INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

State of Play of Research in the Field of Rare Diseases: 2015-2018

IRDiRC

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IRDiRC can be found at www.irdirc.org

Disclaimer:

The report is a presentation of the current literature, organized in order to identify and highlight trends and breakthroughs in research in the field of rare diseases. The report does not focus on initiatives to improve the organization of healthcare systems or on articles covering aspects of the orphan drug market. In addition, trends and breakthroughs in genomics, and -omics in general, are not reported unless they bear specific rare disease features.

The report is based on published articles and press releases, therefore a time lapse between scientific breakthroughs and their publications is inevitable and the report may not perfectly reflect the initiatives at the time at which they are launched.

The findings and conclusions in this report are those of the contributors, who are responsible for the contents; the findings and conclusions do not necessarily represent the views of the European Commission or members of IRDiRC. Therefore, no statement in this report should be construed as an official position of the European Commission or any member of IRDiRC.

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Acronyms

ADAPT-SMART	Appropriate Patient Therapies a Sustainable, Multi-Stakeholder Approach from Research to Treatment-outcomes
API	Application-Programming Interface
ATMP	Advanced Therapy Medicinal Products
BBMRI	Biobanking and BioMolecular Resource Research Infrastructure
CEGRD	Commission Expert Group on Rare Diseases
CFDA	China Food and Drug Administration
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorization
CMG	Centers for Mendelian Genomics
COMP	Committee of Orphan Medicinal Products
CoNGO	NGOs in Consultative Relationship with the United Nations
CORD	Canadian Organization for Rare Disorders
CPG	Clinical Practice Guidelines
CPMS	Clinical Patient Management System
CT	Clinical trials
EBB	EuroBioBank
ECOSOC	Economic and Social Council Of the United Nations
EGA	European Genome-phenome Archive
EMA	European Medicines Agency
EMBL-EBI	European Molecular Biology Laboratory's European Bioinformatics Institute
EPAR	European Public Assessment Report
ERIC	European Research Infrastructure Consortium
ERN	European Reference Network
EUCERD	EU Committee of Committee of Experts on Rare Diseases
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HTA	Health Technology Assessment
HRQL	Health-Related Quality of Life
ICORD	International Conference on Rare Diseases & Orphan Drugs
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMI	Innovative Medicines Initiative
IND	Investigational New Drug application
IRDiRC	International Rare Diseases Research Consortium
IRUD	Initiative on Rare and Undiagnosed Diseases
MAPPs	Medicines Adaptive Pathways to Patients
NBS	Newborn Screening Programs
NCI	National Institute of Cancer
NCP	National Contact Point
NGS	Next-generation sequencing
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NORD	National Organization for Rare Disorders

NRDRS	National Rare Diseases Registry System of China
OECD	Organization for Economic Co-Operation and Development
OMIM	Online Mendelian Inheritance in Man
PFT	Patient-funded trials
PRIME	PRIority Medicines
PRO	Patient-Reported Outcome
RDCRN	Rare Diseases Clinical Research Network
RDI	Rare Diseases International
TGA	Therapeutic Goods Administration
UDN	Undiagnosed Disease Network
UDNI	Undiagnosed Diseases Network International
UDP	Undiagnosed Diseases Program
WHO	World Health Organization

Part 1: Analysis of the literature

Executive Summary

The report aims to inform stakeholders at large of developments in the field of rare diseases research in order to support decisions of policy makers and research funders, as well as inform the rare disease community at large of the achievements and observed trends which shape the future of research and development for rare diseases.

It is based on a systematic survey of articles published in scientific journals and press releases between September 2015 and June 2018. This report does not cover initiatives to improve the organization of healthcare systems or articles covering aspects of the orphan drug market. In addition, trends and breakthroughs in genomics, and -omics in general, are not reported unless they bear specific rare disease features.

The findings and conclusions in this report are those of the contributors, who are responsible for the contents. No statement in this report should be construed as an official position of members of IRDiRC.

In order to track the progress on the IRDiRC goals, for each chapter, the section was subdivided in general rare diseases research and development, research related to diagnosis, research related to therapies, and research related to methodologies.

Several major policy initiatives were taken during this period, focalized on the set up of rare diseases policy framework in several countries, among which a number of countries that see or expect to see such a framework for the first time. There are a number of new policies developed related to fast track strategies and gene therapies, attempting to give patients earlier access to new medication, and assisting to add the development of gene therapies. Furthermore, data sharing continues to have a more and more important role, and as such several new policy initiatives have seen the light.

Several new (international) collaborations have seen the light in this period; noteworthy are a number of these collaborations that involve worldwide regulators; regulators and health technology (HT) assessors; regulators and patient associations, and funding agencies.

Reports on outcomes of previous major initiatives demonstrate the advances of these initiatives, most remarkably the development of rare diseases research networks, such as the Rare Diseases Clinical Research Networks, but also their European and Japanese counterparts, the European Reference Networks and Initiative on Rare and Undiagnosed Diseases. More and more attention has also been given to the several initiatives for undiagnosed patients, such as undiagnosed diseases networks and a number of matching initiatives, trying to set up technological solutions to provide a (faster) diagnosis for patients, often after the use of sequencing technologies.

Introduction and Methods

Introduction

The International Rare Diseases Research Consortium (IRDiRC) was established in 2010 and unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organizations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide in order to work towards its 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."

In order to work towards this bold and ambitious vision, IRDiRC has set three goals for 2017-2027:

- Goal 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
- Goal 2: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
- Goal 3: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

Methods

This report is a compilation of information published in scientific journals and press releases over the period of September 2015 to June 2018. The scientific literature was systematically scanned using the key words "rare diseases" and "orphan drugs" and their synonyms. In addition, the summary tables of eighty top ranking journals in various fields were systematically scanned. Only the articles tackling a general issue, not disease specific, were retained for this report. All the selected articles describing major initiatives or major research outcomes were highlighted in the Orphanet electronic newsletter, OrphaNews, which also publishes news about specific rare diseases.

In order to track the progress on the IRDiRC Goals 2017-2027, the material was subdivided in four sections, being general rare diseases research and development, diagnosis, Goal 1, Goal 2 and Goal 3.

The report does not necessarily reflect the opinion of the IRDiRC members, but the analysis of the Scientific Secretariat through the conducted literature survey and funding analysis.

