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The international rare disease research consortium (IRDiRC): making rare disease research efforts more efficient and collaborative around the world

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Abstract

The International Rare Disease Research Consortium, or IRDiRC, is a global consortium of key stakeholders from different facets of rare disease research that together seek to drive advances in diagnostics, therapeutics, and patient outcomes. The consortium facilitates a global and cross-disciplinary exchange of ideas to tackle key issues in rare diseases through the development of recommendations, data standards, tools, and guidelines that harmonize research efforts and improve efficiency. While IRDiRC has made significant contributions to the development of new therapies and diagnostics since its establishment in 2011, much work remains to alleviate the burden of rare diseases. The consortium has demonstrated its success in providing a global platform to advance rare disease research through collaborative efforts worldwide and continues to identify and address barriers to health equity for all rare disease patients.

Keywords: Rare Disease, patient advocates, orphan drug, clinical research

INTRODUCTION

While each rare disease may individually impact only a small number of people, collectively, there are over 10,000 different rare conditions[1,2] affecting more than 300 million individuals worldwide[3]; rare diseases (RDs) pose a major challenge in healthcare. The vast number of RDs and relatively small patient population creates substantial barriers in both scientific knowledge and clinical expertise, which, in turn, negatively impacts the availability of diagnoses and treatments, patient outcomes, and overall quality of life.

Biomedical research is the basis for all new diagnostic or therapeutic development, yet a vast disparity exists when it comes to research in RDs compared to more common diseases. With the cost of developing a new therapy estimated at over US $1 billion[4], there is often little incentive to focus on RDs with limited market potential. Although the orphan drug market has experienced rapid growth in recent years, it remains to be seen whether this trend can continue. While the US Orphan Drug Act (1983) and the European Union's regulation on Orphan Medicinal Products (2000) have gone some way towards providing incentives to develop treatments for RDs, much work is still needed to tackle the health disparities often faced by patients with a rare disorder.

To help address these issues, the European Commission (EU) and the US National Institutes of Health (NIH) launched the International Rare Disease Research Consortium (IRDiRC) in 2011 to bring together a global multi-stakeholder leadership consortium of research funders, patient advocacy groups, companies, scientists and regulatory experts to maximize the output of rare disease research. IRDiRC was originally conceived with two main goals: to contribute to the development of 200 new therapies and the means to diagnose most rare diseases by 2020. While it is difficult to measure the direct contribution of IRDiRC, collaborative approaches and consolidation of research activities by IRDIRC members have likely played a substantial role in achieving these goals. Notably, the Consortium's activities contributed to reaching the target of delivering 200 new therapies 3 years ahead of schedule in 2017. Furthermore, considerable progress was also made to improve the availability of diagnostics. To capitalize on this early success, IRDiRC embraced a bold new vision to *enable all people with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention.* With this renewed focus, IRDiRC set three new ambitious goals for the next decade (2017-2027): (1) All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline; (2) 1,000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options; (3) Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients[5,6].

A global community

Recognizing that rare diseases are a global challenge, IRDiRC has made significant efforts to seek members from across the world. Over the twelve years since its foundation, IRDiRC has expanded its initial membership of 21 organizations to 60, with representatives from Asia, Africa, Europe, North America, South America, and Australia. One unique aspect of IRDiRC is the diversity of the stakeholders who participate, encompassing representatives from funding bodies, both public and private, industries such as pharmaceutical companies, device manufacturers and diagnostics, and patient advocate organizations. Thus, IRDiRC provides a forum where stakeholders with unique perspectives on different parts of a patient's journey can convene and address the significant obstacles hindering the diagnosis and treatment of RDs.

Each member organization nominates a representative who is part of the Consortium Assembly (CA) that acts as the overall governing committee overseeing IRDiRC activities. From this assembly, a Chair and Vice-Chair are elected for time-limited terms to help manage the day-to-day operations of IRDiRC. Three Constituent Committees (CC) representing Funders (FCC), Patient Advocates (PACC), and Companies (CCC), whose membership is drawn from the CA, act as coordinating bodies for the constituents that they represent and help to identify gaps and priorities, execute activities aligned with their space, and report back to the CA on scientific and programmatic needs. In addition to the Constituent Committees, IRDiRC has four Scientific Committees (SCs) that represent key areas in RD research: Diagnostics (DSC), Interdisciplinary (ISC), Therapies (TSC), and Regulatory (RSC). Membership of these committees is comprised of subject matter experts drawn from academia, patient advocates, regulatory bodies, diagnostics, and the pharmaceutical industry, and is not restricted to Consortium members. Membership on the SCs is time-limited to enable key stakeholders the opportunity to serve and contribute their knowledge, with staggered terms of service to reduce disruption to committee activities. The main role of the Scientific Committees is to identify and execute actionable activities that advance the goals of IRDiRC, report on progress made towards those goals, and advise the CA on research priorities, meeting regularly in order to achieve those goals.

