Report

IRDiRC Consortium Assembly Meeting

9 December 2024
Online

IRDiRC

MEETING REPORT CONTENTS

09 December 2024:

1. **Welcoming, Presentation of the Meeting and Presentation of New Members and Changes of constituent members representation**

2. **Summary of activities in 2024**
   - Task Forces and Working Groups
   - Publications

3. **Planning for year 2025**
   - Timeline Task Forces and Working Groups
   - IRDiRC events in Brussels
   - Key Performance Indicators
   - WHO resolution

4. **AOB**

THE REPORT

The International Rare Diseases Research Consortium (IRDiRC) organized an online meeting of the Consortium Assembly (CA) on December 9th, 2024.

1. Welcoming, Presentation of the Meeting and Presentation of New Members and Changes of constituent members representation

➢ New IRDiRC Members

IRDiRC is pleased to announce the change of representation of Companies Constituent Committee (CCC) member, **Takeda Pharmaceuticals – Neta Zach**, Head of Neuromuscular Disease Area Unit, USA.

➢ IRDiRC Leadership

David Pearce and Samantha Parker were re-elected as Chair and Vice Chair of the IRDiRC Consortium Assembly for a mandate of 3 years, from January 2025 to December 2027.

Violeta Stoyanova Beninska (European Medicines Agency) was elected chair of the Regulatory Scientific Committee (RSC).

2. Summary of activities in 2024

Five activities have been ongoing in 2024.

- *Functional Analysis*
- *Preparing for genetic N-of-1 treatments of patients with ultra-rare mutations*
- *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*
- *Funding models to support the spectrum of rare disease research and development*
- *Newborn Screening Initiative*

Functional Analysis

Chairpersons: Biruté Tumiene (DSC), Gareth Baynam (ISC)

Objectives

- Further development, standardization and quality improvement of the experimental and computational methods of functional analysis

- Foster ecosystem building, infrastructure development and partnerships for the effective chain from fundamental research to clinical applications of functional analysis
- Foster equity in RD diagnostics and treatment through the application of indiscriminative multiplexed assays of variant effect maps to fundamental research and clinical practice in rare diseases

Results and Outputs

- Two late-stage manuscripts, one of them planned to be submitted to Nature Reviews Genetics
- One of the chairs of this Task Force has informed about the strategic thinking and priority setting on functional analysis in Australia at the *National Centre for Indigenous Genetics* and at *Phenomics Australia*
- One of the Task Force members was invited to present at the Chan Zuckerberg Initiative (CZI) Science in the Society Meeting that took place in 2024. The same member was also the recipient of a $1.8 million grant from CZI to help scale (100-100 fold), speed up (4 fold) and reduce cost (by 90%) of functional analysis through "*Village in a Dish*" approach.

Foreseen impacts on the RD Community

The Task Force plans to chart the way forward toward industrialization and increased equity of access of functional analysis.

N-of-1 Therapies

Chairpersons: Annemieke Aartsma-Rus, Anneliene Jonker, Dan O'Connor (TSC)

Objectives

The overall goal 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.

- Raise awareness of the N-of-1 concept and challenges with all stakeholders
- Identify major challenges hampering N-of-1 therapy development and timely patient access
- Allow for development of proposed solutions and create better opportunities for strategic planning and delivery

Results and Outputs

- Landscape analysis for State-of-the-Art of N-of-1 therapies
- Future perspectives on N-of-1

The Task Force produced two manuscripts:

1) *The state-of-the-art of N-of-1 therapies and the IRDiRC N-of-1 development roadmap.* Published in Nature Reviews Drug Discovery; Link: https://www.nature.com/articles/s41573-024-01059-3
2) *From roadmap to a sustainable end-to-end individualized therapy pathway.* Submitted to Therapeutic Advances in Rare Disease