1. Policy Initiatives (September 2015-June 2018)

1.1 Recent Policy Initiatives in Asia-Australia

1.1.1 Fast-track approval of medicines in Australia

In order for drugs that address an unmet clinical need for Australian consumers to reach the market faster, among which drugs for rare diseases, the Australian Therapeutic Goods Administration (TGA) set out different expedited pathways in October 2016 (1). These pathways, priority review and provisional approval, will not only aim in providing timely access to new medications, but will also help in aligning with international agencies, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

1.1.2 Australian genomics policy framework

The COAG Health Council (CHC) set up Australia's first 'Genomics Policy Framework' in 2017, which aims to leverage on benefits of genomic knowledge and technology into the health system (2). The initial goals of the framework are to improve population and individual health, by the sharing of genomic information to contribute to (inter-) national collaborations and partnerships. Other goals are to address the lack of coordination of activities, and to jointly address policy issues and challenges.

1.1.3 APARDO: rare disease alliance for the Asia Pacific region

A new rare diseases alliance for the Asia Pacific region, APARDO, was formally launched at the Orphan Drugs Congress in Singapore in June 2015 (3,4). This effort is building on the work of national alliances and disease-specific groups of seven different countries in the region, with the objective to contribute to rare disease policy and practice throughout the region. Ultimately, the joint alliance aims to further the access to care and treatment for people with rare conditions and diseases.

1.1.4 Government funded programs fueling rare disease research in Japan

The Japanese government has funded various programs into rare and intractable diseases, or so-called *Nan-Byo*. In a review published in *Expert Opinion in Orphan Drugs*, the authors reflected in the current status of systems to research rare diseases in Japan (5). In particular, it focuses on the government-funded research programs to strengthen epidemiological studies, basic research, clinical research, and applied research, and looks further in detail into research programs for specific diseases and clinical trials for orphan drug development.

1.1.5 China has released new policy for orphan drug development

Due to its large national population, the number of people in China living with a rare disease is among the highest in the world, therefore facing a great challenge in managing patients with rare diseases. In October 2017, the General Office of the Communist Party of China Central Committee and the General Office of the State Council of the People's Republic of China jointly set out "Opinions on Promulgating the Reform of Review and Approval System for Drugs and Medical Devices to Encourage Innovation (the Opinion) (6)." This opinion outlines regulatory guidelines for several bottlenecks in research and development of drugs and medical devices, covering among others review and approval processes, clinical trial management, drug innovation, and promotion in product lifecycle management.

1.1.6 China officially releases its first national list of rare diseases

In order to facilitate greater awareness on rare diseases, five Chinese authorities jointly issued their first list of rare diseases, including 121 rare diseases (7). The effort is thought to help the management of rare diseases in China, by providing a reference for organizations to carry our diagnosis and treatment of rare diseases, and safeguard the health-related rights and interests of patients with rare diseases. The classification of the list is founded on shared international standards, which will assist in international cooperation in orphan drug development. It is expected that the list will be expanded in later years, adding more indications.

1.1.7 Enforcement of rare diseases management Act of Korea

Rare diseases Management Act of Korea was enacted on Dec 29, 2015, and enforced on Dec 30, 2016. This law stipulates comprehensive policies of prevention, treatment and research of rare diseases to reduce individual and social burden of rare diseases and improve people's health and welfare. Governmental systems, patients aid program, undiagnosed disease program, and research programs has been established based on this law (8).

1.2. Recent Policy Initiatives in Europe

1.2.1 Publication of the strategy on the development of European Reference Networks

Earlier this year, the Board of Member States of the European Union published the strategic guidelines for the implementation of the European Reference Networks (ERN) (9). These guidelines were approved at the 2nd European Reference Networks Conference. In this document, guidelines are outlined for healthcare providers that are planning to lead or join an ERN. Key points are that ERNs must improve the access to diagnosis, treatment and the provision of high-quality healthcare to patients, it should add value for EU citizens to the pathologies in the scope of the ERN, and the ERNs' objective should be focused on building on existing skills and experience.

1.2.2 Approval of European Reference Networks

On December 2016, the Board of Member States of ERNs voted to approve the ERNs. European Reference Networks are networks connecting expert centers in the field of rare diseases and specialized healthcare, organized across borders (10). The concept of ERNs has been developing and maturing over the past five years, since the publication of the Directive on the application of patients' rights in cross border healthcare; consequently, the approval of the Networks constitutes a watershed moment for all stakeholders in highly specialized healthcare. The development marks a major innovation in care for Europe's millions of rare disease patients: although pan-European structures exist in the research domain, this is the first such enterprise in the health sphere. ERNs have been organized around broad disease groups, to ensure that no patient with a rare disease is left 'without a home' under an ERN.

1.2.3 Launch of the first version of the Clinical Patient Management System (CPMS)

In November 2017, the first version of the Clinical Patient Management System (CPMS) went live (11). This tool is a web-based application to support the ERNs in the diagnosis and treatment of rare or low prevalence complex diseases or conditions across national borders. It is expected that this tool will realize one of the ERNs core tasks, to bring expert specialized care to all patients in Europe, as it will allow for virtual consultation across national borders, ensuring that the needed expertise can travel to the patient, instead of the other way around.

1.2.4 European policy: the European Commission's public consultation on transformation of healthcare in the digital market

In the current era of data, data has become increasingly important in healthcare and research, also very important in the context of rare diseases. In order to define the need and scope of policy measures that will support digital innovation in refining people's health, and tackle general challenges to healthcare structures, the European Commission launched a public consultation on transformation of healthcare in the digital market in April 2017 (12). After the consultation period, it was concluded that a comprehensible EU framework is needed for healthcare in the digital single market that takes into consideration both the collective and individual health needs (13).

1.2.5 Children's medicines: statement in the EU

In October 2017, ten years after the launch of the Paediatric Regulation (14), The European Commission presented a report to the European Parliament and the Council about the progress on children's medicines (15). While more research continues to be needed, especially in the field of pediatric oncology, there is a clear increase in the number of Pediatric Investigation Plans, especially in immunology/rheumatology, infectious diseases, and cardiovascular diseases and vaccines. The increase in Pediatric Investigation Plans has led to a consequent surge in new treatments for children, especially in areas where the needs of adult and pediatric patients overlap.

