4. IRDiRC Roadmap 2023

4.1. Selection process

Open nominations for new Task forces for the IRDiRC Roadmap 2023 started in September 2022 when the call was announced through email by the Scientific Secretariat to the Consortium Assembly members and Scientific Committees. The procedure adheres to defined IRDiRC protocols: drafting a comprehensive Task Force proposal encompassing elements like background of the topic, objectives of the task force, scope of action, timelines, expertise requirement, estimated costs, and planned output. Proposals were sent to the Scientific Secretariat for compilation and analysis, and were subsequently shared with the Operating Committee for input, identification of synergies between proposals, and provision of recommendations. The Scientific Secretariat created an online vote, allowing the Consortium Assembly members to vote anonymously and select the top four priorities for the IRDiRC's Roadmap 2023.

Six Task Forces were proposed for the Roadmap 2023:

- "EMPOWER (Equitably Making Clinical PhenOtype Work Everywhere Respectfully)" proposed by the Diagnostic Scientific Committee (DSC);
- "A framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey" proposed by the Patient Advocacy Constituent Committee (PACC);
- "Functional Analysis" proposed by the Diagnostic Scientific Committee (DSC);
- "Funding models to support the spectrum of RD research and development" proposed by the Funders Constituent Committee (FCC);
- "Models for support of data and/or registries within regular funding mechanisms" proposed by the Funders Constituent Committee (FCC);
- "Preparing for genetic N-of-1 treatments of patients with ultra-rare mutations" proposed by the Therapies Scientific Committee (TSC);

The Operating Committee expressed their recommendations through an online survey (November 2022). Results of this survey are available through Annex1. Four Task Forces were shortlisted and presented to the Consortium Assembly (CA) members for approval and validation during the IRDiRC meeting that took place in December 2022. An open call for Task Force members for the new activities was officially launched in January 2023.

4.2. List of activities

4.2.1. Preparing for genetic N-of-1 treatments of patients with ultra-rare mutations

a. Introduction

The N-of-1+ therapy approach is transforming the drug development landscape and has the potential to facilitate treatment of patients with ultra-rare diseases for whom no previous treatment has been developed. However, while the development of therapies specific to very few patients has a lot of promise, the largest challenge faced by these initiatives is that the drug development, regulatory frameworks and reimbursement systems were not designed for N-of-1+.

b. Objectives

The overall objective of this Task Force is to connect different N-of-1+ efforts to reduce duplication, achieve global consensus and create a roadmap towards development and implementation of N-of-1+ treatment. This task aims to (1) produce a reference document summarizing the current state-of-the art, to raise awareness of the N-of-1+ concepts and challenges with all stakeholders, (2) to identify the major challenges hampering N-of-1+ therapy development and timely patient access, in order to allow for development of proposed solutions and create a better opportunity for strategic planning and delivery of N-of-1 therapies.

c. Organisation

This task is co-chaired by

- Annemieke Aartsma-Rus – Leiden University Medical Center, The Netherlands
- Anneliene Jonker – University of Twente, The Netherlands
- Daniel O'Connor – The Association of the British Pharmaceutical Industry (ABPI), UK

d. Output

An article is in preparation.

4.2.2. A framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey

a. Introduction

This research project builds upon the work of the IRDiRC Working Group on Goal 3 who produced a framework of the patient journey identifying key areas for developing methodologies to assess the impact of diagnoses and therapies on rare disease patients and families. While there are some studies on the impacts of living with a rare disease and some that chronicle the natural history, there has been relatively little

research measuring the impacts of “diagnosis/no diagnosis/misdiagnosis” as well as “availability/no availability” of therapeutic interventions and their efficacy.

b. Objectives

The objectives of this Task Force are to (1) Develop, operationalize, and test a comprehensive framework of holistic, multidimensional, and evolving life-long experiences of patients and families living with a rare disease; (2) Develop, operationalize, and validate multidimensional indicators and measures (qualitative and quantitative) of impacts associated with diagnosis, treatment, support, and community integration that can be used to capture changes along the patient “journey”; and (3) Investigate qualitative case studies to represent a number of parameters that could inform on impacts.

c. Organisation

This task is co-chaired by

- Durhane Wong-Rieger – Rare Diseases International (RDI), Canada
- Samuel Wiafe – Rare Disease Ghana Initiative, Ghana

d. Output

An article is in preparation.