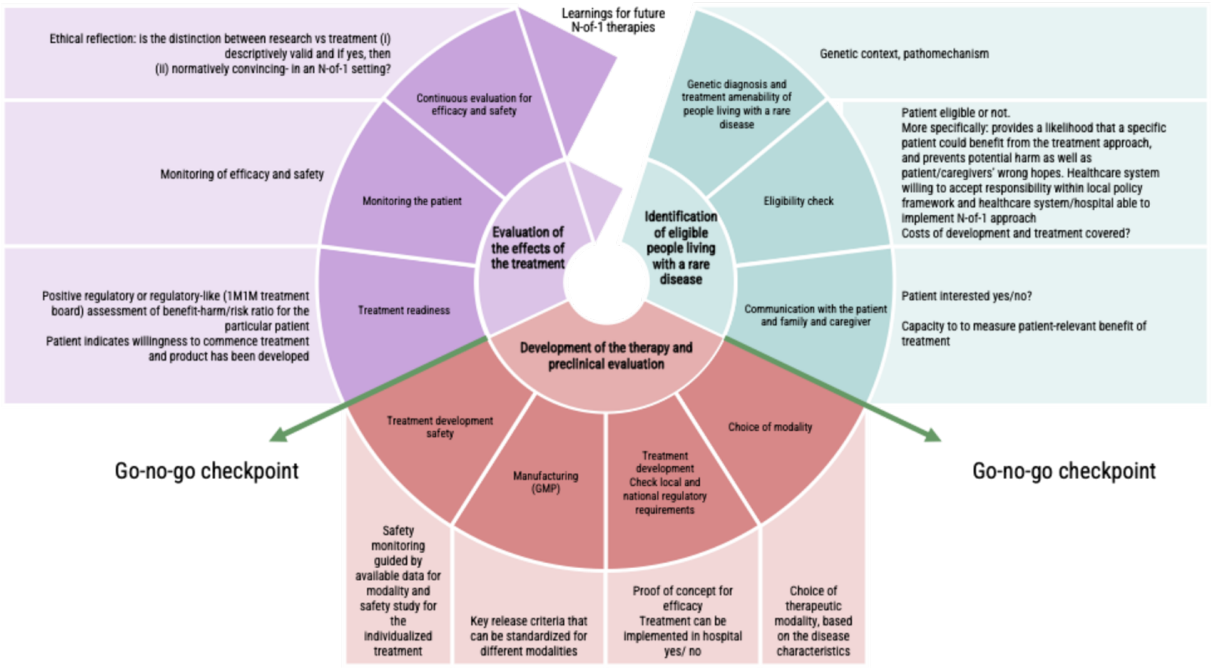

Figure 1 – Roadmap for N-of-1 development

Foreseen impacts on the RD community

- **Increased awareness**
  i. More eligible patients identified – a patient reached out due to the first paper published
  ii. Less non-eligible patients told they are eligible
  iii. More streamlined development due to roadmap
  iv. Increased awareness in the research and development community
- **Increased alignment and data sharing**
  i. List of educational tools available
  ii. Quicker development
  iii. More successful developments

Framework to assess impacts

Chairperson: Durhane Wong-Rieger (PACC)

Objectives

- Develop, operationalize and test a comprehensive framework of holistic, multidimensional and evolving life-long experiences of patients and families living with a rare disease, derived from/or leading to a natural history study;
- Develop, operationalize and validate multidimensional indicators and measures, both qualitative and quantitative, of impacts associated with diagnosis, treatment, support and community integration that can be used to capture changes along the patient "journey";
- Investigate qualitative case studies to represent a number of parameters that could inform on impacts.

Results and Outputs

The expected output of the Task Force is to provide a characterization of the ecosystem determinants, the methodologies and key performance indicators that support the development of a lived experience framework for patients. One manuscript is in preparation and the final draft is projected for mid-January 2025.