1.2.6 Fast track routes for medicines that address unmet medical needs

Fast track routes allow innovative medicines that target a disease for which no treatment is available, or that provide patients with a major therapeutic advantage over existing treatments to get to the market faster. In July 2015, the EMA revised its guidelines on the implementation of accelerated assessment and conditional marketing authorization (16). These guidelines are both for "innovative medicines that target a disease for which no treatment is available, or that provide patients with a major therapeutic advantage over existing treatments." It is anticipated that the updated guidelines will improve the use of the tools by drug developers and therefore allow drugs that treat unmet medical needs to reach patients faster.

1.2.7 EMA initiative to the collection of high-quality data on medicines through patient registries

In order to better address the collection of post-marketing data, the EMA launched an initiative on patient registries (17,18). Patient registries are often used in the post-marketing authorization phase to further assess the safety and/or efficacy of an individual product. This initiative aims to make better use of current registries, harmonizing products and data structures, and thereby both serving to aid in the establishment of new registries and allowing to be used as a basis for post-authorization data for regulatory decision-making.

1.2.8 A ten-year report on Conditional Marketing Authorization by the EMA

Ten year after the launch of Conditional Marketing Authorization (CMA), the EMA analyzed the data collected using this regulatory gateway (19). Of the 30 drugs that were granted a CMA and that address seriously debilitating or life-threatening diseases, 14 were orphan medicines. During the time the CMA is granted, the sponsor is obliged to collect further information. The report indicated that in the analyzed period, no drug was revoked or suspended. The analysis concluded that the tool had a positive impact in providing early access to new medicines for patients who previously had no or only unsatisfactory treatment options. The report also identified a number of possible areas for improvement, including engagement with stakeholders, in particular with Health Technology Assessment (HTA) bodies, and early dialogue with EMA to support the generation of high-quality data and timely discussion of additional post-authorization studies and their feasibility.

1.2.9 The orphan maintenance assessment reports to be published by the EMA after marketing authorization

Starting January 2018, the EMA publishes a so-called orphan maintenance assessment report for every orphan-designated medicinal product (20). Following requests from stakeholders, the orphan maintenance assessment report will be part of the drug's European Public Assessment Report (EPAR) after a drug has obtained marketing authorization, thereby summarizing the reasoning of the Agency's Committee for Orphan Medicinal Products (COMP) on whether or not a medicine designated as an orphan medicine during its development still fulfills the orphan designation criteria. The orphan maintenance assessment reports will be published for all

positive and negative COMP opinions, as well as withdrawals, thereby allowing for more transparency of the agency.

1.2.10 National Contact Points established to address questions about Cross border healthcare

The Cross-border Healthcare Directive aims to provide all European Union citizens with "equal access to quality healthcare, responding to their specific needs." This is especially important for rare disease patients as expertise on the particular disease may be scattered across member states. Keeping with this directive, all EU member states now have at least one National Contact Point (NCP) in place(21). According to the European Commission website, each of these NCPs has their own dedicated, multilingual website, and the European Commission provides support by helping to clarify issues related to both the Directive and to Social Security regulations. Their contact points assist in providing information about the options they have and about the procedures that they need to follow in order to benefit from cross-border healthcare opportunities.

1.2.11 EMA: regulators possible collaboration

A report on a meeting between the EMA and EU healthcare payers in September 2017 illustrates how collaboration between regulators and healthcare payers could create further synergies facing the challenges and opportunities in the field of pricing and reimbursement decisions at a regional, national and international level (22). The meeting aimed to be complementary to EMA's existing collaboration with HTA bodies and especially with the European Network for Health Technology Assessment (EUnetHTA). Furthering collaboration should improve patients' access to new medical products and make them more affordable. EMA's Executive Director, Professor Guido Rasi said: "their role is key to develop medicine and gathers evidence that generates efficient decision-making".

1.2.12 RD Action: "State of the art" report 2018

In order to provide an overview report of the progress on rare diseases and orphan medicinal products against the backdrop of various policy frameworks in Europe, the European project RD Action, provided an overview report (23). This report emphasizes several positive developments in Europe's rare disease community, such as the adaptation of national plans or strategies in 25 EU Member States, the approval of European Reference Networks, further collaboration between healthcare and research; several patient organizations driving forward projects and progress in rare diseases; and the path of stability of Orphanet. The report also states concerns, such as the lack of replacement body for the previous European Union Committee of Experts in Rare Diseases; and the lack of plans for future joint actions.

1.3 Recent Policy Initiatives in North America

1.3.1 The FDA is leveraging new tools and policies to advance the creation of innovative genetic and genomic-based tests

In April 2018, the FDA released two guidance documents for designing, developing, and validating tests that next generation sequencing (NGS) tests, which will play an important role in the continued advancement of individualized, genetic-based medicine (24). The recommendations aim to provide a flexible framework to obtain data, and to give developers new tools to assist in the development and validation of these technologies. As NGS technologies continue to develop, the FDA will update the regulations in order to allow developers to make best use of these novel and innovative technologies, thereby allowing these technologies to become accessible to patients as quickly as possible.

1.3.2 Statement from the FDA Commissioner Scott Gottlieb on the agency's new efforts to advance the patient voice in medical product development and FDA regulatory decision-making

Orphan drug development is a continuous trajectory, which sees the involvement of many different stakeholders as experts, including patients. In order to assure for a more efficient and safe drug development, the FDA continues to reflect on how to make the science of drug development and review more modern and more patient-centered, so that approved products impact the metrics that real-world patients and families value most (25). As a result, the FDA has published a new guideline on patient-focused drug development, to address, in a stepwise manner, how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for drug development and regulatory decision-making (26).

1.3.3 The FDA Commissioner Scott Gottlieb explained that the agency is readying to release a new framework to help speed a path to market access for new gene therapies that will be different than that for traditional drugs

Gene therapy is at a key point for orphan drug development; the first gene therapies have been formally approved, whereby gene therapy has become a therapeutic reality for numerous rare and common diseases. It is expected that more and more new gene therapies will follow. In order to address some of the challenges connected to these new therapeutic developments, the FDA readies to release draft guidance documents addressing its framework for the manufacturing and clinical development of gene therapy products (27). It is expected that this new framework to help speed the path to market for new gene therapies.

