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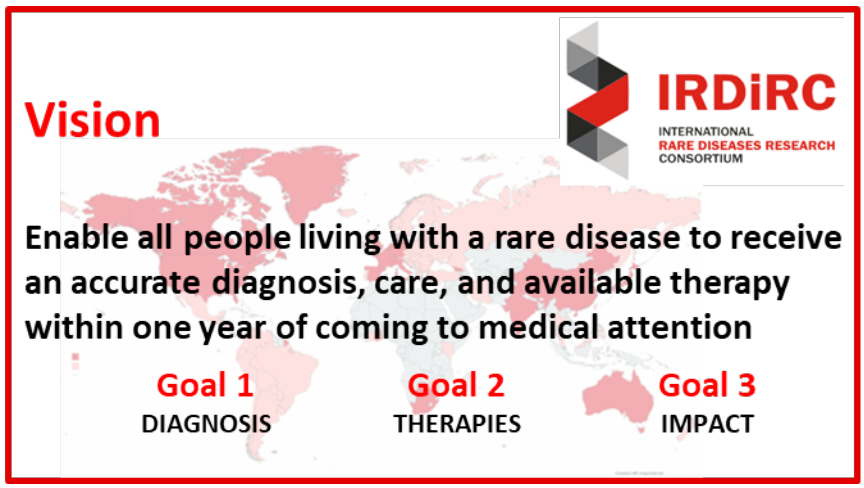
Supplementary information

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

In the format provided by the authors

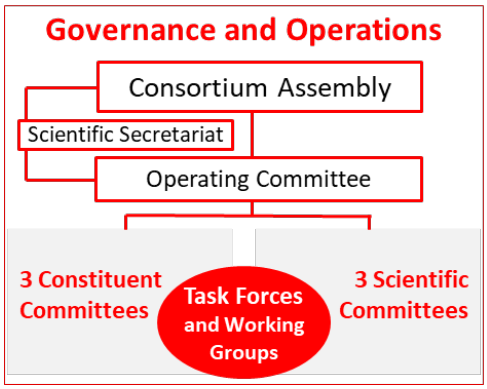
Visual summary

(A)



(B)

(C)



(D)

Rare Disease Investments by IRDiRC Members

- **49,749** Research Projects funded since 2010
- **1,387** Clinical Trials supported since 2010

(E)

Rare Disease Metrics
Since 2010

- **886** New RDs
- **438** New Drugs for RDs
- **1,847** New RD Genes

(F)

(G)

Communication and Outreach

- **28** Peer-reviewed Papers
- **~ 850** Citations
- **9** IRDiRC Reports
- **4** International Conferences
- **26** Recognized Resources
- **Website, Social Media**

(A) Vision and Goals

Vision

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

Goals for 2027

1: Diagnosis To provide patients with a diagnosis within one year of coming to medical attention or ensure that undiagnosable individuals enter globally coordinated diagnostic and research pipeline

2: Therapies To approve 1000 new therapies for rare diseases, with special attention to diseases without approved options

3: Impact To develop methodologies to assess the impact of diagnoses and therapies on rare disease patients

The IRDiRC Vision and Goals for 2027 were established in 2017, following a profound process stimulated by the accomplishment of the initial goal of 200 new therapies for rare diseases three years ahead of time.

In expressing the need and urgency of people living with a rare disease to benefit from therapies and diagnoses developed by the research community, the vision widens IRDiRC's horizon beyond its core research mission and calls for engagement of all stakeholders, in order to identify and address the major gaps towards the three new ambitious goals set for 2027.