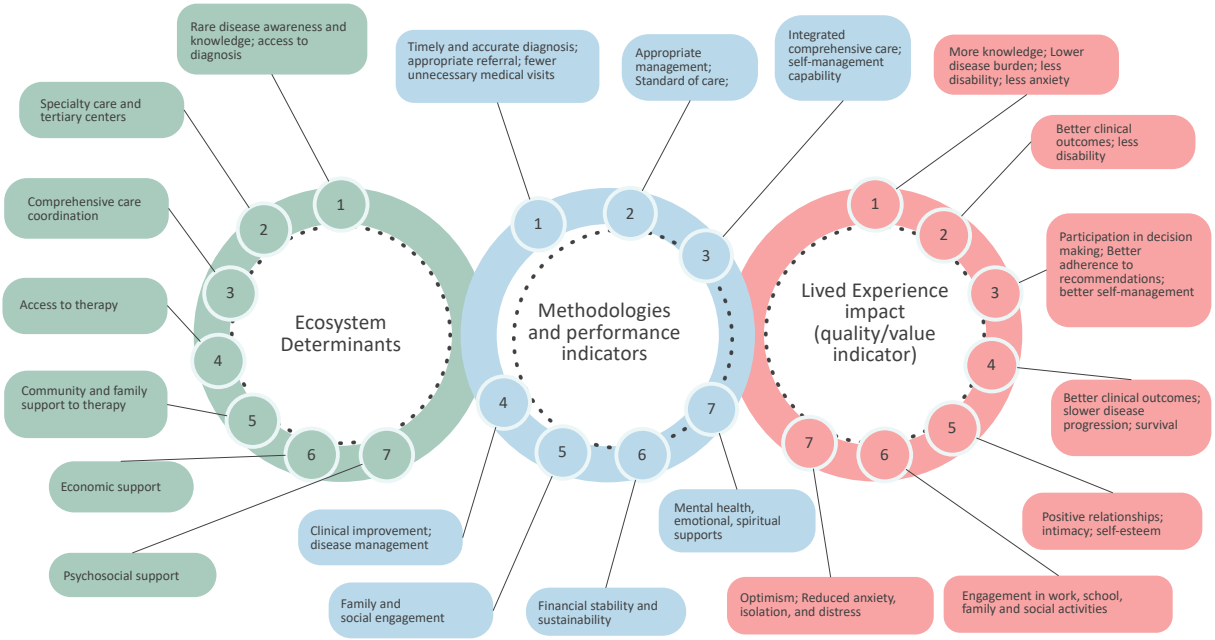

Figure 2 – Characterization of ecosystem determinants

Funding Models to Support the Spectrum of RD Research and Development

Chairperson(s): Adam Hartman (FCC), Lucia Monaco (former IRDiRC Chair)

Objectives

- **Identify key motivating factors for different types of funders of rare disease research** – why, when. This includes questions such as, what can funders do to ensure that projects they fund will continue their development as stages where they do not provide support?
- **Identify how different types of funders decide at which point in a research study's lifecycle they will provide support.** This might include novel multi-modal mechanisms that could be tested in the future.
- **Identify the key influencing factors for effective public-private partnerships** at different stages of treatment's life cycle.
- **Identify models of public-private partnerships,** including means of sharing information (with attention to tech transfer issues and regulatory requirements)

Results and Outputs

- The methodology of the Task Force comprised of a literature review of existing funding models, key motivating factors, limitations and sustainability plans
- An online survey was shared with IRDiRC members on the investment mapping and a questionnaire
- The questionnaire for key opinion leaders' (KOLs) interviews were included in a publication and toolbox
- For the research database, the ODD designations awarded from 2017 onwards by EMA and FDA were reviewed, and the analysis was included in a publication
- One manuscript published *"The complexity of funding rare disease research: an IRDiRC assessment of the landscape"* in Rare Disease and Orphan Drugs Journal; Link: https://www.oaepublish.com/articles/rdodj.2024.18
- Another manuscript is in preparation, along with the toolbox planned to be delivered in spring 2025
- The results of the Task Force will be disseminated at different conferences and workshops at the University of Milan, RE(ACT) congress, NCATS Rare Disease Day, etc.