4.2.3. Funding Models to Support the Spectrum of Rare Disease Research and Development

a. Introduction

The successful development of therapies for any disease requires support from early stages (basic/fundamental research), through more mature preclinical, translational, or early clinical stages, then more mature clinical stages, and finally, post-marketing studies. How different funders decide when to fund at a given stage in a treatment's development is fairly opaque. Knowledge of the factors that contribute to this process might help other funders understand better how to facilitate the development of these treatments.

The IRDiRC Chrysalis Task Force addressed some of these questions for companies but led to the realization that this knowledge was lacking for other types of funders. Furthermore, it is unclear how the decisions of one type of investor might impact the decisions of other funders or the funding ecosystem for rare diseases. A better understanding of the landscape (and even a recognition of the variability) would likely ultimately benefit those living with rare diseases. Both successes and failures might be very informative.

b. Objectives

This task aims to (1) identify key motivating factors for different types of funders of rare disease research – why, when, etc. This includes questions such as, what can funders do to ensure that projects they fund will continue their development at stages where they do not provide support?, (2) identify how different types of funders decide at which point in a research study's lifecycle they will provide support. This might include

discussions about different types of funding instruments (and perhaps identify novel multi-modal mechanisms that could be tested in the future), (3) identify the key influencing factors for effective public-private partnerships at different stages of a treatment's life cycle, (4) identify models of public-private partnerships, including means of sharing information (with attention to tech transfer issues and regulatory requirements).

c. Organisation

This task is co-chaired by

- Adam Hartman - National Institute of Neurological Disorders and Stroke (NINDS) at NIH, USA
- Lucia Monaco - Former Fondazione Telethon, Italy

d. Output

An article and funding tool guide is in preparation.

4.2.4. Functional Analysis

a. Introduction

With the introduction of high-throughput methods of large-scale mutagenesis, followed by the large-scale functional assessment of induced variation, and supported by computational methods, new horizons open up. Multiplexed assays of variant effect (MAVE) and the application of CRISPR/Cas9 or RNAi for gene disruption and multi-omics for the screening of functional biological impacts provide the means for proactive, large-scale, functional assessment of genome and their variation, including the development of variant effect maps for basic and clinical research communities. However, there needs to be more guidance on applying these novel methods, required infrastructure, and standards to the field of rare diseases (RD) that are frequently characterized by ultra-rare or unique private mutations.

b. Objectives

This task aims to (1) foster further development, standardization, and quality improvement of the experimental and computational methods of functional assays and their uptake by the RD research community and clinical practice, (2) foster ecosystem building, infrastructure development and partnerships for the effective chain from fundamental research to clinical applications of functional assays, (3) foster equity in RD diagnostics and treatment through the application of indiscriminative multiplexed assays of variant effect and variant effect maps to the fundamental research and clinical practice in rare diseases).

c. Organisation

This task is co-chaired by

- Gareth Baynam, Rare Care Center, Perth Children's Hospital, Australia
- Biruté Tumiene - Vilnius University Hospital, Lithuania

d. Output

An article is in preparation.

4.2.5. A specific case : Models for support of data and/or registries within regular funding mechanisms

The task force proposal “Models for support of data and/or registries within regular funding mechanisms” proposed by Catherine Nguyen (INSERM) did not receive the highest ranking and was not integrated into IRDiRC's roadmap. Nevertheless, the topic is considered crucial, particularly in the European context, where registries of European Reference Networks (ERNs) at the national level are essential.

This specific question arised during a meeting of the Operating Group of the EJP RD in November 2022, on how the European Joint Programme on Rare Diseases (EJP RD) could address topics that IRDiRC did not prioritize.