(B) IRDiRC Member Organizations

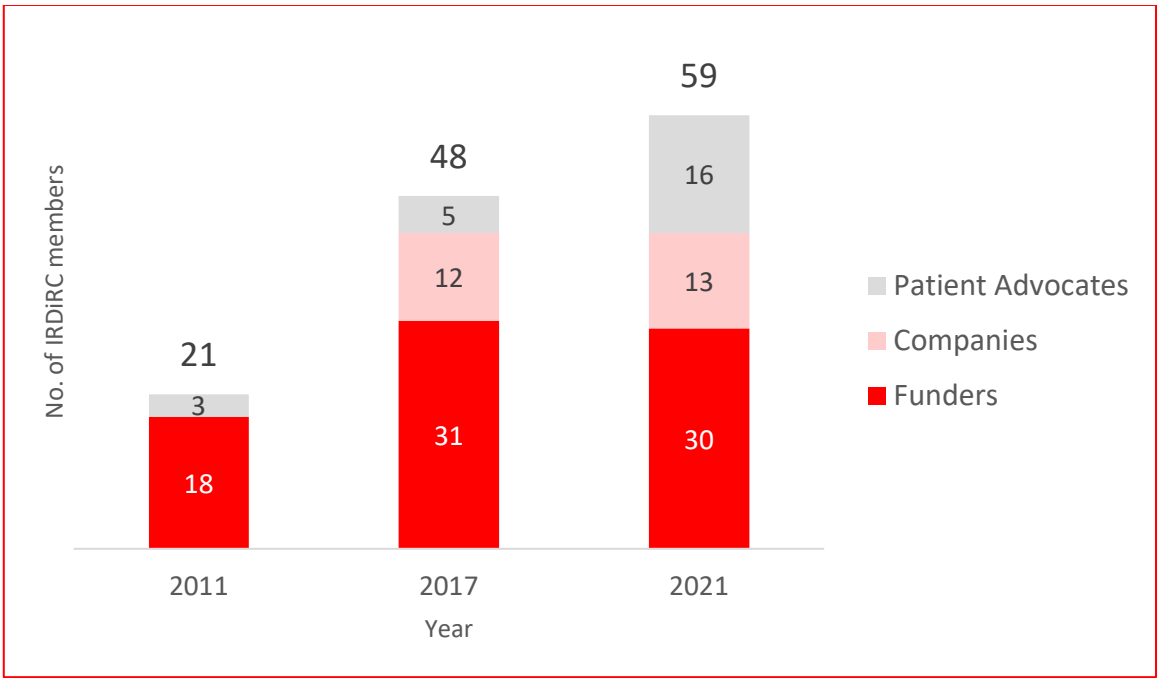


Figure B1

Growth of IRDiRC member organizations since its creation in 2011.

While IRDiRC was mostly composed of funders in 2011, the overall number of members constantly increased, and the nature of these organizations became more diverse with the incorporation of industry and the increased number of umbrella patient advocacy organizations. Today this diversity reflects the vision and actions of IRDiRC toward the development of diagnoses and therapies for rare diseases, but also their accessibility to patients worldwide.

