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Research on rare diseases: ten years of progress and challenges at IRDiRC

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Although individually rare, the >6,000 known rare diseases (RDs) affect about 300 million people worldwide[1]. The diversity, complexity and multiplicity of RDs results in severe disparities in scientific knowledge, clinical expertise, availability of diagnoses and treatments, patient outcomes and quality of life.

RD research has benefited substantially from advances in genomics, with the genetic causes of >4,000 RDs now having been identified. Novel therapeutic platforms such as RNA-based therapies and viral vectorbased gene therapies have high potential for RDs. However, the success rate of each step of the research and development pipeline is progressively smaller and the vast majority of RDs have no approved treatments.

To tackle these problems, in 2011 the European Commission and the US National Institutes of Health launched IRDiRC by summoning key stakeholders engaged in RD research and development. Today, IRDiRC has nearly tripled in size, with the 59 member organizations of the Consortium Assembly organized in three Constituent Committees (Funders, Companies and Patient Advocates), supported by the international experts of

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The International Rare Diseases Research Consortium (IRDiRC) is a global collaborative initiative launched in 2011, aimed at tackling rare diseases through research. Here, we summarize IRDiRC's vision and goals and highlight achievements and prospects after its first decade.

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the Diagnostics, Therapies and Interdisciplinary Scientific Committees (see Supplementary information). While pursuing their own strategic research and investment agendas through their research projects and clinical trials, IRDiRC members adhere to the IRDiRC policies and guidelines[2]. The driving force of IRDiRC is the sharing of collective intelligence in a non-competitive space.

IRDiRC set two initial goals: to contribute to the development of diagnostic tools for most RDs and of 200 new therapies for RDs by year 2020. When, in 2017, the therapeutic goal was surpassed, IRDiRC members and experts and the wider RD community embraced the aspirational vision to "Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention"[3]. The vision inspired the three goals for 2027: 1) to improve and accelerate RD diagnosis, 2) to contribute to developing 1,000 new therapies, focusing on RDs without approved treatments, and 3) to develop methodologies to measure impact of diagnoses and therapies on RD patients (see Supplementary information).

To quantify progress towards its goals, IRDiRC monitors the numbers of newly identified RDs, of genes linked to RDs and of new orphan medicinal products (see Supplementary information). Between 2010 and 2020, 886 new RDs have been identified and the genes linked to RDs increased from 2364 to 4211; 438 new drugs gained orphan designation and marketing approval in the USA and/or the European Union. Despite the growth in these indicators, a huge number of patients are awaiting diagnosis and cannot benefit from approved therapies. Continued monitoring stimulates IRDiRC to identify major hurdles towards RD diagnosis and treatment and to address them through dedicated activities.

Activities toward IRDiRC vision and goals

Task Forces (TFs) and Working Groups (WGs) are the instruments adopted by IRDiRC to address actionable topics identified by the Consortium and reflecting the evolving priorities for RDs. Selected activities are presented here; all completed[4], ongoing or planned ones and the resulting publications and outputs are listed in Supplementary information.

Shortening the diagnostic journey

Several TFs have been aimed at promoting and expediting RD diagnosis. The 'Matchmaker Exchange' TF built a federated network allowing genomic matchmaking of cases with similar phenotypes through a now widely adopted informatics tool. The 'Solving the Unsolved' TF identified mechanisms of RDs undiagnosable by exome sequencing, and suggested approaches to solve them, offering the basis for current IRDiRC activities towards Goal 1.

Developing new therapies

Today, less than 6% of RDs have approved treatments and most drug development efforts are concentrated on a limited number of diseases. Addressing this need, the 'Orphan Drug Development Guidebook' TF created a resource freely accessible to academic and industrial drug developers, describing the available tools and initiatives specific for RD development and best practices for their use. The guidebook is being expanded to include tools and

information on drug repurposing for RDs, building on the outcomes from the 'Sustainable Economic Models of Drug Repurposing' TF.

Fostering clinical research

RD clinical research faces many obstacles. Due to the low prevalence, the 'gold standard' randomized controlled trial approach is often not applicable; the 'Small Population Clinical Trials' TF produced recommendations about trial designs appropriate to small populations, of interest to regulators and researchers. Concurrently, to maximize the impact of clinical trials, the 'Patient Centered Outcome Measure' TF provided methodological support on patient-relevant outcome measures for RDs.

To enhance accessibility, current activities are exploring innovative clinical trial approaches to increase the number of patients joining clinical trials, or are developing a machine-readable and computable patient consent framework.

Stimulating multi-stakeholder engagement

Multistakeholder collaboration is essential to shorten the time to diagnosis, accelerate the development of therapies and improve access. The 'Chrysalis' TF is exploring key criteria to make RD research more attractive to industry for research and development and has identified gaps in the funding landscape to meet those criteria.

The 'Clinical Research Networks' TF analysed the attributes of several RD networks and the different mechanisms already established or in need of development to reach international interoperability.

Access to care and methodologies to assess impact

In 2017, IRDiRC included the challenge of accessibility in its vision. Accordingly, IRDiRC took action by leveraging the competence of clinical experts and patient advocates. The 'Rare Disease Treatment Access' WG issued the first essential list of medicinal products for RDs to improve the standards of care and is now identifying the barriers to drug access, especially in low-and-middle income countries. Finally, a dedicated WG tackled the need for impact assessment methodologies for RD diagnosis and therapies, and identified metrics, tools and needs to adequately measure the burden of RDs on patients, families and health-care systems.

Moving forward

While still addressing key issues toward its diagnostic and therapeutic goals, IRDiRC is tackling topics critical for its vision, such as telehealth, medical technologies and primary care for RDs through strategic collaborations with patient and health organizations.

IRDiRC in the RD community

IRDiRC has developed RD community engagement instruments to present its activities, provide a forum for discussions and influence global RD research (see Supplementary information). Recommendations, tools or guidelines by TFs and WGs, and IRDiRC reviews and commentaries are published as peer-reviewed articles or IRDiRC reports.

Four international IRDiRC conferences engaged researchers, clinicians, patient advocates, industry leaders and policy makers from all continents. Dissemination via the IRDiRC website, newsletters, social media and member/partner channels effectively widens awareness and influence beyond the RD community.

IRDiRC participates in multinational RD initiatives and is cited as a reference in policy documents, member programs and national RD plans. Also, it stimulates sharing of resources through the 'IRDiRC Recognized Resources' label for platforms, tools, standards and guidelines responding to criteria of quality, relevance and long-term sustainability[5].

Outlook

Ten years from its inception, IRDiRC is recognized as an original and influential initiative, uniting major stakeholders from across the globe to facilitate progression of research towards concrete solutions for RDs. IRDiRC's vision and goals are acknowledged internationally; the policies, recommendations, guidelines and resources developed by its members and experts are available and adopted worldwide and are contributing to advancing research toward the vison to assure the best care possible for each RD patient. Continued monitoring and interactions with the RD community keep IRDiRC focused on urgent and relevant needs and stimulate collaborations with initiatives and organizations with expertise and capacity beyond the research and development field, to fulfil its goals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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