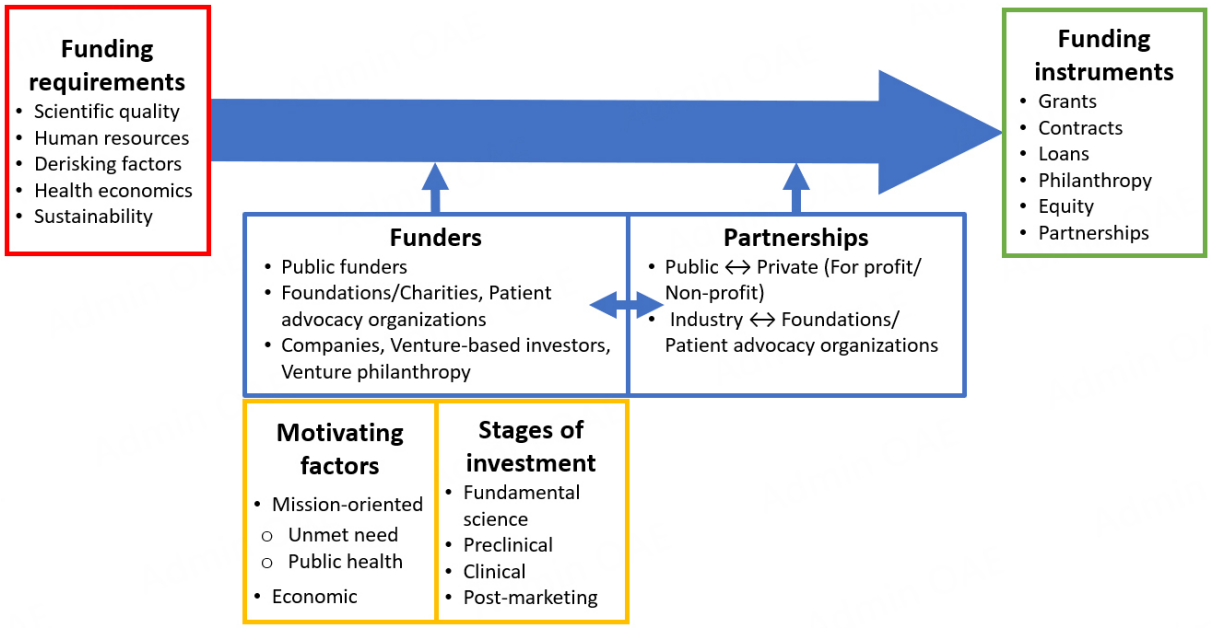

Figure 3 - Foreseen impacts on RD community

- Improved understanding of the broader funding landscape
- Adaptation of different funding strategies by different funding bodies
- Increase in Public-Private Partnerships (PPPs)

Orphan Drug Designation Database – to provide a quantitative clinical-regulatory insight into the status of FDA and EMA orphan drug designations awarded in 2017 with description of preclinical and clinical discontinuations that have taken place. This is being conducted within the context of IRDiRC FCC to identify potential funding priorities to accelerate Orphan Drug Development. The analysis showed that success wasn't just getting to marking authorization, but also the stage transition, how a drug moves from preclinical studies to Phase I, II, III, IV (marketing approval). When looking at the probability of success in stage transition, the group checked the technologies used, if the drug represented a small molecule or gene therapy, what was the size of the company and how it was supported (by foundations, patient organizations), if there were any incidents.

Comments from audience: this analysis highlights how there are no clear boarders for funding, when it comes to pre-clinical financing or transition from early-stage to late-stage, it shows there are "mixed models of funding" along the process, and it shows the complexity of the landscape. One participant mentioned that a similar approach was done at a smaller scale, by taking one disease (e.g. one type of cancer) and checking the factors for failure when moving to the next stage of development.

Newborn Screening Initiative

1) **Newborn Screening I – Real World Applications and Technologies (6 publications) –** *access the full special edition here:* https://www.oaepublish.com/specials/rdodj.1270

- Newborn screening in Mexico and Latin America
- Systematic review of real-world newborn sequencing
- Role of federated data analysis in accelerating newborn genome screening
- Incorporating a new disease in newborn screening programs in Europe
- Overview of newborn sequencing initiatives in Europe
- Newborn sequencing for metabolic disorders

2) **Newborn Screening II - Policy, Ethics and Patient Perspectives (5 publications) –** *access the full special edition here:* https://www.oaepublish.com/specials/rdodj.1271

- Patient organizations: advocating for timely newborn screening & improved quality of life
- Newborn screening in South Africa: the past, present, and plants for the future
- Overcoming challenges in sustaining newborn screening in low-middle-incole countries: the Philippine newborn screening system
- The Australian landscape of newborn screening in the genomics era
- Development of newborn screening policies in Spain 2003-2022: what do we actually need to reach an agreement?

In summary, in 2024, 9 manuscripts were published as result from Task Forces, 7 produced by different committees, 10 from external collaborations, with a yearly total of 26 publications.

Since 2015, 50 peer-reviewed articles were produced by IRDiRC, 31 Task Forces and Working Groups were launched and 5 are currently ongoing. In addition, 5 international conferences were organized and quarterly Consortium Assembly meetings.

3. Planning for Year 2025

➢ *CA has validated 5 new activity proposals for 2025*

- Task Force on Preventive Medicine in RD (led by TSC)
- Working Group on Young Patient Involvement in therapy development (led by TSC)
- Task Force on Regulatory Convergence (led by FCC, CCC, RSC)
- Task Force on Stigma (led by ISC, PACC)
- Task Force on Bridging Diagnostics to Therapy and Care (led by DSC, TSC, ISC)

The public call for candidates is planned to be launched in January 2025. By the end of February, the selection of shortlisted candidates is foreseen, and the kick-off meetings of the new Task Forces is planned for March. The in-person workshop with the group is planned for Q4 of 2025.

a) Facilitating the development of Preventive Medicines at scale for RDs

Background

Among patients, industry, and policymakers there is a growing interest in disease prevention in order to improve population health, and many initiatives in non-communicable diseases have led the way in developing prevention strategies. Despite this, a review of orphan designations at the European Commission shows that the vast majority of designations are for 'treatment' of a condition – currently only 80 designations are listed for prevention out of a total of 2029 EC designations (less than 4%) and the majority of these are clustered around just a few conditions. This clearly demonstrates that more must be done to develop a proactive approach to developing preventive medicines at scale, rebalancing the delivery of healthcare away from acute care into prevention.

