


REVIEW



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CIBERER: Spanish national network for research on rare diseases: A highly productive collaborative initiative

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Abstract

CIBER (Center for Biomedical Network Research; *Centro de Investigación Biomédica En Red*) is a public national consortium created in 2006 under the umbrella of the Spanish National Institute of Health Carlos III (ISCIII). This innovative research structure comprises 11 different specific areas dedicated to the main public health priorities in the National Health System. CIBERER, the thematic area of CIBER focused on rare diseases (RDs) currently consists of 75 research groups belonging to universities, research centers, and hospitals of the entire country. CIBERER's mission is to be a center prioritizing and favoring collaboration and cooperation between biomedical and clinical research groups, with special emphasis on the aspects of genetic, molecular, biochemical, and cellular research of RDs. This research is the basis for providing new tools for the diagnosis and therapy of low-prevalence diseases, in line with the International Rare Diseases Research Consortium (IRDiRC) objectives, thus favoring translational research between the scientific environment of the laboratory and the clinical setting of health centers. In this article, we intend to review CIBERER's 15-year journey and summarize the main results obtained in terms of internationalization, scientific production, contributions toward the discovery of new therapies and novel genes associated to diseases, cooperation with patients' associations and many other topics related to RD research.

KEYWORDS

genetics, new therapeutic approaches, novel genes, rare diseases, research network

1 | INTRODUCTION

In 2006, a public consortium known as “Center for Biomedical Network Research” (CIBER, *Centro de Investigación Biomédica En Red*) was created under the umbrella of the Spanish National Institute of Health Carlos III (ISCIII). This highly innovative research structure comprises 11 thematic areas dedicated to the main public health priorities of the National Health System (NHS),¹ one of them being devoted to research on rare diseases (CIBERER).

In this article, we review CIBERER's 15-year journey and summarize the most outstanding results obtained in terms of internationalization, scientific production, gene discovery, contributions toward the discovery of new therapies and novel genes associated to diseases, cooperation with patient associations and many other topics related to RD research.

2 | CIBER CONSORTIUM, COLLABORATION, AND NETWORKING IN BIOMEDICAL RESEARCH

The CIBER constitutes a relevant research consortium of excellence in the fields of Biomedicine and Health Sciences within the Spanish NHS and the Science and Technology Research System. CIBER is structured into 11 thematic areas and comprises 427 research groups

selected through a competitive process, contributing more than 6000 researchers and a core staff of 804 people (Table 1).² CIBER is a national collaborative network consortium belonging to ISCIII, the national body that translates relevant biomedical research results to the NHS. CIBER's thematic areas are: Bioengineering, Biomaterials, and Nanomedicine (CIBERBBN), Diabetes and Metabolic Diseases (CIBERDEM), Physiopathology of Obesity and Nutrition (CIBEROBN), Liver and Digestive Diseases (CIBEREHD), Respiratory Diseases (CIBERES), Epidemiology and Public Health (CIBERESP), Mental Health (CIBERSAM), Frailty and Healthy Aging (CIBERFES), Cardiovascular Diseases (CIBERCV), Cancer (CIBERONC), and Rare Diseases (CIBERER) (www.ciberisciii.es).

CIBER is integrated by researchers from universities, research centers, hospitals, health administrations and health services, in addition to an important research structure rooted in patient care. There are 104 institutions associated to the CIBER structure. The main aim of the CIBER is to promote collaborative research, favoring synergies from a multidisciplinary approach to science. CIBER relies on a team of expert managers allocated to different technical departments. There are areas supporting the internationalization and project departments managing more than 150 research projects, 30 at European level and 5 in the American continent, besides many collaborations among various research groups. The Technology Transfer Area oversees licensing agreements with industry and manages patent portfolios; the Contracting and Purchasing Department manages most

TABLE 1 Characteristics of the CIBER structure and distribution of the 11 thematic areas