An Operating Committee, comprised of the Chair and Vice-Chairs of the Consortium Assembly, Constituent Committees and the Scientific Committees, works in concert with the Scientific Secretariat to efficiently coordinate and manage the activities of IRDiRC. The Scientific Secretariat is a dedicated office within IRDiRC that manages the daily activities, providing administrative support, organizing meetings (teleconferences, in-person events), facilitating interactions both within and outside of IRDiRC, and disseminating information and communications. The Operating Committee plays a pivotal role in the exchange of information between the Constituent and Scientific Committees, evaluating new proposals and recommendations to present to the wider Consortium Assembly. The organizational structure of IRDiRC is summarized in Figure 1.

Task forces and working groups

To accomplish these goals, IRDiRC coordinates the formation of Task Forces (TFs) and Working Groups (WGs) to address key issues identified by the Constituent and Scientific Committees and prioritized through discussion by the CA. The TFs and WGs are designed to be time-limited activities that tackle an actionable topic in a small group setting, with members (who do not need to be IRDiRC members) selected based not only on expertise in the area of interest, but also those with diverse backgrounds to ensure that different perspectives are taken into account during discussions. The ultimate goal of these TFs and WGs is to propose solutions through policy recommendations, technical standards, guidelines, or tools that advance RD research, diagnosis, and therapeutic development. The activities of the TFs and WGs in the first decade of IRDiRC (2011-2021) have previously been summarized by Monaco *et al.*, while a full listing of all completed and ongoing TFs/WGs is available on IRDiRC's website[7,8].

IRDiRC continues to identify and address key issues in RD research with a number of recently completed and ongoing TFs/WGs. The *Targeting shared molecular etiologies to accelerate drug development for rare diseases* TF recently published a review highlighting the potential of using basket clinical trial design for rare diseases to accelerate the development of new therapies and address the unmet needs of patients[9]. Current TF/WG efforts are focused on many different aspects of RDs, from funding of research and development through access to treatment and the impact on patients. Efforts focused on enabling the development of new therapeutics include the *Drug Repurposing Guidebook* and *Preparing for Genetic N-of-1 Treatments of Patients with Ultra-rare Mutations* TFs. The *Functional Analysis* TF seeks to develop a framework for a robust and effective ecosystem to support research into RDs, while *Funding Models to Support the Spectrum*

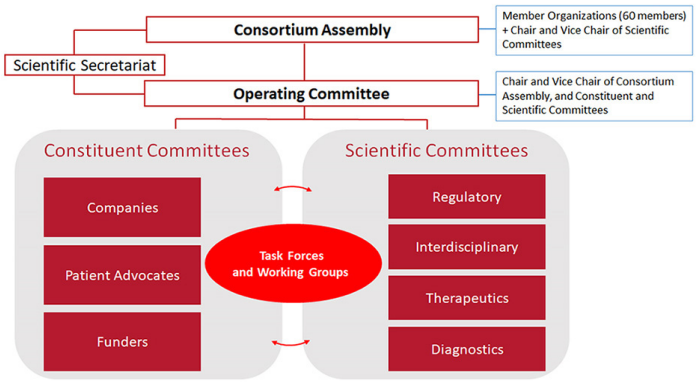

Figure 1. Organizational structure of IRDiRC. The Consortium assembly comprises members of all participating organizations and oversees the activities of IRDiRC. The Constituent and Scientific Committees act in an advisory role to identify key issues that can be addressed through Task Forces and Working Groups, reporting to an Operating Committee that works alongside the Scientific Secretariat to communicate recommendations and progress to the Consortium Assembly. Organizational structure of IRDiRC. The Consortium assembly comprises members of all participating organizations and oversees the activities of IRDiRC. The Constituent and Scientific Committees act in an advisory role to identify key issues that can be addressed through Task Forces and Working Groups, reporting to an Operating Committee that works alongside the Scientific Secretariat to communicate recommendations and progress to the Consortium Assembly. IRDiRC: International Rare Disease Research Consortium.

of Rare Disease Research and Development and the *PLUTO PROJECT-Disregarded Rare Diseases* seeks to understand some of the barriers that may limit research and development efforts. Recognizing that most RD patients present first to their primary care provider and will continue to receive care from them, the *Primary Care* TF seeks to identify challenges and opportunities for research. To facilitate clinical research, *the Machine-Readable Consent and Use* TF aims to develop tools and standards to facilitate research with human subjects to enable collaborative efforts. Developing new technologies for both diagnosis and treatment are essential aspects of the fight against RDs, which are addressed by the *Integrating New Technologies for the Diagnosis of Rare Disease* TF, which will develop a framework for integrating new -omics and artificial intelligence technologies to improve diagnostics, and the *MedTech for Rare Disease* WG will identify opportunities to support medical device development for RDs. Finally, to address key challenges in access to treatment, IRDiRC has established the *Enabling and Enhancing Telehealth for Rare Diseases Across the Globe* TF that will identify barriers and opportunities to enhance access to RD experts through telehealth, while the *IRDiRC-RDI Global Access* WG will focus on access for patients in low- to middle-income countries, ensuring that "no one is left behind". A full list of completed and ongoing TFs/WGs can be found here https://irdirc.org/activities/task-forces/.