Objectives

- From a medicine's development perspective in small populations, what are the specific challenges that need to be resolved when successfully developing medicines in the preventive space?
- How can the regulatory and access system evolve to support and optimise the field and mitigate the uncertainties?
- Are there activities, incentives or policies that could help, noting the low uptake of prevention orphan designation?
- How do we balance evidence generation from formal clinical trials versus real world data collection?
- How to we ensure the preventive intervention opportunities from an early diagnosis are not missed, what healthcare infrastructure is needed to link the diagnosed patient to a potential therapeutic intervention?
- How do we encourage global leadership in preventive medicines for rare disease patients?

Foreseen impacts

- This Task Force will help provide through leadership and practical solutions on what an optimised framework for preventative medicines will need to include, with the aim of developing a set of proposals and case studies that highlights the innovative potential and public health gains/goals in rare diseases, providing additional tools for small populations research and creating future strategy and policy implications.
- This is crucial when considering the avalanche of future patients that might be presenting through newborn screening and other improvements in diagnostic capabilities, and the current lack of activity as seen in orphan designations and approved therapies to date.

b) Engagement of young people living with Rare Diseases in Therapy Development

Background

Patient engagement (PE) is the effective and active collaboration of patients, patient advocates, patient representatives and/or carers during the entire medicines' lifecycle in corporation with the other relevant stakeholders. From a research perspective, PE has been shown to improve inclusion/retention rates and research outcomes, preventing clinical trials failure and reducing trial-related costs but most importantly ensuring that health treatments and technology are being developed with the end user in mind. However, PE is mostly focused on the adult study population, whereas the added value of the perspectives of the population of young people living with a rare disease have been largely underestimated, and therefore under investigated. There are considerable practical challenges and a lack of appropriate tools for meaningful engagement of young people.

Objectives

- Understand and map out the different patient engagement activities in therapy development by age groups (e.g. early childhood 2-5 years; middle childhood 6-11 years; adolescents 12-17 years; and young adults 18-25 years that have transitioned to adult care since conditions), also looking into difference if young people lived with the condition their entire life, or if they were diagnosed later on.
- Understand and identify existing methodologies, tools, processes for PE of young people living with a rare disease and consider what is missing
- Understand new opportunities for engaging young people in the whole therapy development process by for example creating a decision tree in each development milestone with mapped activities and methodologies, available tools and processes to be used for patient engagement of young people in rare diseases taking into account their age and developmental stages.

Foreseen impacts

- Engaging young people in therapy development have the potential to impact all along the development milestones and within all stakeholders involved:
  - Young people: therapies that bring improvements to their condition with a therapy/technology that is developed with them in mind
  - Researchers: setting priorities and designing research with the input of parents/carers and young people
  - Healthcare professionals (including nurses): therapies for their patients
  - Health systems and payers: reimbursement of therapies where patients were involved within the development and targeting relevant outcomes for them
  - Funders, regulators and policy makers: public accountability and transparency
  - Companies: involving patients during all the development process stages to bring therapies targeting their needs

c) Toward clarifications, improvement and international convergence in regulatory approvals of RD therapies with a focus on Advanced Therapy Medicinal Products

Background

The current regulatory and manufacturing environment for RD therapies is extremely complex. The current scheme struggles with adapting to the peculiarity of ultra rare diseases, more and more often treated with gene or cell therapies, and this lengthens their route to patients and increases costs of therapies. The need to navigate different regulatory procedures in different jurisdictions further complicates the picture. Small biotechnology companies tend to privilege FDA as the US market has the highest commercial interest while academic and not for profit developers limit their action to their own country/regions as enlarging to others is too complex and expensive.

Objectives

The overall objective of the task force is to identify barriers towards mutual recognition of the approval of therapies by different jurisdictions and propose concrete solutions. This general objective requires actions on two parallel tracks:

- Policy: propose solutions/changes in regulation and guidelines to remove the legal and administrative barriers to regulatory convergence
- Investments: engage with regulatory agencies to provide research funders with specific recommendations in areas where investments are used to require agency dialogue/approval

Foreseen impacts

- This activity will have a short-term impact on the RD community as it will highlight the need for policy change and trigger investments in research projects on "regulatory science". This will deliver to patients advocates and to policy makers a list of changes to the system that needs to be implemented and to research funders a list of topics where specific investments are needed to enable the international regulatory alignment.
- In the medium to long term, the impact for drug developers could be relevant as the alignment in requirements and procedures between different jurisdictions may allow to reduce the costs, time and burden of approval of new products.
- The essential impact however will be on patients as the joint assessment/mutual recognition will reduce the disparities in terms of medicines available in different geographies. This will not automatically lead to improved access as the regulatory approval per se is not sufficient to ensure patients access to a therapy, but it is an essential step in that direction.