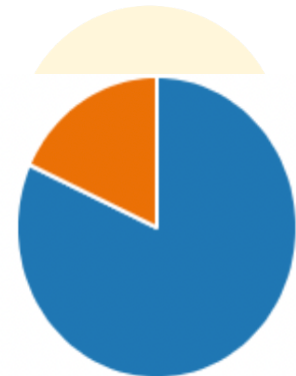
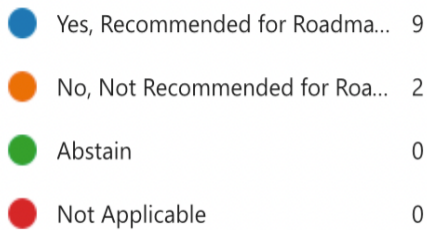
The Operating group agreed to consider the long-term sustainability of the registries as a key priority and include this topic into the Rare Diseases Partnership (RDP) Strategic Research and Innovation Agenda (SRIA). Indeed, some of our EJP RD partners' experience with prominent pharmaceutical companies emphasized this aspect: as an example, a substantial investment made in creating registries that spanned up to four years, involving a substantial patient population with a shared rare disease was ultimately abandoned due to the absence of a viable sustainability plan despite producing over 25 valuable research papers and discoveries.

Besides, the role of various initiatives, such as European Rare Disease Research Infrastructure (ERDRI) and European Health Data Space (EHDS) and the ERN Joint Action, as well as the support from the industry, could play a crucial part in achieving sustainability for registries.

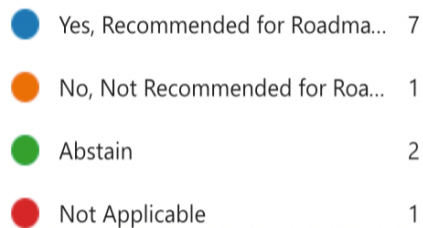
5. Annex 1 – Results from the online survey to define the IRDiRC’s Task forces 2023

The results of the anonymous online survey answered by the Operating Committee of IRDiRC:

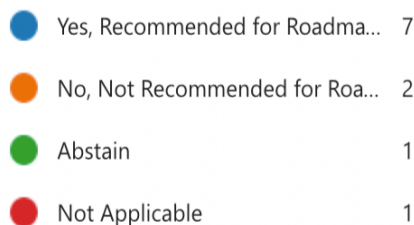
1. Framework to assess impacts associated with diagnosis, treatment, support, and community integration that can capture changes along the rare disease patient and family journey – 9 votes "Yes", 2 votes "No";



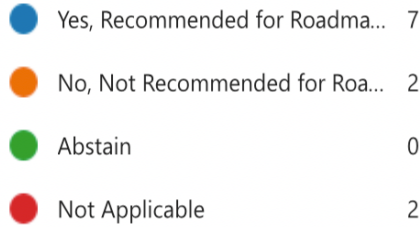
2. Funding models to support spectrum of RD research and development – 7 votes "Yes", 1 vote "No", 2 votes "Abstain", and 1 vote "Not applicable";



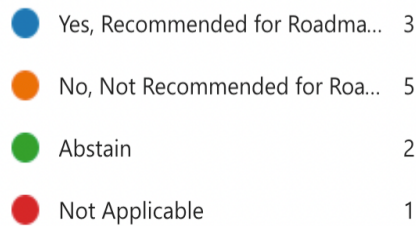
3. Preparing for Genetic N-of-1 Treatments of Patients with Ultra-Rare Mutations – 7 votes "Yes", 2 votes "No", 1 vote "Abstain", 1 vote "Not applicable";



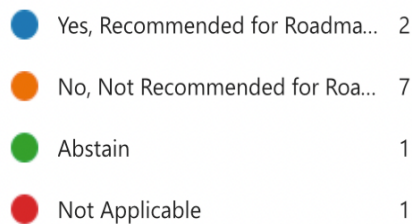
4. Functional Analysis – 7 votes “Yes”, 2 votes “No”, 0 vote “Abstain”, and 2 votes “Not applicable”;



5. EMPOWER (Equitably Making Clinical Phenotype Work Everywhere Respectfully) - 3 votes “Yes”, 5 votes “No”, 2 votes “Abstain”, 1 vote “Not applicable”;



6. Models for support of data and/or registries within regular funding mechanisms – 2 votes “Yes”, 7 votes “No”, 1 vote “Abstain”, 1 vote “Not applicable”.