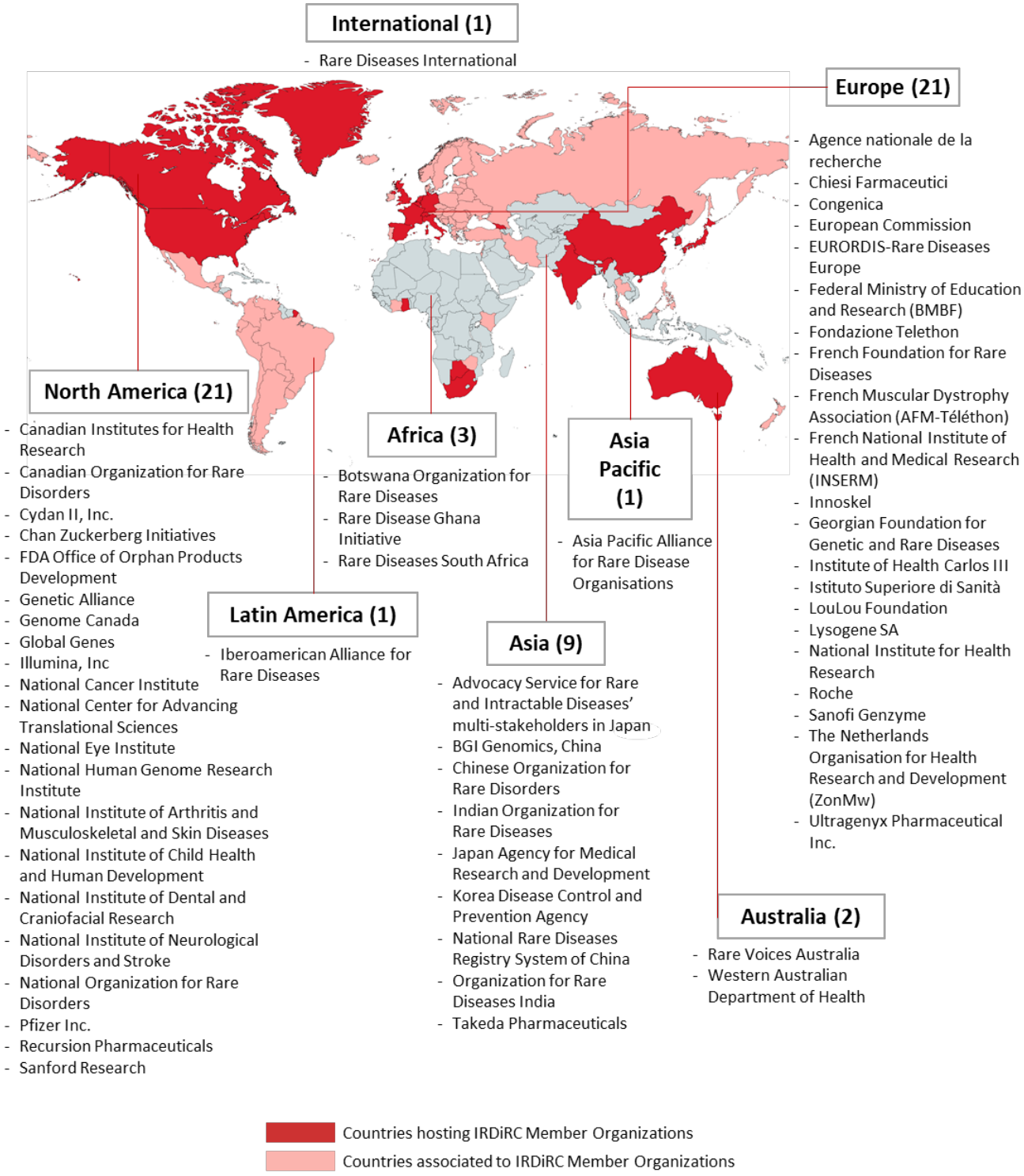


Figure B2

Distribution of IRDiRC member organizations across geographical regions as of December 2021. Countries colored in red are hosting a member organization while countries colored in pink are hosting organizations that are affiliated to umbrella IRDiRC member organizations such as international patient advocacy groups.