1.3.4 New framework to help speed the path to market for new gene therapies.

The National Institute of Health (NIH) presented its Strategic Fiscal Plan 2016-2020. One of the priorities in this Plan are to advance the opportunities presented by rare diseases to advance

research (28). This Strategic Plan was prepared at the request of the United States Congress, and NIH expects to use this framework to turn scientific discoveries into better health. In addition, NIH also plans to advance the goals of Precision Medicine. According to NIH, it is uniquely positioned to advance developments as well as capitalize on the opportunities, presented by rare diseases over the next 5 years. Finally, NIH predicts that the research supported by them will directly contribute to FDA-approved therapies for at least a dozen rare diseases.

1.3.5 Perspectives for the Priority Review Voucher program

The US Congress created the Priority Review Voucher program in 2007 to encourage development of drugs for neglected diseases(29). An article published in The American Journal of Tropical Medicine and Hygiene reviews the program that was introduced to encourage development of drugs for neglected diseases (30). Written as a response to an earlier paper in the journal, authored by industry experts who have encountered the voucher program. It weighs both the positives and negatives and concludes with a recommendation to commence a debate with policy makers, regulators, academics, pharmaceutical manufacturers and public healthcare advocates refining and enhancing the program moving forward.

1.3.6 United States passed the 21st Century Cures Act

In December 2016, the United States passed the 21st Century Cures Act (31). This Act is designed to help accelerate medical product development and bring novel Innovations and advances to patients faster. The Act is divided in three parts: 21st Century Cures; Helping Families in Mental Health Crisis; and Increasing Choice, Access, and Quality in Health Care for Americans. The Act includes a funding in various areas for public health and research initiatives, and significant regulatory changes to the FDA, impacting trial design, patient access to investigational drugs, and the orphan drug program. The National Institutes of Health will receive a major funding share tied to three main projects: Precision Medicine, BRAIN Initiative, and Cancer Moonshot (32–34).

1.3.7 House of Commons Standing Committee on Health reports on access to treatment and drugs for Canadians with rare diseases

In April 2018, the Canadian Standing Committee on Health adopted a motion indicating that the "the Committee should undertake a study on the barriers to access to treatment and drugs for Canadians affected by rare diseases and disorders, including the Special Access Program, in order to develop recommendations on actions that the federal government can take, in partnership with the provinces and territories, to remove these barriers; that the Committee report its findings and recommendations to the House no later than December 31, 2018; and that the Committee request that the government table a comprehensive response to the report (35)." For this report, the Committee conducted testimonials from a dozen of witnesses including individual patients, clinicians, researchers, bureaucrats, and pharmaceutical companies and the Canadian Organization for Rare Disorders (CORD).

1.4 Joint Initiatives

1.4.1 NGO Committee for Rare Diseases – United Nations, New York

In 2016, a new NGO Committee for Rare Diseases was established under the umbrella of the Conference of NGOs with Conference of NGOs with Consultative Status to the United Nations Economic and Social Council (CoNGO) (36,37).The purpose of this Committee is to serve as advocacy platform uniting around the issue of rare diseases a diversity of constituents which need to be more closely connected and collaborating with each other, including: the international NGO community, major UN agencies, national governments, the academic and scientific world as well as the private sector. The NGO Committee has as objective to improve the visibility and understanding of rare diseases within the United Nations system, but also more globally, by helping to increase and disseminate current knowledge on rare diseases across the world. The Agrenska Foundation of Sweden and EURORDIS-Rare Diseases Europe initiated the Committee.

1.4.2 Report of the inauguration of the NGO Committee for Rare Diseases

On November 8, 2016, the NGO Committee for Rare Diseases was formally inaugurated at the United Nations headquarters in New York, and a report was written on the event (38). This event included the representatives from different initiatives, including the President of CoNGO Mr. Cyril Ritchie, the Director of the Economic and Social Council Of the United Nations (ECOSOC) Dr. Navid Hanif, World Health Organization (WHO) representative Dr. Nata Menabde, and IRDiRC, International Conference on Rare Diseases & Orphan Drugs (ICORD), International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Orphanet. Around 100 participants from around the world, and more than 1,600 people connected to the live webcast through the Committee's dedicated website. Discussion on challenging and opportunities for tackling rare diseases were reported on, highlighting the need for collaboration and harmonization: "differences in values and priorities are not an obstacle to working together." The report also underscored that the complexity and diversity could be an advantage as this intersectionality can lead to strong commitment from the grassroots to the global level.

1.4.3 Rare diseases mentioned for the first time at WHO 71st World Health Assembly

In May 2018, the World Health Assembly of the WHO took place in Geneva. For this occasion, an official statement on rare diseases was presented for the first time (39). This statement, a collaboration between a number of organizations holding the status of 'special relations' with the WHO, among which are several disease specific organizations such as Thalassaemia International Federation, and the umbrella organizations that are members of the NGO Committee for Rare Diseases. The statement calls on Member States to "not leave behind significant but often neglected rare diseases, each of which affect relatively small numbers of patients but collectively affect at least 300 million people globally". Important take home

messages included are: to acknowledge the severity of the problem; to promote national strategies; to advocate for available and affordable medicines; and to develop synergies across borders.

1.4.4 First Rare Diseases International policy event

For the occasion of Rare Disease Day 2017, Rare Diseases International (RDI) held an event with people living with a rare diseases and policymakers (40). The event was the first of its kind to be organized in Geneva and gathered international experts in the fields of public health, human rights, epidemiology, scientific research and patient advocacy to discuss why and how rare diseases should be included in the global health agenda. It concentrated on the vital role international collaboration plays in supporting rare diseases as a global public health and research importance, aligning with the message of the United Nations' 2030 Sustainable Development Agenda of 'leaving no one behind' (41).

1.4.5 OECD investigation on how health systems can improve sustainable access to innovative pharmaceutical therapies

The Organization for Economic Co-Operation and Development (OECD) is launching an investigation on how to improve patient access to innovative pharmaceutical treatments and to ensure the sustainability of health spending as well as continued innovation that meets patient needs (42). As such, the OECD is inviting international stakeholders for submissions to identify issues with the current system, in order to understand which topics are of most importance to stakeholders in question, and to gather new ideas. The diverse submissions will be used to inform the synthesis of evidence and develop recommendations for governments of OECD. The report is expected in late 2018.