Funding

IRDiRC is primarily a volunteer organization with members of the consortium assembly, constituent committees, scientific committees, and task forces/working groups donating their time towards consortium activities. The EU, through the European Joint Program on Rare Diseases (EJPRD), provides funding for project managers, an office manager, a communications manager, and a project coordinator, with their efforts split between IRDiRC and other EJPRD activities. Additional funding is available to support travel and meeting/conference resources for PACC members and the SC chairs/vice-chairs at Consortium Assembly meetings, as well as those participating in in-person TF workshops (WGs do not meet in person).

Members of IRDiRC are not charged a membership fee, but there is a requirement to demonstrate financial investment of US $10 million over 5 years in rare disease research, which can be internal or external. This requirement applies to both the funders and company members but is waived for patient advocate groups. Smaller funding bodies that cannot meet the threshold on their own can form a funders group that meets the threshold, but may only nominate one representative from the group to serve on the CA. In general,

IRDiRC does not receive funding from its members, nor does IRDiRC provide funding for research.

Partnering on common goals

The Consortium recognizes that it cannot meet its goals by working alone. Therefore, IRDiRC partners with other organizations with like-minded goals in order to combine resources and expertise to drive innovation, and make impactful changes to the lives of those living with a RD.

IRDiRC is funded through the European Joint Programme on Rare Disease (EJP-RD), with significant overlap between IRDiRC's membership and the partner organizations of the EJP-RD. Similar to IRDiRC's focus on three central goals, the EJP-RD organizes its work around five central "Pillars"[10]. Under Pillar 1 *Fundings and Calls*, the EJP-RD encourages members to support the objectives of IRDiRC and implement its policy recommendations, and develops transnational calls targeting topics of importance identified by IRDiRC. Pillar 2 *Coordinated Access to Data and Services* aligns closely with the goals of IRDiRC:(1) All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline; (2) 1,000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options. IRDiRC's activities are not specifically targeted at education and training, yet they contribute indirectly to Pillar 3 *Training and Empowerment* through the development of best practices, tools, data standards, and policy/regulatory frameworks. Finally, Pillar 4 *Innovation and Clinical Trials* embodies a central theme of IRDiRC's work, which is to identify opportunities to apply cutting-edge techniques and knowledge in RD research, diagnostics and therapeutic development, and create a framework to support clinical trials to test the efficacy of new therapies.

Since 2020, IRDiRC has partnered with the BLACKSWAN Foundation and the EJP-RD to host a joint RE(ACT)-IRDiRC Conference that brings together scientific experts to present and discuss cutting-edge work related to RD research and development. Previously, the BLACKSWAN Foundation and IRDiRC held separate events but recognized the benefits of combining their efforts to maximize the impact of this conference as they worked towards common goals. The joint RE(ACT)-IRDiRC conference was hosted virtually in January 2021 due to the ongoing COVID-19 pandemic, while the 2023 edition took place as an in-person event in Berlin, scheduled back-to-back with IRDiRC's CA meeting to maximize attendance.

Building upon the work of the *Clinical Research Networks for Rare Diseases* TF, IRDiRC partnered with the EJP-RD to host a conference on clinical research networks (CRN) in December 2022 featuring a roster of international experts to share knowledge on CRN structure and activities, while stimulating discussion and collaboration on pathways towards interoperability between networks. This meeting was scheduled back-to-back with the IRDiRC CA meeting to encourage key stakeholders in all rare disease fields (scientists, funders, patient advocates) to participate in a more robust discussion.

The European Rare Disease Research Coordination and Support Action (ERICA) consortium, comprised of all 24 European Reference Networks (ERN), was established to expand upon the work of the individual ERNs to create a platform to tackle highly complex or rare disease cases with specialists from different countries and specialties. The work of ERICA supports the 1st goal of IRDiRC to ensure that all patients receive a diagnosis within 1 year of coming to medical attention, or are entered into a global diagnostic and research pipeline. As such, IRDiRC is actively involved in the governance of the ERICA consortium through its representation on the ERICA advisory board by the Chair of the IRDiRC CA.