CIBER acronym	CIBER name	Number of research groups (2020)	Total number of researchers in 2020	Number of publications in 2020	Mean number of publications per group (2020)	Publications in Q1 (2020)	Percentage of publication in Q1	Publications in D1 (2020)	Percentage of publication in D1
BBN	Bioengineering, biomaterials and nanomedicine	45	558	739	16.4	558	76	211	29
CV	Cardiovascular diseases	40	499	757	18.9	441	58	157	21
DEM	Diabetes and associated metabolic diseases	31	250	362	11.7	269	74	100	28
EHD	Liver and digestive diseases	44	402	690	15.7	396	57	204	30
ER	Rare diseases	57	561	727	12.8	454	62	196	27
ES	Respiratory diseases	33	394	789	23.9	391	50	156	20
ESP	Epidemiology and public health	51	557	1367	26.8	764	56	347	25
FES	Frailty and healthy aging	20	145	249	12.5	153	61	51	20
OBN	Physiopathology of obesity and nutrition	33	451	747	22.6	454	61	114	15
ONC	Cancer	50	618	711	14.2	456	64	238	33
SAM	Mental health	23	423	852	37.0	516	61	197	23
Totals (CIBER)	Spanish national biomedical network research (Centro de Investigación Biomédica en Red)	427	4858	7990	18.7	4852	61	1971	25

service contracts; and the Institutional Relations Area manages the negotiation of agreements and scientific contracts, providing legal support to the Innovation Unit. Lastly, the Communication Area is dedicated to the dissemination of CIBER's results, both internally (newsletters), and externally.

3 | CIBER'S RESOURCES AND INFRASTRUCTURES

CIBER has access to numerous infrastructures distributed nationwide. CIBER is part of and contributes to the National Biobank Network through the CIBERER-Biobank, a public, non-profit biorepository centralizing the reception of RD biological samples; the CIBERES-Pulmonary Biobank Platform, which includes samples and matched clinical information from patients with lung diseases; and FATBANK, whose adipose tissue biobank constitutes a national referent. CIBERES-Pulmonary Biobank Platform has acted as the coordinator of the National Biobank Network Platform until recently.

Other specialized centralized platforms are: (1) the so-called Singular Scientific and Technical Infrastructures (ICTS), which are large installations, resources, facilities, and services, unique in its kind, dedicated to cutting edge and high-quality research and technological development, as well as to promote exchange, transmission and preservation of knowledge, technology transfer, and innovation. CIBER coordinates NANBIOSIS, an important ICTS for the development of nanotechnology or biomaterials-based products from their design phase to their preclinical validation stage; (2) Bioinformatics platforms: both CIBEREHD and CIBERER areas, have developed platforms performing data quality control services, gene expression analysis, genomic mapping, variant analysis, and data mining; (3) BiblioPRO, a virtual library of documents in Spanish on health-related quality of life and health outcomes perceived by patients (Patient Reported Outcomes-PRO); (4) Neuroimaging Platform, a database containing thousands of neuroimages developed by CIBERSAM; (5) Patient registry platforms: the REHEVASC platform collects medical records from patients with rare liver diseases from 17 hospitals nationwide and the National Chronic Hepatitis C Database in collaboration with the Spanish Association for the Study of the Liver (AEEH); and the RENACER Patient Registry is a joint initiative of the CIBERCV and the Spanish Agency of Medicines and Medical Devices that, in collaboration with the Spanish Society of Cardiology and other medical societies, registers cardiovascular disease patients. Additionally, CIBEREHD coordinates the Hepamet cohort and the European NAFLD Registry (non-alcoholic fatty liver disease), and CIBERER takes part in the National Registry of patients with RDs, being the promoter of GenRaRe, a clinical registry of genetic diseases.

In addition to the aforementioned infrastructure, CIBER participates in the ITEMAS Network, a platform promoted by the ISCIII supporting healthcare innovation. Its objective is to ensure that ideas of health professionals on innovation are delivered to health services.

4 | CIBERER: THE CENTER FOR BIOMEDICAL NETWORK RESEARCH ON RARE DISEASES

CIBERER, the thematic area of CIBER devoted to RDs (www.ciberer.es/en) was launched in 2006. At present, it is composed of 75 research groups (57 CIBERER groups plus 18 associated clinical groups) belonging to consolidated research structures from universities, health institutions, research centers and hospitals nationwide. CIBERER is organized into seven different research programs: (a) Translational Genomic Medicine; (b) Inherited Mitochondrial and Metabolic Medicine; (c) Neurological Diseases; (d) Pediatric and Developmental Medicine; (e) Sensorineural Pathology; (f) Endocrine Medicine; and (g) Hereditary Cancer, Hematological and Dermatological Diseases.

The vision of CIBERER is to be a center where collaboration and cooperation between biomedical and clinical research groups are prioritized, with special emphasis on the aspects of genetic, molecular, biochemical, and cellular research on RDs. This research is the basis for providing new diagnostic and therapeutic tools, favoring the translation of research from the scientific environment of the laboratory to healthcare settings. CIBERER is aligned with the new Horizon European Program and it shares the International Rare Diseases Research Consortium (IRDiRC) vision and goals.³ IRDiRC is an initiative launched in 2010 by the European Commission and the National Health Institutes of the United States to achieve 1000 new therapies and innovative diagnostic tools, in addition to a global network of national registries, by 2027.