1.4.6 Mutual recognition agreement between EU and US regulators

The mutual recognition agreement between the European Union and the United States to acknowledge the inspections of manufacturing sites for human medicines directed in their respective states advanced further (43). Currently, in 14 Member States the FDA can trust the results of the inspection to replace their own inspections. The agreement between EU and US regulators reinforces confidence on each other's inspection capability and resources. The agreement is supported by confirmation on both sides that the EU and US have comparable regulatory and procedural frameworks for inspections of manufacturers of human medicines, thereby benefitting both the US and the EU.

2. Major Initiatives (September 2015-June 2018)

2.1 Rare Diseases Research and Development – General

2.1.1 The European Genome-phenome Archive: an EMBL-EBI effort to archive human data consented for biomedical research

An article published in Nature Genetics illustrates the European Genome-phenome Archive (EGA), launched by the European Molecular Biology Laboratory's European Bioinformatics Institute (EMBL-EBI) (44). This archive is characterized as a "permanent archive where genetic and phenotypic data can be stored by researchers for specific approved uses." At present, the EGA stores processed and raw data from many types of experiments, which include single nucleotide polymorphism and copy number variation genotypes, whole genome sequence and phenotype data. This information is collected and distributed in accordance with the consent and confidentiality determined with the research participants, which is then published in conformity with the strict protocols governed by the EGA project.

2.1.2 The Human Phenotype Ontology: Semantic Unification of Common and Rare Disease

Disease phenotypes are essential for diagnosis, research and characterization of rare diseases. In order to get a better overview of disease phenotyping and its usage, a concept-recognition procedure that analyses the frequencies of Human Phenotype Ontology (HPO) disease annotations was developed. With this tool, over 5 million Pubmed abstracts were analyzed, described in a publication in the American Journal of Human Genetics (45). The authors state that by using this procedure the HPO has been able to compile "250,000 phenotypic annotations for over 10,000 rare and common diseases." The authors believe that rare-disease phenotypes will prove to be useful in evaluating and comparing the phenotypic overlap between Mendelian and common disease. They emphasize that this is especially important when common and rare diseases share risk alleles or have phenotypic overlap due to their linkage by genomic location.

2.1.3 The work of IGNITE network to advance genomic medicine implementation and research

In order to widespread clinical implementation of genomic medicine, there are numerous challenges that need to be overcome. In order to do so, the NIH funded the Implementing GeNomics in pracTicE (IGNITE) network (46). This network, which is comprised of six projects and a coordinating center, supports the "development, investigation and dissemination of genomic medicine practice models that seamlessly integrate genomic data into the electronic health record and that deploy tools for point of care decision making." A paper in BMC Medical Genomics described the Network and member projects, including network structure,

collaborative initiatives, clinical decision support strategies, methods for return of genomic test results, and educational initiatives for patients and providers (47).

2.1.4 NIH budgets for utilizing genomics to understand rare disease

In order to advance the understanding of the genomic basis of both rare and common diseases, the National Human Genome Research Institute (NHGRI) launched the Center for Common Disease Genomics (48). This center will use genome sequencing to investigate genomic contributions of diseases. Simultaneously, NHGRI also announced the next phase of the Centers for Mendelian Genomics (CMG), which investigates the genomic underpinnings of rare diseases. Here scientists will "build on an international network of research collaborations and sequence the genomes of individuals with a wide range of rare disorders seen around the world."

2.1.5 Japan's Initiative on Rare and Undiagnosed Diseases (IRUD)

Japan has a long history of trying to combat rare diseases, or so-called *Nan-Byo* in Japanese. In order to ensure systematic diagnosis by medical experts through phenotypic and genotypic data matching, a network called the Japan's Initiative on Rare and Undiagnosed Diseases (IRUD) was established (49). IRUD is a nationwide consortium that assists networking of patients, medical doctors at hospitals and community clinics, and researchers. The network aims to integrate their efforts and expertise, and exploit the information obtained by genome analysis to provide the diagnoses to patients with rare and undiagnosed diseases. The network enables primary healthcare clinics to collaborate with more than 400 hospitals including 37 IRUD Clinical Centers, where complex cases can be reviewed by multi-disciplinary IRUD Diagnosis Committees made up of medical specialists and clinical geneticists. It follows the examples of other rare disease networks, such as the NIH's Undiagnosed Diseases Program and the UK's Deciphering Developmental Disorders project.

2.1.6 One of the many first in China: The National Rare Diseases Registry System

In 2016, China recently started its first nation-wide patient registry system for rare diseases, the National Rare Diseases Registry System of China (NRDRS), which aims to promote the rare diseases research in China (50). Lead by Professor Zhang Shuyang from Peking Union Medical College Hospital, this joint initiative integrates resources and knowhow from 20 leading medical institutes of China and provides informatics system for more than 50 rare diseases and disease groups. Their first objective for 2016 to 2020 is to register 50000 cases and to perform whole exome sequencing/panel sequencing of at least 10000 cases. A series of large-scale cohort studies will also be carried out on the basis of the registry system. This platform is open to domestic and international collaboration and will provide support in communication between experts, organization of patient recruitment, data aggregation and analysis and collaboration on the patient advocacy for rare diseases worldwide.

2.1.7 RDCRN Investigators and Patient Advocacy Groups – A Partnership

One of the characteristics of the US Rare Diseases Clinical Research Network (RDCRN) Program is the requirement for each Consortium to include patient advocacy groups as research partners. In an article published in Orphanet Journal of Rare Diseases, the role patients and patient advocacy groups play in the RDCRN, and the impact of this role in the Network's success was reviewed (51). It highlights the different aspects of the role, being patient advocacy group participation in protocol review, study design, Consortium conference calls, attending Consortium meetings, or helping with patient recruitment. Overall, the article concludes that this partnership in the RDCRN has had a positive impact on the network and has been vital to its overall success.

2.1.8 RD-Action publishes guidelines for implementation of the codification of rare diseases in health information systems

In order to correctly track rare disease patients in healthcare systems and to track rare disease patients, it is important to have a systematic codification system for rare diseases. In order to code patients, from 1997 onwards, Orphanet worked on the classification of rare diseases, followed by the introduction of Orphacodes for the codification of patients. In 2014, the Commission Expert Group on Rare Diseases recommended the introduction of a codification policy in national plans, and to consider to introduce the Orphacodes in the Member States health information system. In order to support the implementation, a guideline document entitled "Standard procedure and guide for the coding with Orphacodes" has been released, with recommendations on coding situations, as a major step towards the practical implementation of rare disease codification (52).