Comments from audience: an interesting potential example can be represented by ultra rare diseases, however there is an uncertainty about clinical trials for such diseases, the lack of sufficient data could be an issue. It is an ongoing learning process as there are different clinical endpoints that are introduced and were not known before, the way clinical trials are designed or if there are differences in the scientific advice/phase could show an interesting angle of discussion.
One of the issues of the ultra rare diseases, when it comes to gene therapies (AAVs, ASOs, etc), is that there will always be some that are not of interest for the pharmaceutical companies or biotech because of the lack of profitability. One solution would be to identify a pathway less complex than it is designed

now, maybe through funders, philanthropy, patient organizations. Defining that pathway is one of the objectives of this group, at least to have a goal point for the other stakeholders. Another participant inquired if the definition of an ATMP is the same across regions. The first effort would be to clarify the definition of a gene therapy, whether it is an AAV, ASO, CRISPR. Another participant highlighted that the focus should not be on ultra rare diseases, as in most regions (e.g.) they are not even defined. In USA, antisense oligonucleotides are handled by the Center for Drugs, while AAV gene therapies are handled by the Center of Biologics. Some goals could be achieved by working with AAVs, as an approach to get convergence. In addition, it is not foreseen to limit the analysis just to EMA or FDA, but open it to other geographies. Efforts should be made to align the accessibility around the world, and not limited to countries where are big regulatory agencies.
In the last months, Canada has changed its federal legislation to have reciprocity of approval, in the case any health authority that has actually approved a therapy (not being particularly specified as EMA/FDA) to ensure an easier process. The starting point will be children's medicine, and the second on the list is rare diseases and orphan drugs. Another participant highlighted that it is necessary to be more specific when addressing this subject, but it will be particularly interesting to look into other regions, not limited to USA or Europe. The definition of ATMP is different, maybe the focus should be on specific gene therapies. On the European Regulatory Agency side, the information is publicly available.

d) Stigma and Rare Diseases

Background

Stigma is defined as a discrediting attribute that distinguishes an individual from others by reducing them "from a whole and usual person to a tainted, discounted one". Stigma is an overtly expressed challenge by approximately 1 in 3 PLWRD. Stigma generates inequity, marginalisation, discrimination and exclusion which impairs access to, and benefit from health, social and community participation and services. Stigma can, and frequently prevents the start/progress through the rare disease diagnostic, therapeutic and care odyssey. Stigma's physical, mental and social consequences are likely a key contributor to the lower quality of life reported by PLWRD compared to those with more common diseases. Until such time as addressing RD stigma worldwide is prioritised, comprehensively reviewed with international lens, and the pathways for implementing culturally safe and responsive mechanisms are identified and acted upon, the global goals for diagnosis, care and social inclusion cannot be met.

Objectives

- Identify the state-of-play and unlock new knowledge to address stigma to accelerate diagnosis and enhance equitable care and support.
- The Task Force will deliver a survey and whitepaper to identify technology and human factor solutions.
- The overall achievement will be to guide and accelerate co-designed patient-driven research that also harnesses the power of technology for inclusivity and scale.

Foreseen impacts

- Patients – better healthcare access and engagement
- Clinicians – improved compliance
- Scientists – a framework for research to address stigma associated with rare diseases
- Health systems
- Payers – reducing healthcare expenditure by improving physical and mental health
- Policy makers – policy decisions that better address stigma and rare diseases

e) Bridging diagnostics to therapies and care

Background

Most of rare diseases do not have specific therapies, and the persons living with a rare disease experience barriers to obtaining treatment. The development of new therapies for rare diseases requires specific research infrastructures.