Table B1

Current IRDiRC member organizations' representatives (in alphabetical order by family name) Alba Ancochea, Iberoamerican Alliance for Rare Diseases (Latin America); Diego Ardigò, Chiesi Farmaceutici S.p.A. (Italy); Katherine Beaverson, Pfizer (USA); Virginie Bros-Facer, EURORDIS-Rare Diseases Europe (Europe); Ivana Cecic, Genome Canada (Canada); Lisa Chadwick, National Human Genome Research Institute (USA); Faye Chen, National Institute of Arthritis and Musculoskeletal and Skin Diseases (USA); Kelly du Plessis, Rare Diseases South Africa (South Africa); Dominique Dunon-Bluteau, Agence Nationale de la Recherche (France); ShiYin Foo, Cydan (USA); Pamela Gavin, National Organization for Rare Disorders (USA); Chris Gibson, Recursion Pharmaceuticals, Inc (USA); Satish Gopal, National Cancer Institute (USA); Shef Gordon, National Eye Institute (USA); Alaa Hamed, Sanofi Genzyme (USA); Adam L. Hartman, National Institute of Neurological Disorders and Stroke NIH/NINDS (USA); Kevin Huang, Chinese Organization for Rare Disorders (China); Oxana Illiach, Canadian Organization for Rare Disorders (Canada); Ritu Jain, Asia Pacific Alliance of Rare Disease Organisation (Asia Pacific); Oleg Kvlividze, Georgian Foundation for Genetic and Rare Diseases (Georgia); Ralph Laufer, Lysogene (Germany); Daniel Lavery, Loulou Foundation (United Kingdom); Jiwon Lee, Korea Disease Control and Prevention Agency (South Korea); Ning Li, BGI (China); Volker Liebenberg, illumina Inc. (USA); Christopher McMaster, Canadian Institutes of Health Research (Canada); Nicole Millis, Rare Voices Australia (Australia); Yoshinao Mishima, Japan Agency for Medical Research and Development (Japan); Lucia Monaco, Fondazione Telethon (Italy); Ramaiah Muthyala, Indian Organization for Rare Diseases (India); Madhu Natarajan, Takeda Pharmaceuticals (USA); Katherine Needleman, Food and Drug Administration, Office of Orphan Products Development (USA); Catherine Nguyen, French National Institute of Health and Medical Research (France); Yukiko Nishimura, Advocacy Service for Rare and Intractable Diseases' multi-stakeholders in Japan (Japan); Irene Norstedt, European Commission (Europe); Kristen Nowak, Western Australian Department of Health (Australia); Marie-Christine Ouillade, AFM-Telethon (France); Willem Ouwehand, National Institute for Health Research (United Kingdom); Anne Pariser, National Center for Advancing Translational Sciences (USA); Melissa Parisi, National Institute of Child Health and Human Development (USA); Samantha Parker, InnoSkel (France); David Pearce, Sanford Research (USA); Raquel Peck, Chan Zuckerberg Initiative (USA); Manuel Posada, Instituto de Salud Carlos III (Spain); Tom Pulles, Ultragenyx (Switzerland); Christian Rubio, Global Genes (USA); Daniel Scherman, French Foundation for Rare Diseases (France); Ralph Schuster, Federal Ministry of Education and Research (Germany); Eda Selebasto, Botswana Organization for Rare Diseases (Botswana); Prasanna Kumar Shirol, Organization for Rare Diseases India (India); Zhang Shuyang, National Rare Diseases Registry System of China (China); Domenica Taruscio, Istituto Superiore di Sanità (Italy); Sharon Terry, Genetic Alliance (USA); Sonja van Weely, The Netherlands Organisation for Health Research and Development (Netherlands); Jason Wan, National Institute of Dental and Craniofacial Research (USA); Christina Waters, Congenica (UK); Samuel Agyei Wiafe, Rare Disease Ghana Initiative (Ghana); Durhane Wong-Rieger, Rare Diseases International (International).

(C) IRDiRC Governance and Operating Model

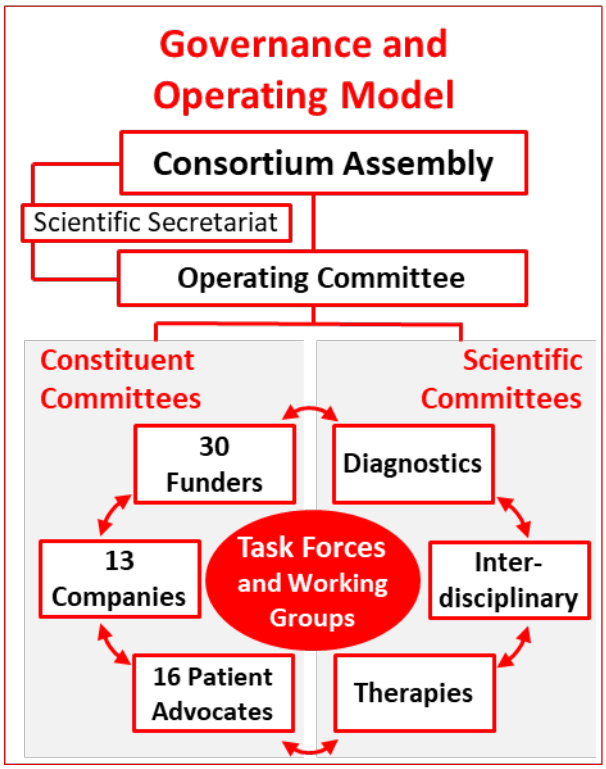


Figure C1

IRDiRC Governance and Operating Model.