2.2 Rare Diseases Research and Development – Diagnosis (Goal 1)

2.2.1 The Undiagnosed Diseases Network of the National Health Institute in the United States

In an article in JAMA, a description of the Undiagnosed Disease Network (UDN)- an extension of the Undiagnosed Diseases Program (UDP) set up by the NIH, was published (53). The NIH Common Fund supports the Undiagnosed Diseases Network (UDN) as an exemplar of this model of precise diagnosis. UDP evaluates patients and families who have not been able to receive a diagnosis. Participants in the UDP are chosen based on objective signs and symptoms, the unique nature of the problem, and an estimate by the UDP of its ability to make a diagnosis. According to the article comprehensive clinical assessment represents only the beginning and the UDN acts an extension, which allows the analysis and sharing of data which enhances the working of UDP.

2.2.2 Undiagnosed Diseases Network International

Modeled after the UDP, the Undiagnosed Diseases Network International (UDNI) was launched in July 2015, in order to help provide a diagnosis for rare disease patients worldwide (54). This launch was discussed after two international conferences on undiagnosed diseases. In an article in Molecular Genetics and Metabolism, the authors describe the consensus framework of principles of UDNI, best practices and governance. According to the authors the UDNI involves centers with internationally recognized expertise, a Patient Advisory group and its scientific resources and know-how aim to fill the knowledge gaps that impede diagnosis.

2.2.3 GeneMatcher: a matching tool for connecting investigators with an interest in the same gene

GeneMatcher is a web-based tool developed with the goal of identifying additional individuals with rare phenotypes who had variants in the same candidate disease gene, developed as part of the Baylor-Hopkins Center for Mendelian Genomics (55). Described in an article published in Human Mutation, it is designed to enable connections between clinicians and researchers with the goal of connecting genes to Mendelian phenotypes and increasing our understanding of these rare disorders (56). The tool does not collect identifiable data and can accept phenotypic data. According to the authors, "since its launch on September 2013, it has collected 2433 individual genes from 539 submitters spread across 49 countries creating 450 matches encouraging collaborations from various corners of the world."

2.2.4 Matchmaker Exchange now connects seven genomic matchmakers and two knowledge sources

In both research and clinical settings, numerous rare disease patients lack a clear etiology after exome and genome sequencing. If an additional case with the same variant in the same gene, and overlapping phenotype could be found, this may provide sufficient evidence to identify the causative gene, but case data often sits in isolated databases. The 'Matchmaker Exchange' project was launched to address this challenge and find genetic causes for patients with rare disease, and formally set up in 2015 (57,58). In order to do so, Matchmaker Exchange established a federated network connecting databases of genomic and phenotypic data using a common application-programming interface (API). To date, seven databases are connected and exchange data using the API (59).

2.2.5 The human diseasome: phenotype similarity model for common, mendelian, and infectious diseases

Authors of a study published in Nature generated a human disease network, in which diseases that have similar signs and symptoms cluster together, and have used this network to identify closely related diseases based on common etiological, anatomical as well as physiological underpinnings (60). This is a resource of disease-associated phenotypes for over 6,000 common, rare, infectious and Mendelian diseases. The authors emphasize that through this approach, they have not only obtained phenotypic characterization of common and infectious

diseases, but also characterization for genetically-based diseases in OMIM for which currently "no phenotypic characterization exists either in the HPO annotations or as a clinical synopsis in OMIM." The disease–disease similarity network in this study shows that diseases of different systems and pathological processes can be separated on the basis of phenotypic relatedness and identify similarity between etiologically related disease groups where overlapping phenotypes are observed.

2.2.6 The Exomiser: a tool that goes one step further for variant identification

Whole-exome sequencing is a very successful approach in the identification of novel Mendelian disease–associated genes, and for the diagnostics of rare disease patients. The authors of an article published in Nature Protocol describe a protocol for the Exomiser, an application that uses clinical data, model organism phenotype data, as well as random-walk analysis of protein interactome data for novel disease-gene discovery or for differential diagnostics of Mendelian disease (61,62). This tool has been used throughout a number of projects for disease-gene discovery and diagnostics such as the US USP as well as PhenomeCentral portal. The article provides an overview of the data sources used by the tool, which includes human and animal data sources integrated into algorithm, to prioritize exome sequences

2.2.7 23andMe direct-to-consumer genetic tests receives marketing authorization in the United States

In 2017, the FDA allowed the first direct-to-consumer test that provide information on an individual's genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional (63). This Personal Genome Service Genetic Health Risk test, marketed by 23andMe, is a simple saliva test which tests for increased risk for developing for 10 diseases or conditions among which a number of rare diseases. Along with this authorization, the FDA is establishing criteria, called special controls, which according to them will provide reasonable assurance reliability and accuracy.

2.2.8 Newborn Screening Connect Registry (NBS Connect): beneficial for clinicians and patients?

Newborn Screening Connect (NBS Connect) is a web-based self-reported patient registry and resource for individuals and families affected by disorders included in the newborn screening panel that was launched in 2012. In an article published in July 2017 in the Orphanet Journal of Rare Diseases, the authors show its benefits for clinicians and for hypothesis-driven research (64). This network gathers information on recent studies and provides a resourceful database that contributes to research. The NBS Connect network aims to help in understanding the long-terms outcomes of rare disorders and developing a better knowledge of how to improve care for patients.

2.2.9 FaceMatch: a new tool for facial recognition to help diagnosing intellectual disabled patients

In an article published in BMC Blog Network, FaceMatch "Searching for a diagnosis" project was highlighted (65,66), which is an out-of-the-box initiative to solve part of the diagnostic odyssey of many children. The promising project is using computer face-matching technology developed to help in the diagnosis of individuals with undiagnosed intellectual disabilities. Parents can decide to participate in the FaceMatch project on their own initiative or can be invited by a doctor to take part in the project. The main goal of FaceMatch is to match as many faces of people around the world with similar facial features to help find a diagnosis earlier and potentially discover new important genes in brain development.