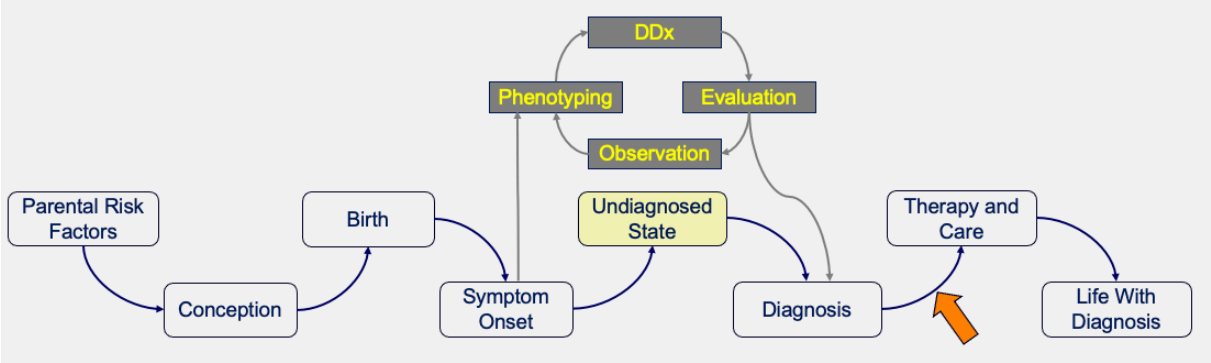

Figure 4 – Scheme of bridging diagnosis to therapy and care

As resources and projects exist in practice, barriers still remain in regard to access (geographical, resource limitations), awareness (resources, specialized knowledge), research (initiation and funding) related to mechanisms, natural history, clinical trials, and regulation.

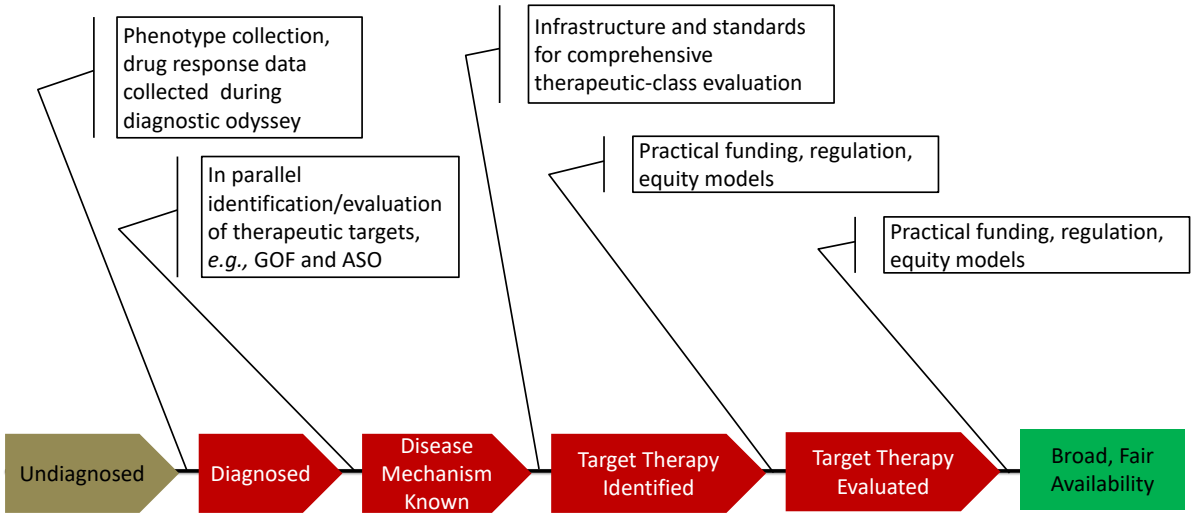

Figure 5 – Pathway from undiagnosed cases to having broad, fair, available therapy

Objectives

The primary objective of the Task Force is to create a list of critical elements required for the transition from diagnosis to therapy, including barriers, opportunities and recommendations for implementation.

- Exhaust opportunities to connect newly diagnosed individuals to existing therapies, both approved and on a research basis. For example:
    - Towards SoC procedures/disease management guidelines
    - Towards an approved, experimental, compassionate use or off-label therapy
    - Towards self-management
    - Towards psychological support
    - Towards educational, disability, social and work support
- Prioritization of case-specific tasks needed to instate available therapies
- Prioritize work needed to bridge existing gaps between new diagnoses and effective therapy or research

Foreseen impacts

- Development of resources for further work
- Framing of current issues
- Research and practical recommendations
- Implementation in clinical practice recommendations

- Clarification of stakeholder perspectives to help in ongoing conversation
- Funders: multiple funders take up the recommendation for research

Comments from the audience: A participant inquired about what will be the deliverable in terms of disease diagnostics. *Response:* This analysis will be starting point that will guide the interested party to a specific resource. A second element of this TF will be to look at the number of cases (e.g. 10-12 diseases) and model the potential pathways. Another participant mentioned that few rare diseases have an approved therapy, but some of them might have an off-label therapeutic, and if this will also be investigated. *Response:* the aim of this TF is that every patient receives the best possible care, independent of where they are located, if another solution can be considered, then this will be included in the analysis. A funders committee representative asked if learnings from previous projects (e.g. PLUTO) or SIMPATHIC will be incorporated. *Response:* This TF will link will several existing elements of work from former projects or currently ongoing ones.