IRDiRC member organizations include funding bodies and companies that commit to invest at least 10 million US dollars over 5 years toward their own research and development programs on rare diseases, as well as umbrella patient advocacy organizations focused on rare diseases and representing a large country or region. Member organizations' representatives constitute the Consortium Assembly, IRDiRC's decision-making body, and elect a Chair and Vice Chair.
Members' representatives are organized into the three Constituent Committees of Funders, Companies and Patient Advocates, which collaborate with international experts, nominated into the Diagnostics, Therapies and Interdisciplinary Scientific Committees.
All six Committees nominate a Chair and a Vice Chair, who work with the Assembly Chair and Vice-Chair in the Operating Committee. Scientific Committees' Chairs and Vice-Chairs are also part of the Consortium Assembly. The mandate of all Chairs and Vice Chairs and of Scientific Committees' members last for three years and can be renewed once.
Operations are coordinated by the Scientific Secretariat, a team of professionals supported by the European Commission within the Coordination pillar of the European Joint Programme on Rare Diseases, and previously by the Support IRDiRC project funded by the European Commission.
IRDiRC Constituent and Scientific Committees are stimulated to identify gaps and key issues in rare disease research and to tackle these through Task Forces (TFs) and Working Groups (WGs) aimed at producing guidelines, recommendations and resources, also in collaboration with external stakeholders. More and more, proposals for new TFs and WGs are the product of close interaction and exchanges among all six Committees and involve also external partnerships.
The Consortium Assembly periodically prioritizes proposals for TFs and WGs into annual Road Maps. This dynamic operative model relies on the voluntary and free participation of IRDiRC members and experts engaged in the specific activities.

Table C1

Chairs and Vice Chairs of the IRDiRC Consortium Assembly and IRDiRC Committees (in chronological order)

Consortium Assembly (previously: Executive Committee)

Chairs	*Vice Chairs*
• Ruxandra Draghia-Akli	• -
• Paul Lasko	• -
• Christopher Austin	• Hugh Dawkins
• Lucia Monaco	• David Pearce

Funders Constituent Committee

Chairs	*Vice Chairs*
• Daria Julkowska	• Hugh Dawkins
• Adam L. Hartman	• Catherine Nguyen

Companies Constituent Committee

Chairs	*Vice Chairs*
• Mathew Pletcher	• Madhu Natarajan
• Katherine Beaverson	• Samantha Parker

Patient Advocates Constituent Committee

Chairs	*Vice Chairs*
• Sharon Terry	• Béatrice de Montleau
• Durhane Wong-Rieger	• Yukiko Nishimura / Samuel Wiafe

Diagnostic Scientific Committee

Chairs	*Vice Chairs*
• Kim Boycott	• Han Brunner / Michael Bamshad / Gareth Baynam
• Gareth Baynam	• Sarah Bowdin
	• Birute Tumiene

Therapies Scientific Committee

Chairs	*Vice Chairs*
• Josep Torrent-Farnell	• -
• Yann Le Cam	• -
• Diego Ardigò	• Virginie Hivert
• Daniel O'Connor	• Anneliene Jonker

Interdisciplinary Scientific Committee

Chairs	*Vice Chairs*
• Hans Lochmüller	• Petra Kaufmann
• Petra Kaufmann	• Domenica Taruscio
• Domenica Taruscio	• Dixie Baker
• Stephen Groft	• Dixie Baker
• Philip John Brooks	• Marc Dooms

(D) Investments on Rare Diseases by IRDiRC Member Organizations

IRDiRC member organizations commit to contributing to the consortium's goals by applying IRDiRC's principles and guidelines to the execution of their own agenda, according to their institutional strategies and priorities on rare diseases.