2.2.1 Cliniface: a platform for 3D facial analysis for rare diseases diagnosis

Cliniface is a 3D facial analysis hub that enables collaboration with clinicians, researchers and computer scientists to advance understanding of facial characteristics and their relationship with rare disease (67). 3D facial analysis is a prototypical precision public health tool (68). Cliniface evolved with the critical support of RD-Connect funding through a reciprocal funding arrangement with Australia's National Health and Medical Research Committee and the European Union. It has been developed to assist clinical diagnosis, screening, medical (drug) treatment monitoring, clinical trials and surgical planning for rare diseases. It is developed using open source software, and is available for download. Cliniface is being used together with the rare diseases knowledge management platform, Patient Archive.

2.3 Rare Diseases Research and Development – Therapies (Goal 2)

2.3.1 ADAPT SMART: a platform for coordinating Medicines Adaptive Pathways to Patients

The Accelerated Development of Appropriate Patient Therapies a Sustainable, Multi-Stakeholder Approach from Research to Treatment-outcomes (ADAPT-SMART) project was launched in September 2015 (69). This project, funded through the Innovative Medicines Initiative (IMI) is a platform that enables coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities, which aims to foster access to therapies for patients with unmet needs. The ADAPT-SMART Coordination and Support Action will act as a neutral collaborative framework to establish the platform that will engage with all relevant stakeholders, including patients, industry, regulators, HTA, payers, clinicians, governments/policy makers.

2.3.2 Symposium on the development of European cooperation on health technology assessment

In late 2015, a symposium was held addressing European cooperation in evaluation of health technologies - an approach initiated more than a decade ago with the creation of the European Network for Health Technology Assessment (EUnetHTA) (70). It focused on the collaboration between the agencies responsible for the evaluation of health technologies in Europe and went into detail on how to facilitate the exchange of knowledge and best practices. Five European programs were highlighted during the symposium, being SEED, AdHopHTA, MedtecHTA, Advance HTA, Integrate-HTA (71–75). In the next years, the collaboration is aimed to lead towards a sustainable structure and mode of operation for the production of common documents to prepare the opinions of National Commissions, the development of early dialogues with industry, post-registration data, and the establishment of new methodological guides.

2.3.3 EMA launches Priority Medicines Scheme

In March 2016, the EMA launched a new scheme, PRIority MEdicines (PRIME) to strengthen support to medicines that target an unmet medical need (76). The scheme focuses on medicines that may offer a big therapeutic benefit over prevailing medications, or help patients for whom there are no treatment options available. These medicines are considered priority medicines within the European Union. Through the scheme early and enhanced support is offered to drug developers, to optimize data generation and to enable accelerated assessment of medicine applications, which ultimately is intended to help patients gain access to new drugs as quickly as possible. The EMA has outlined the process once a candidate medicine has been selected for PRIME which is described in detail on their website.

2.3.4 The story so far: a report on the incentives provided for orphan medicinal products in Europe

In early 2016, the European Commission published a State of Play report, that reviews incentives to support research into, and the development and availability of, orphan medicinal products (77). The report provides the statistics that possibly endorse the success of these incentives, such as the number of orphan designations, and the number of protocol assistance procedures. The report details the measures taken by individual member states towards encouraging OMP development, as well as the union measures that were taken in the 15 years following the Orphan Regulation (14), such as fund commitment to rare diseases research and drug development specifically.

2.3.5 Orphan drug development in China

In an article in Intractable & Rare Diseases Research, an overview of the challenges and opportunities of Chinese rare diseases research, in particular rare diseases drug development, is provided (78). There is a huge unmet need in China, with one of the highest number of rare disease patients worldwide, coming up to over 10 million patients suffering from a rare disease. Opportunities present in the 13th National Five-Year plan, which includes rare

diseases, are a national priority with increasing governmental support, and the China Food and Drug Administration (CFDA). The article concludes by providing recommendations, stating "To ensure future success, Chinese drug companies should leverage the valuable knowledge assembled over the past three decades by Western countries in the area of orphan drug development."

2.4 Rare Diseases Research and Development – Access (Goal 3)

2.4.1 Involving patients in discussions on benefits and risks of medicines

The EMA published a final report on the experience gained during its pilot project to involve patients directly in the assessment of the benefits and risks of medicines in its Committee for Medicinal Products for Human Use (CHMP)(79). In the two-year pilot, patients were invited to attend the CHMP discussions and provide their opinion on the risks and benefits of a number of medications, among which a number of orphan drugs. The conclusion of the report is that patient involvement during the pilot was valued as very positive and that patients should continue to be invited to oral explanations when their input could be valuable to the assessment of a medicinal product.

2.4.2 Launch of the Parliamentary Advocates for Rare Diseases

In October 2017, the new Parliamentary Advocates for Rare Diseases network, a network of European and national members of parliament advocating to improve the lives of people living with a rare disease, was launched (80). The collaboration is the result of an effort led by EURORDIS-Rare Diseases Europe to ensure that European stakeholders work and join together to tackle the challenges and often also inequalities- which rare diseases create. The network was launched during an event entitled 'Juggling Care and Daily Life: The Balancing Act of the Rare Diseases Community' at the European Parliament in Brussels. The event also included the presentation of highlights of the survey on the impact of rare diseases on daily life with data concerning the real impact on patients and carers living with a rare disease, which was set up in the INNOVCare (81) project. The results demonstrated just how pervasive this impact can be, across different aspects of daily life.

2.4.3 Patient-Reported Outcome labeling in the United States

An article published in Value in Health analyzed patient reported outcome labeling (PRO) of FDA new drug approvals during 2011 to 2015(82). PRO are used to measure treatment benefit, directly reported by the patient who experiences it. Additionally, they compare the findings with those reported between 2006 and 2010, before FDA released its final guidance for industry on the use of PROs to support labeling claims. The authors found that during the 2011-2015 period, 16.5% of the new drugs had PRO labeling, which was mostly based on primary end points and some of them were based on secondary end points. In the previous

period, 24.1% of drugs had a PRO labeling. Therefore, they concluded that there was an overall decline in PRO labeling during 2011 to 2015 compared to 2006 to 2010 but which was similar for drugs that traditionally rely on PROs for assessing treatment benefit. According to the authors “it is in the interest of drug manufacturers to provide high quality data to regulators, payers, and prescribers to maximize the value of products and fully inform patients” and both the sponsors and the FDA should work towards better PRO reporting strategy.