6. Annex 2 – List of EJPRD Members/Institution Beneficiaries that are members of IRDiRC Committees and Task Forces 2022

6.1 IRDiRC Committees

6.1.1 Funders Constituent Committee (11)

- AFM-Téléthon, France
 - Agence Nationale de la Recherche (ANR), France
 - Canadian Institutes for Health Research (CIHR), Canada
 - Federal Ministry of Education and Research (BMBF), Germany
 - Foundation for Rare Diseases, France
 - Georgian Foundation for Genetic and Rare Diseases (GeRaD), Georgia
 - French National Institute of Health and Medical Research (INSERM), France
 - Istituto Superiore di Sanità (ISS), Italy
 - National Institute of Health Carlos III (ISCIII), Spain
 - Fondazione Telethon, Italy
 - The Netherlands Organisation for Health Research and Development (ZonMw), The Netherlands
- 6.1.2 Patient Advocacy Constituent Committee (1)
- EURORDIS, France
- 6.1.3 Diagnostics Scientific Committees (4)
- Academisch Medisch Centrum bij de Universiteit van Amsterdam (AUMC), The Netherlands
 - Fundacio Centre de Regulacio Genomica (CNAG-CRG), Spain
 - Vall D'Hebron Research Institute, Spain
 - Vilnius University Hospital Santaros Klinikos, Lithuania
- 6.1.4 Therapies Scientific Committees (1)
- EURORDIS, Spain
- 6.1.5 Regulatory Scientific Committees (1)
- AFM-Téléthon, France
- 6.1.6 Interdisciplinary Scientific Committees (4)
- Istituto Superiore di Sanità (ISS), Italy
 - University Medical Center Groningen, The Netherlands
 - University of Cambridge, UK
 - Vall D'Hebron Research Institute, Spain
- 6.2 Task Forces in Year 2022**
- 6.2.1 IRDiRC-RDI Global Access Working Group (3)
- Istituto Superiore di Sanità (ISS), Italy
 - National Institute of Health Carlos III (ISCIII), Spain
 - EURORDIS, France
- 6.2.2 Sustainable Economic Models in Drug Repurposing (3)
- AFM-Téléthon, France
 - Agence Nationale de la Recherche (ANR), France
 - EURORDIS, France
- 6.2.3 Model Readable Consent and Use Conditions (3)
- Academisch Ziekenhuis Groningen (UMCG), The Netherlands
 - University of Leicester (ULEIC), UK

- European Research Infrastructure for Biobanking (BBMRI), Europe
- 6.2.4 Shared Molecular Etiologies Underlying Multiple Rare Diseases (4)
- Aachen University Hospital (UKA), Germany
 - Imagine Institute, France
 - National Institute of Health Carlos III (ISCIII), Spain
 - University of Cambridge, UK
- 6.2.5 Integrating New Technologies for the Diagnosis of Rare Diseases (1)
- Academisch Medisch Centrum bij de Universiteit van Amsterdam (AUMC), The Netherlands
- 6.2.6 Primary Care (3)
- Leiden University Medical Center (LUMC), The Netherlands
 - University Hospital Tübingen, Germany
 - Vilnius University Hospital Santaros Clinics, Lithuania
- 6.2.7 Enabling and Enhancing Telehealth for Rare Diseases Across the Globe (2)
- University Hospital Frankfurt, Germany
 - Vilnius University Hospital Santaros Clinics, Lithuania
- 6.2.8 Drug Repurposing Guidebook (8)
- Academisch Ziekenhuis Groningen (UMCG), The Netherlands
 - EURORDIS, Europe
 - Fondazione Telethon, Italy
 - Agence Nationale de la Recherche (ANR), France
 - Foundation for Rare Diseases, France
 - National Institute of Health Carlos III (ISCIII), Spain
 - EATRIS, Europe
 - Stichting Katholieke Universiteit (RUMC), The Netherlands
- 6.2.9 Pluto Project on Disregarded Rare Diseases (4)
- Vilnius University Hospital Santaros Clinic, Lithuania
 - National Institute of Health Carlos III (ISCIII), Spain
 - Fondazione Telethon, Italy
 - Universitaetsklinikum Aachen (UKA), Germany