Funders' and Companies' investment commitment is monitored by IRDiRC and research projects supported by IRDiRC members are included in a database operated by Orphanet and accessible to IRDiRC members, annotated with the name of the disease(s) under investigation and several other indicators relevant to rare diseases. The database includes 56,873 research projects and 1,380 clinical trials on RDs supported by 37 IRDiRC member organizations since 2010 (accession date: 4 January 2022)

Thorough analyses of the funding activities by IRDiRC members are reported in *the State of Play of Research on Rare Diseases*, which is periodically issued by IRDiRC (next edition due: February 2022). Here, we present the distribution of annotated research projects and clinical trials across medical domains (*Table D1*).

Medical Domain	% Research Projects	% Clinical Trials
Rare neoplastic disease	37,2	45,4
Rare neurologic disease	22,5	13,3
Rare developmental defect during embryogenesis	9,4	2,7
Rare inborn errors of metabolism	6,6	6,4
Rare ophthalmic disorder	3,7	1,9
Rare immune disease	3,4	2,5
Rare infectious disease	2,9	2,4
Rare systemic or rheumatologic disease	2,7	4,8
Rare skin disease	2,4	1,8
Rare hematologic disease	2,2	7,5
Rare respiratory disease	1,5	5,2
Rare bone disease	1,5	1,0
Rare endocrine disease	1,0	1,6
Rare cardiac disease	0,0	1,3
Other domains	3,0	2,2

Table D1

Percent distribution across medical domains of research projects and clinical trials supported by IRDiRC member organizations since 2010.

Data refer to the 35% of research projects and 100% of clinical trials in the IRDiRC/Orphanet database (accession date 4 January 2022) that have been annotated with the relevant RD and assigned to the preferential medical domain according to the linearization rules for Orphanet classifications. Medical domains studied by less than 1% of research projects or clinical trials are clustered in "Other domains". Full annotation is ongoing.

(E) Rare Disease Metrics

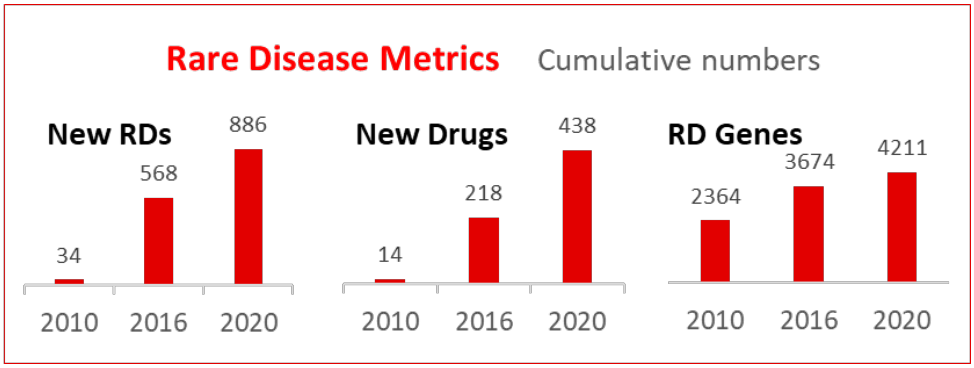


Figure E1

Evolution of the cumulative numbers of new rare diseases, genes linked with rare diseases and new orphan medicinal products from 2010 to 2020.

To monitor progress toward its goals, IRDiRC implemented a set of metrics to quantify their evolution since 2010.

Cumulative number of new rare diseases

Often genetic, the identification of new rare diseases and their molecular etiology is essential to advance clinical research and improve the life of patients. The number of new rare diseases is extracted from the Orphanet newsletter: OrphaNews - section on New Syndromes. This section presents a list of peer-reviewed publications describing new candidate rare diseases. Between 2010 and 2020, the cumulative number of new rare diseases evolved from 34 to 886.

Cumulative number of genes linked to a rare disease

Discovering the genes linked with rare diseases is essential to achieve an accurate molecular diagnosis and shorten the time of the patient diagnostic odyssey. In the last years, application of exome sequencing in the field of rare diseases extraordinarily increased the yield of diagnosis. Between 2010 and 2020, the cumulative number of genes linked to a rare disease evolved from 2364 to 4211.