The specific CIBERER's objectives are mainly based on the development of new treatments and the improvement in access to the diagnosis of RDs. In order to achieve this challenge, CIBERER maintains close collaboration with all the stakeholders involved in the RD field, both at a national and international level to (a) Establish and provide access to harmonized and relevant RD data and information; (b) Carry out the molecular and clinical characterization of RD; (c) Promote translational, preclinical, and clinical research (d) Rationalize ethical regulations and procedures. To cover all these aspects, the following lines of action were defined: networking, excellence research, collaborative and cooperative research, translation, and transfer of results, as well as social visibility of RDs. In addition, the internationalization of research, the effective relationship with the productive sector and the institutional visibility are continuously being promoted to complement the aforementioned lines of action.

5 | CIBER AND CIBERER'S SCIENTIFIC PRODUCTION

The global scientific productivity of the CIBER Consortium in its 15 years of existence has been very relevant, thus becoming one of the top 10 national institutions according to its scientific production. As shown by the relevant statistics, an indexed publication with a CIBER affiliation is displayed every 66 min in Medline; specifically ~ two publications/day have CIBERER affiliation (727 publications in 2020; Table 1 and Figure 1).

Regarding its participation in projects and leadership, currently, CIBERER has more than 30 active grants underway in the frame of

different national and international calls. Furthermore, CIBERER has financed 85 intramural projects in the past 10 years, for an overall amount of more than 4.5 million euros. Moreover, CIBERER has recently received close to 8 million euros to deploy two projects focused on the genetic aspects of the COVID-19 pandemic and the implementation of the IMPaCT project (see below).

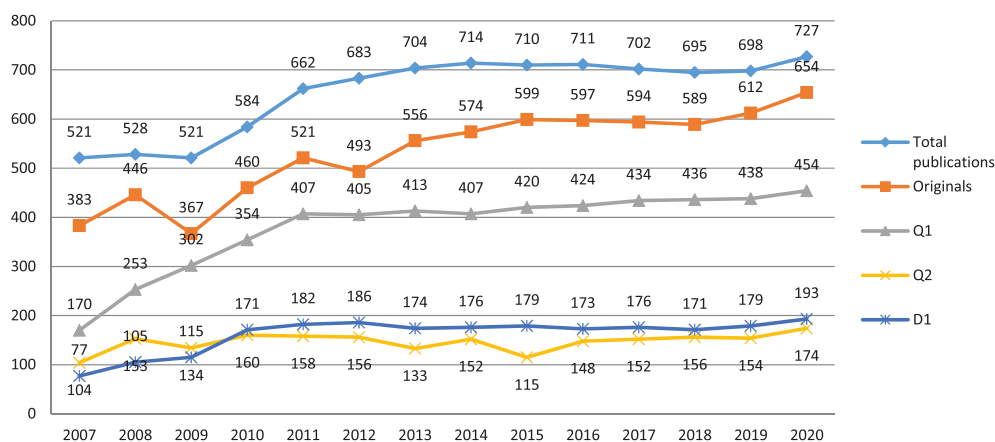
6 | INTERNATIONAL PARTICIPATION OF CIBERER

CIBERER researchers participate and are beneficiaries of relevant national and international projects within the scope of RDs. Some of the initiatives in which CIBERER is engaged are: (a) Since 2010, CIBERER supports the coordination of Orphanet-Spain⁴ within Orphanet, the portal for RDs and orphan drugs that has become a consortium of 40 countries, within Europe and across the globe.⁵ CIBERER is in charge of translation of Orphanet contents into Spanish, which is relevant for more than 470 million people in the world regarding medical, scientific and social aspects of RDs.⁵ This resource, along with MAPER, a database of available RD research resources in Spain, makes CIBERER an institution generating and giving access to the largest amount of information about RD related activities in Spain; (b) European Joint Program on Rare Diseases⁶ (EJPRD); this specific Joint Action for RD has brought together all those European institutions working in this field with the aim of improving the integration, effectiveness, production and social impact of RD research. The EJPRD brings together more than 130 institutions from 35 countries to create a sustainable ecosystem enabling a virtuous cycle between research, care and medical innovation; (c) The IRDiRC consortium⁷ is a global effort to contribute to the development of new therapies and to accelerate and facilitate RD diagnosis. CIBERER played an active role during the genesis of the consortium, being involved in the bilateral meetings held between the European Union (EU) and the National Institutes of Health (NIH), and participating since then and up until recently in the consortium's interdisciplinary working group, in which CIBER members continue performing different responsibilities; (d) The 1 + Million Genomes⁸ is one of the most ambitious initiatives in precision medicine