An EU Task Force to assess the burden of rare diseases has recently been established, comprised of international experts who will meet regularly to map the burden of disease indicators, and identify barriers in accessing primary, secondary, and tertiary health care services for people with RDs[11]. This EU Task Force will collaborate with IRDiRC to assess the impact of RDs on patients based on previously published recommendations[12].

Critical Path Institute (C-Path) is an independent nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA) created under the auspices of the FDA's Critical Path Initiative program in 2005. IRDiRC and C-Path share common goals to improve and streamline the process of medical product development by fostering precompetitive collaboration. A current focus is on clinical outcome assessments for rare diseases that optimize the incorporation of the patient's voice in the evaluation of treatment efficacy.

In addition to the partnerships described above, IRDiRC and its members often participate as invited speakers or panel participants in international scientific, patient group, and industry meetings such as the Orphan Drug Congress Europe, American Society of Gene & Cell Therapy (ASGCT), and the Orphan Drugs and Rare Diseases Global Congress. IRDiRC has also been a supporting partner for international conferences such as the ECRD (European Rare Disease and Orphan Products) conference organized by EURODIS (European Organization for Rare Diseases) with Orphanet, and the Orphan Drug Congress Europe.

Global collaboration through a global pandemic

The global COVID-19 pandemic that began in December 2019 posed significant challenges not only for RD research but also for patients seeking care for rare or undiagnosed diseases. To understand the impact of the pandemic on the RD community, IRDiRC conducted a survey of its members in the summer of 2020 when many countries and communities were in the midst of full lockdown measures to counter the threat from COVID-19[13]. While it was evident that the pandemic did have an impact on funding, research activities, and patient access to diagnostics, therapies and clinical trials, in general, the sentiment of the IRDiRC membership was that the three stated goals were still achievable by 2027. The first goal of patients receiving a diagnosis within 1 year was still achievable if research returned to pre-pandemic levels and healthcare centers remained accessible to patients. The second goal of 1,000 new therapies remains achievable if research funding is restored and research efforts that were previously diverted towards COVID-19 are re-focused on RDs. The third goal of developing methodologies to measure the impact of diagnoses and therapies on RDs was perhaps the least affected by the pandemic, as work towards this goal could be executed by the increased use of teleconferencing linking collaborators globally.

The COVID-19 pandemic highlighted one of the major strengths of the Consortium, which is its ability to work remotely in a highly collaborative manner. Despite the travel restrictions imposed by the pandemic, the work of IRDiRC continued mostly unhindered, in that the inherent global nature of its membership, which already relied heavily on teleconferencing for most of its activities. Events that were previously conducted in person, such as the semi-annual Consortium Assembly meetings, the biennial scientific conference, and Task Forces, pivoted to virtual meetings, enabling continued discussion amongst consortium members. Output from TFs/WGs continued during the pandemic, albeit at a slower pace, demonstrating the resilience of the Consortium to the global health crisis COVID-19.

As the world began to recover from the pandemic and travel restrictions were lifted, IRDiRC maintained the use of the hybrid format meeting to ensure maximum participation from all members, irrespective of their

ability to attend in person. Today, most IRDiRC activities are conducted online via videoconference, including monthly meetings of the Operating, Constituent, and Scientific Committees, as well as TFs/WGs. The Consortium Assembly meets quarterly with two in-person and two virtual meetings, and regular updates from the Scientific Secretariat as necessary throughout the year. This regular cadence of meetings ensures efficient discussion and communication of IRDiRC goals and priorities amongst all members, allowing the Consortium to operate successfully on a global scale.

Evolving priorities

The Consortium was launched in 2011 with the support of five public funders[14], but it was soon recognized that successful collaboration would require interaction with other key stakeholders in RDs, such as patient advocates and industry. By the end of 2011, three patient advocate groups had committed to participation, with companies/industries joining the following year. The interaction between these three key stakeholder groups has been essential to the success of IRDiRC.

Originally, three Scientific Committees, the DSC, ISC, and TSC, were formed to advise the CA on research priorities and provide updates on progress from a scientific viewpoint. While this proved very successful for the first decade of IRDiRC's existence, it was recognized that additional expertise was needed to support efforts in new therapy development. Thus, the Regulatory Science Committee (RSC) was formed in 2022 to address the growing need to develop tools and standards for navigating the myriad of regulatory requirements across the globe, and to offer recommendations on harmonizing these differing requirements into a single standard to reduce the regulatory burden on drug developers.

CONCLUSION

With IRDiRC a little over half-way through its current 10-year goals (2017-2027), much work is still required to address the many challenges faced by RD patients and their families. While much progress has been made towards achieving the three goals set in 2017, IRDiRC recognizes the continued need to engage with stakeholders and foster collaboration on a global scale. With this in mind, IRDiRC continues to solicit new membership from funders, patient advocates, and in particular, industry in an effort to further expand the influence and impact of the Consortium on RD research.

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Availability of data and materials

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All authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication

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