Cumulative number of new orphan medicinal products

The introduction of orphan drug legislation in different jurisdictions starting with the US Orphan Drug Act in 1983 played an important role in the development of new therapies for rare diseases. The number of medicinal products with an orphan designation and marketing approval for the treatment of rare diseases in the USA and/or the European Union is monitored on a yearly basis using the information provided by the FDA and EMA websites. The methodology used to count new orphan medicinal products is described on the IRDiRC website. Between 2010 and 2020, the cumulative number of new orphan medicinal products in the USA and/or the European Union evolved from 14 to 438.

Forecast

In 2017, IRDiRC defined that the Goal 2 of the Consortium is the development of 1000 new therapies for rare diseases by year 2027. By applying linear regression to the number of new therapies, it could be roughly estimated that Goal 2 will be achieved by 2029-2030. This delay in the process of drug development and approval could be explained by several factors such as the difficulty to develop new drugs for the most complex and ultra-rare diseases, the lack of biologic insight for some diseases, the lack of natural history studies and qualitative data for the initiation of drug programs, funding limitations, stakeholder's strategic reorientations, and unexpected events reshaping some priorities as we have seen with the covid-19 pandemic. However, it is important that, despite all these limitations, the rare disease community as a whole remains engaged in achieving the goals established by IRDiRC. The strength of this engagement has been clearly characterized in the analysis of the covid-19 survey sent to IRDiRC members expressing the need to maintain the planned activities and the roadmap of actions (manuscript under review).

(F) IRDiRC Task Forces (TFs) and Working Groups (WGs)