worldwide in which CIBER Consortium and CIBERER play a very active role by leading the Spanish action. CIBERER groups are represented in practically all the work programs of the Spanish "mirror group" of this initiative, (e) The RD-Connect project,⁹ which gave rise to the RD-Connect Community later on, was launched in November 2012 as a 6-year project funded by the European Commission. CIBERER participated as an associated member of the consortium; (f) Genome-phenome Archive (EGA)¹⁰ is one of the two largest archives encouraging the distribution and sharing of genomic and phenotypic data, adopting strict protocols for information management, storage, security and dissemination such as those proposed by ELIXIR, an European platform coordinating, integrating and sustaining bioinformatics resources across its member states where many CIBER groups participate very actively; (g) Global Alliance for Genomics and Health (GA4GH)¹¹ is an international, non-profit alliance launched in 2013 that brings together more than 600 leading organizations working on the generation of models and standards to enable the responsible, voluntary and secure sharing of omics and health-related data. CIBERER is one of its members; (h) European Openscreen,¹² an ERIC (European Research Infrastructures Consortium) integrating high-throughput screening facilities for molecules and drug development comprising more than 140 000 compounds and offering open access to resources for researchers from academic institutions. (i) The European infrastructure EATRIS,¹³ the main support structure for translational biomedical research in biomedicine in Europe, is widely represented in the consortium, with 14 health research institutions. Likewise, many of the CIBER's consorted institutions participate in SCReN, the Platform of Clinical Research and Clinical Trial Units, which in turn is integrated into ECRIN,¹⁴ its equivalent at European level; (j) RD-CODE project¹⁴ promotes the use of the Orphanet nomenclature for implementation into health information systems, thus enabling data sharing at European level in a standardized and consistent manner.

In 2020, The Council of Ministers of the Spanish Government approved "The Spanish Strategy for Personalized Medicine" with a total funding of 77.3 million euros. The first action of the newly adopted strategy, reflected in the Emergency Plan for Science and Innovation, was the Call for the launch of the Infrastructure for Precision Medicine associated with Science and Technology (*Infraestructura de Medicina de*

FIGURE 1 Number of CIBERER publications per year. The total number of original publications in the 2007–2020 period has been 7445 [Colour figure can be viewed at wileyonlinelibrary.com]



Precisión Asociada a la Ciencia y Tecnología IMPaCT). With an endowment of 25.8 million euros, it will foster scientific knowledge and increase the capacity to exploit all the information available improving the quality and efficiency of the healthcare system. This initiative comprises three programs: Predictive Medicine, Data Science, and Genomic Medicine, two of which are led by CIBER (Predictive Medicine and Genomic Medicine; CIBERESP and CIBERER, respectively).

CIBERER also coordinates the ENoD initiative (Undiagnosed Rare Diseases Program); this project has achieved a diagnosis for 29% of the patients eligible for the program, thus facilitating appropriate genetic counseling to many families.

7 | CIBERER PARTICIPATION IN THE EUROPEAN REFERENCE NETWORKS

European reference networks (ERNs)¹⁵ are virtual networks involving healthcare providers across Europe. They aim to tackle complex or RDs and conditions that require highly specialized treatments and a concentration of knowledge and resources. There are 24 ERNs involving 25 EU countries plus Norway, with over 900 healthcare units located in more than 300 hospitals and covering all major disease groups. CIBERER groups participate in nine ERNs: EURO-NMD, METAB-ERN, ERN-RND, Endo-ERN, ITHACA, BOND, TRANSPLANTCHILD, ERN GUARD-HEART, and EuroBloodNet (Table 2).

8 | MAIN CONTRIBUTION OF GENETIC RESEARCH BY CIBERER

In the past 15 years, CIBERER researchers have contributed to the discovery and description of new entities and/or associated genes. At least 100 new genes associated with human disease have been described by CIBERER groups in the last decade, in many cases (71) leading the publication as first or senior authors (Supplementary Table 1). Similarly, CIBERER researchers have described a number of new disorders. The main contributions occurred in the fields of rare bone diseases, central and peripheral nervous system, metabolics, oncogenetics, or vision and hearing impairments, among others.