IRDiRC Events

- *Consortium Assembly – Scientific Committees Meeting*
  - In-person in Brussels, Belgium, on March 3-4, 2025

Comments from audience: One participant mentioned that meeting with the whole committee could offer the opportunity to brainstorm for future Task Force proposals. Some TF should emerge from these discussions to collectively identify what is important for the group.

- *2025 RE(ACT) Congress and IRDiRC Conference*
  - Back-to-back with CA-SC Meeting
  - Dates: March 5-7, 2025, in Brussels, Belgium
  - More information: https://www.react-congress.org/

- *International Rare Disease Conference of China (IRDCC)*
  - Organized by CHARD on May 24, 2025 at Haiku, Hainan Province, China. Dr. David Pearce is among confirmed speakers.

Key Performance Indicators

- IRDiRC's role is to foster collective intelligence to identify gaps and key issues in RD research and provide recommendations and tools that will support the transformation of the RD research ecosystem and accelerate the development of diagnostics and therapies.
  - Collective intelligence à foster meetings and participation
  - Identification of gaps à support the creation of the roadmap, TFs & WGs

- Recommendations and tools à delivery of timely outputs
- Sharing knowledge à increase IRDiRC visibility and outreach
- RD ecosystem evolution à impacts, funding landscape

➢ **Indicators – Metrics**
The content of indicators and metrics remains restricted for internal use.

➢ **Use Cases for KPIs activity impacts**

- **MatchMaker exchange**: The Application Programming Interface (API) was developed in collaboration with members of Global Alliance for Genomics and Health (GA4GH) and IRDiRC to ensure interoperability with other genomic services
- Integration of the **IRDiRC Guidebook** into the European Joint Programme on Rare Diseases Innovation Management Toolbox
- **Shared molecular etiologies** (SaME) TF led to a collaboration between IRDiRC members, ERN-BloodNet and patient groups to investigate the SaME approach in rare bleeding disorders

World Health Assembly (WHA) Resolution on Rare Diseases

➢ IRDiRC supports the World Health Assembly Resolution and released a statement in December, accessible here: https://irdirc.org/irdirc-position-statement-world-health-assembly-resolution-on-rare-diseases/

➢ Editorial article in The Lancet, titled "Hope for rare diseases" that endorses the WHA Resolution, available here: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)02414-0/fulltext

Abbreviations

ATMPs - Advanced therapy medicinal products

AAVs – Adeno-associated viruses

API - Application Programming Interface

ASOs – Antisense oligonucleotides

CA – Consortium Assembly

CCC – Companies Constituent Committee

CHARD - The China Alliance for Rare Disease

COA – Clinical Outcome Assessment Consortium

CZI – Chun Zuckerberg Initiative

DSC – Diagnostics Scientific Committee

EC – European Commission

EMA – European Medicines Agency

ERDERA – European Rare Diseases Research Alliance

FCC – Funders Constituent Committee

FDA – Food and Drug Administration

GA4GH - Global Alliance for Genomics and Health

KPIs – Key Performance Indicators

IRDiRC – International Rare Diseases Research Consortium

ISC – Interdisciplinary Scientific Committee

IRDCC – International Rare Disease Conference of China

KOL – Key Opinion Leaders

LMIC – Low-Medium Income Country

NCATS – National Center for Advancing Translational Sciences

ODD – Orphan Drug Database

PACC – Patient Advocacy Constituent Committee

PE – Patient Engagement

PLWRD – Persons Living With a Rare Disease

PPP – Public-Private Partnership

RD – Rare Disease

RSC – Regulatory Scientific Committee

SaME – Shared Molecular Etiologies

SC – Scientific Committee

SIMPATHIC – Accelerating drug repurposing for rare neurological, neurometabolic and neuromuscular disorders

SME – Small medium enterprise

SoC – Standard of Care

TSC – Therapies Scientific Committee

WHA – World Health Assembly

Acknowledgements

This report was written by IRDiRC project managers Alexandra Tataru and Galliano Zanello (Fondation Maladies Rares, Paris, France).