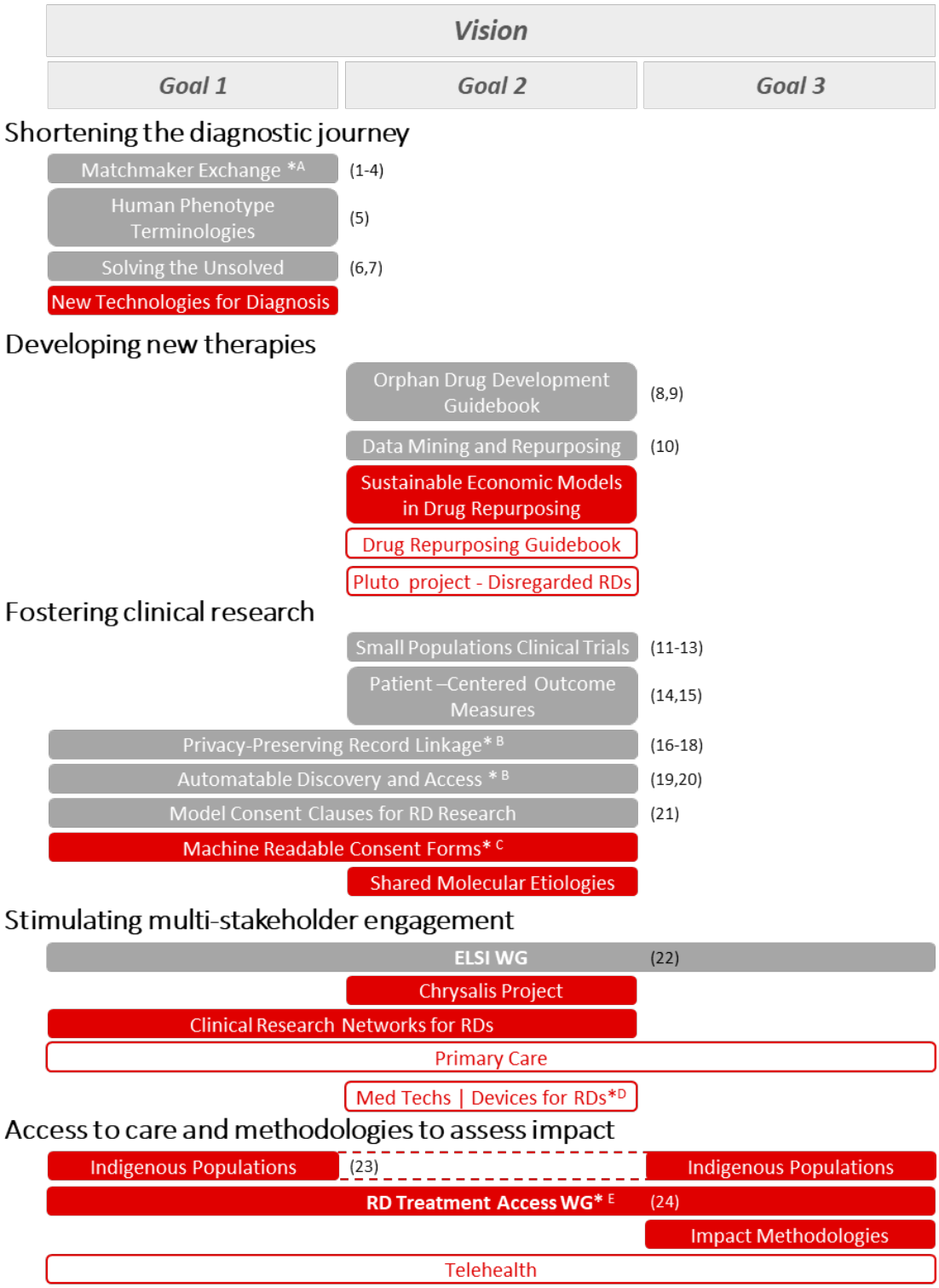


Figure F1

IRDiRC Task Forces and Working Groups distributed by IRDiRC Vision and Goals and by major themes. Gray background: completed activities; red background: ongoing activities; white background: planned activities (2022). * Activities performed in collaboration with**:** A) Clinical Genome Resource; B) Global Alliance for Genomics and Health; C) European Joint Program for Rare Diseases; D) University of Twente; E) Rare Diseases International (WG second stage). Numbers in parentheses refer to *References F1*.

References F1

TF and WG Outputs

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(G) IRDiRC Communication and Outreach

Throughout the years, IRDiRC has developed numerous instruments and channels to engage with the community at large. These instruments were used to reach out to different types of stakeholder profiles, to be able to present IRDiRC activities, provide a forum for discussions and influence global research directions with regards to IRDiRC vision.

Recommendations, tools or guidelines developed by TFs and WGs and reviews and commentaries on IRDiRC core principles were published in the form of **peer-reviewed articles** (28 in total) or of **IRDiRC reports** (*References F1 and G1*). These publications were widely cited (852 citations for 26 publications between 2015 and 2020, with a mean relative citation ratio of 2.17; iCite analysis performed on 4 January 2022). Additional dissemination via the IRDiRC website, newsletters, social media (Twitter) and member/partner channels were effective in widening awareness.

IRDiRC organized four **international conferences** (2013 Dublin, 2014 Shenzhen, 2017 Paris and 2020 online). Topics covered by the conferences represented an evolution in the frontiers of RD research and the maturity of IRDiRC. The first conference covered the formation and governance of IRDiRC, and the later ones reflected the discussions of the Scientific Committees and Task Forces. These conferences engaged multiple stakeholders (academics, researchers, clinicians, patient advocates, industry leaders and policy makers) and were attended by 300-600 participants and speakers from all continents.

The developments and outputs cemented IRDiRC as a forum where experts gather to openly address challenges and fulfil the vision of the RD community. Likewise, IRDiRC collaborates and provides **advice in large multinational initiatives** such as the Global Commission for Ending Diagnostic Odyssey, Orphan Drug Incentives Expert Group and the European Joint Programme on Rare Diseases, to tackle challenges in regional and international settings. Reference of IRDiRC in policy documents (e. g. Rare2030), member programs, national RD plans are further demonstrations of significant impact in the community. Participation and invitation to international working groups and programs in the RD space were testaments of IRDiRC gaining influence in decision and policy making.

Finally, IRDiRC has applied the **IRDiRC Recognized Resources** quality label through a peer-reviewed process to 26 resources, including 10 informatic platforms or tools, 8 guidelines or advisory committees, 5 databases, and 3 standards for the RD community.

References G1

Publications and Reports on IRDiRC core principles (most recent first)

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Related Links

https://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_linearisation_rules.pdf
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https://icite.od.nih.gov/