CIBERER's groups have contributed with the discovery of many new diseases and genes associated to previously known disorders. For example, one of the many contribution was the finding in 2011 of a new gene (MAX) associated to hereditary pheochromocytoma (PCC) in 8 single patients.¹⁶

9 | ORPHAN DRUGS, NEW THERAPIES, AND REPURPOSED DRUGS CONTRIBUTED BY CIBERER

In the past 10 years, CIBERER has contributed with the designation of 25 orphan drugs by either the European Medicines Agency (EMA) or its American counterpart, the Federal Food and Drugs Administration

TABLE 2 CIBERER representation in the European reference networks

European reference network (ERN)	Acronym	CIBERER group-Institution
Rare neuromuscular diseases	EURO-NMD	Hospital de la Santa Creu i Sant Pau
		Hospital Universitario La Fe
		Hospital Sant Joan de Déu
		Hospital Universitario Vall d'Hebrón
Hereditary metabolic disorders	METAB-ERN	Hospital Universitario 12 de Octubre
		Hospital Universitario Santiago de Compostela
		Hospital Universitario de Cruces
		Hospital Universitario Vall d'Hebrón
		Hospital Sant Joan de Déu
Rare neurological diseases	ERN-RND	Hospital Sant Joan de Déu
		Hospital Vall d'Hebrón
		Hospital Universitario Clinic de Barcelona
Rare hematological diseases	EuroBloodNet	Hospital Universitario Vall d'Hebrón
Rare endocrine conditions	Endo-ERN	Hospital Universitario Vall d'Hebrón
		Hospital Universitario de Cruces
		Hospital de la Santa Creu i Sant Pau
Rare congenital malformations and rare intellectual disability	ITHACA	Hospital Universitario La Paz
		Hospital Sant Joan de Déu
		Hospital Universitario Vall d'Hebrón
Rare bone diseases	BOND	Hospital Universitario La Paz
		Hospital Universitario Virgen de la Arrixaca
Transplantation in children	TRANSPLANT-CHILD	Hospital Universitario La Paz
Rare and low-prevalence complex diseases of heart	GUARD-HEART	Hospital Universitario Virgen de la Arrixaca

(FDA). CIBERER has sponsored 12 of the 25 orphan drugs. These drugs/compounds with an orphan designation are listed in Table 3.

In addition, the different research programs developed by CIBERER over the last decade have resulted in 28 patent applications

TABLE 3 Orphan drug designations with CIBERER as sponsor

Substance	Indication/RD	Sponsor	Agency	Reference
Lentiviral vector carrying the Fanconi anemia-A (FANCA) gene	Fanconi anemia type A	CIBER	EMA FDA	EU/3/10/822 FDA 16-5193
Lentiviral vector containing the human liver and erythroid pyruvate kinase (PKLR) gene	Pyruvate kinase deficiency	CIBER	EMA FDA	EU/3/14/1330 FDA 16-5168
Temsirolimus	Adrenoleukodystrophy	CIBER	EMA	EU/3/16/1669
Hematopoietic stem cells modified with a lentiviral vector containing the CD18 gene	Leukocyte adhesion deficiency type I	CIBER	EMA FDA	EU/3/16/1753 FDA 16-5453
Ubiquinol	Primary coenzyme Q ₁₀ deficiency syndrome	CIBER	EMA	EU/3/16/1765
Metformin	Progressive myoclonic epilepsy type 2 (Lafora disease)	CIBER	EMA FDA	EU/3/16/1803 FDA 17-6161
Etamsylate	Hereditary haemorrhagic telangiectasia	CSIC & CIBER	EMA	EU/3/18/2087
Gefitinib	Fanconi anemia	CIBER	EMA	EU/3/18/2075
Afatinib	Fanconi anemia	CIBER	EMA	EU/3/18/2110
Dimethyl fumarate	Adrenoleukodystrophy	CIBER	EMA	EU/3/19/2236
Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying COL7A1 exon 80	Epidermolysis bullosa	CIBER	EMA	EU/3/20/2253
L-Ergothioneine	Cystinuria	CIBER	EMA	EU/3/21/2445

with a therapeutic potential. Seven of them have been licensed, signing long-term cooperation agreements with leading companies in the pharmaceutical and the biotech sectors. These technologies are being developed to treat different groups of RD including mitochondrial,¹⁷ metabolic,¹⁸ skin,¹⁹ or rare hematological diseases.²⁰ Thus, it is worth highlighting our ex-vivo lentiviral vectors-based gene therapy programs. These are our most advanced programs in clinical phases, three of which are licensed and running in collaboration with Rocket Pharmaceuticals, Inc. Specifically, they are focused on pyruvate kinase deficiency (PKD),²¹ leukocyte adhesion deficiency type I (LAD-1)²² and Fanconi Anemia (FA), the latest being the most advanced one, running under a globally registered clinical trial.²³ In 2019 CIBERER has reported a successful engraftment of gene-corrected hematopoietic stem cells in non-conditioned patients with FA, a DNA repair syndrome generated by mutations in any of the 22 FA genes discovered to date. The authors demonstrated that lentiviral-mediated hematopoietic gene therapy reproducibly confers engraftment and proliferation advantages of gene-corrected hematopoietic stem cells supporting that gene therapy should constitute an innovative low-toxicity therapeutic option for this life-threatening disorder.²⁴

10 | A HAND-IN-HAND COLLABORATION WITH PATIENTS ASSOCIATIONS

CIBERER maintains extensive collaborations with patient associations representing all RDs. Noteworthy is the close collaboration with FEDER (*Federación Española de Enfermedades Raras*; Spanish Alliance of Rare Diseases), an umbrella organization established in 1999 with the aim of being the voice of ~ three million people living with a low-

prevalence disease in Spain. At present, FEDER has more than 370 affiliated associations and has developed a network of strategic alliances and collaborations with EURORDIS (a non-governmental patient-driven alliance of patient organizations representing 949 RD patient organizations in 73 countries.), RDI (Rare Disease International, the global alliance of people living with a RD of all nationalities across all RDs), SWAN (Syndromes Without A Name) and ALIBER (Ibero-American Alliance for RDs).

In 2017, CIBERER constituted the Patient Advisory Council (PAC) with the aim of fostering patients' participation in CIBERER's activities as a means to know first-hand their expectations and needs and to achieve their engagement in CIBERER's research policies. The PAC is integrated by various patient associations, nominated from the different CIBERER research programs and renewed every 2 years.

CIBERER and FEDER have signed collaboration agreements focused on FEDER's participation in both the Scientific Advisory Board (SAB) and the PAC with two designated members, and on CIBERER's participation as advisor at the Information and Guidance Service for patients (*Servicio de Información y Orientación*; SIO) launched and managed by FEDER. Additionally, most Principal Investigators of CIBERER's research groups are involved with patient associations, serving as Scientific Advisors or as members of their Scientific Committees.

11 | THE SPECIALTY OF GENETICS OR MEDICAL GENETICS IN SPAIN

Spain is the only country in Europe that does not currently have this specialty. It is essential that the specialty of Clinical Genetics is

approved in Spain to facilitate the training of specialists in the diagnosis, management and treatment of genetic diseases. The lack of regulation of the specialty causes a great heterogeneity in the type of genetic services provided in the Hospitals with a serious inequity of patient access in the NHS. This situation delays diagnoses and their corresponding treatments in patients, hinders the prevention of new cases in families, reduces the efficiency of the health system (by requesting unnecessary or irrelevant tests) and does not guarantee that all professionals who provide genetic services are adequately trained for this activity, which is detrimental to the health of citizens and the quality of life of patients. CIBERER as many other stakeholders have been reporting this irregular situation for years.

12 | FINAL REMARKS

Although Spain has excellent standards in Public Health Services, comparable to those of the most advanced economies in the world, there are still some hurdles preventing timely diagnosis and treatment of RDs patients and a full deployment of Genomic Medicine in the country. Some of these barriers are: (a) the lack of an official Clinical Genetics specialty; (b) the inequality in access to public and universal high-quality genetics and genomic medicine services; (c) the existence of 17 Spanish Regional Health Systems responsible for implementing health policies; and (d) the partial implementation of Next Generation Sequencing (NGS) technologies in the country, which could reduce the public NHS's spending significantly.

In this context, CIBERER has emerged as a flagship research institution, concentrating interdisciplinary and multi-institutional research efforts and resources devoted to RDs in Spain, with a preferential dedication of its financial resources to the RDs networks integrated by centers and research groups dependent on different administrations and public and private institutions.

After an experience of 15 years, CIBERER has shown a clear orientation to generate an impact on the health of the RD community and become an exceptional partner in Spain in the path to achieve the IRDiRC objectives.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest according to editorial policies and ethical considerations.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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