3. Guidelines and Recommendations

3.1 Rare Diseases Research and Development – General

3.1.1 Nature Genetics urges authors to publish data in managed public repositories

A part of the usefulness of papers comes from the possibility of accessing the data and metadata of a paper. As such, Nature Genetics has stated its preference to largely publish papers that will produce all their data in a public repository such as European Genome-phenome Archive or the Genotype and Phenotype database (83). Of course, some challenges need to be overcome. For instance, the challenge of giving equal opportunity to researchers from lower resource countries, or finding a solution for publishing patient data while taking into account local and national laws. Despite these challenges, they also believe that "usable repositories have been developed and supported by funders and researchers alike, (and therefore) see no reason to make exceptions or concessions to review or publish research articles—from any part of the world—that lack the most basic access to data."

3.1.2 Recommendations for informed consent process in international collaborative rare disease research

Increased international data sharing, due to research consortia and the implementation of novel technologies, provides challenges for the informed consent process. In an article published in the European Journal of Human Genetics, core elements to be addressed in the informed consent documents for international collaborative rare disease research using biobanks and registries are identified (84). They provide guidelines for newly established biobanks and registries as well as for older collections without (or limited) informed consent. The authors provide principles for ethically collecting informed consent for both scenarios, which have been applied and are in current practice within several rare disease research consortia.

3.1.3 How do pediatric biobanks look at various aspects of obtaining consent from the pediatric population

The use of pediatric patients in studies, registries and biobank poses specific challenges and ethical concerns when it comes to consent. In an article in the European Journal of Human Genetics, these ethical concerns, especially with regards to the child's role in these procedures, are discussed (85). The authors of this article provide the results of an international multiple-case study which included four biobanks addressing diverse health concerns with the collection of a variety of data from the pediatric population. The article highlights four themes related to informed consent and children, being: (1) motives to involve

the child, (2) informing the child, (3) the role of dissent, assent and consent and (4) voluntariness of children to participate."

3.1.4 Using the principle of proportionality in genomic data sharing

Sharing of genomic data comes with a certain number of risks. According to the authors the depth and scale of genomic data have led to increasing concerns about the potential identifiability of anonymized research participants and the harms that might result. However, they also state that in the area of rare diseases, where finding a molecular diagnosis is key, an alternative approach that enables broad sharing of individual-level data with limits the depth of the data, is advantageous. Therefore, it is important to take into account the principle of proportionate whilst sharing of genetic data (86). When following this principle, the depth of data has been balanced with the breadth of sharing. As such, the authors have developed a two-tier approach to data sharing, in which first anonymized individual-level genomic data with detailed phenotypic descriptions are shared securely with authorized researchers, and second, a small number of individual variants are shared openly with phenotypic descriptions via the DECIPHER database.

3.1.5 Utilizing the principle of proportionality in genomic data sharing

More and more big data is used in different aspects of healthcare, but its use needs regulation. In a study financed by the European Commission on Big Data in Public Health, Telemedicine and Healthcare, it is identified how Big Data can be capitalized to improve the health of individual patients as well as the performance of member states' health systems (87). The study outlines 10 recommendations that are underpinned by ethical principles as well as privacy rights which will prospectively help the Commission's action to develop a value chain the context of the European Digital Market Strategy.

3.1.6 Study on Big Data in Public Health, Telemedicine and Healthcare

In an article in the European Journal of Human Genetics, a proposal for a new standard model for data access is presented (88). This model for access to data that "cannot be published in open access archives owing to ethical and legal risk," recommends a three-step process to judge who can acquire access to this kind of sensitive information. According to the authors this "triple A" approach should involve: "Authentication, Attestation and Authorization", which is being currently piloted with the Demonstration Projects of the Global Alliance for Genomics and Health.

3.1.7 Recommendations to return research participant's genomic results to relatives

When work began on return of results in genomic research, limited thought was given to return of results to relative. However, study findings may not only have an impact on the study participant him or herself, but also on the participant's family. A paper published in the Journal of Law and Medical Ethics provides recommendations on handling the return of results to the

relatives of participants of genomic research (89). The authors detail the methods by which the results might reach or not reach the relatives and provide ethical and legal considerations for returning results to participants, thereby providing a number of handles for these situations, but also specify the need for further research on this matter.

3.1.8 Patients as key partners in rare disease drug development

Rare disease patients are key throughout different phases of research, including drug development. In a paper on this topic, the authors elucidate how patient engagement can enhance the drug development at each phase (90). According to the authors, in the early stages of drug development, information on the burden of disease as well as the progression of disease symptoms is essential to assess the benefit-risk profiles. This information can be most accurately provided by the rare disease patients themselves. Constructing a body of knowledge in this manner to create patient-reported outcomes or clinician-reported outcomes is substantially important later in the drug development process. At later stages it is important to estimate from patients the reasonable goals of the therapy relative to the risks to determine the safety and efficacy of the drugs.

3.1.9 EC Report: Rare diseases – A major unmet medical need

Between 27 and 36 million people in the European Union suffer from a rare disease, for whom limited information and treatments are available, thus representing a considerable unmet medical need and a major challenge for public health. The European Commission has, over the past couple of decades addressed this issue, in particular through support to European-level research initiatives in the field of rare diseases. The EC Directorate-General for Research and Innovation published at the end of 2017 a comprehensive review of how the results of recent research and innovation projects, funded by the EU, contributing to five key areas of policy challenges related to rare diseases, being improving diagnosis; facilitation the regulatory pathway' effective and equal provision of healthcare; effective management of research and data to benefit all patients; and contributing to global collaboration (91). In addition, the report key policy recommendations aimed at addressing the policy challenges mentioned above, all based on the outputs of the EU-funded rare disease project portfolio.

3.2 Rare Diseases Research and Development – Diagnosis (Goal 1)

3.2.1 Statement on the utilization of whole-genome sequencing in newborn screening

The progress in whole genome sequencing technology has been gaining ground leading to a significant decrease in both the cost and time needed to generate data on the entire sequence of the human genome and an increase in accessibility especially for newborn screening programs (NBS). An article published in European Journal of Human Genetics describes the impact this will have on the potential use of this technology in publicly funded newborn

screening programs (92). The article presents different statements reviewing the current scenario and issues a set of recommendations to help inform and guide scientists and clinicians, as well as policy makers. These recommendations include the primary objective of the program; the need for robust evidence base to conduct these screenings; the setup of cost-effectiveness studies to ensure proper implementation; open dialogue between stakeholders; the need for information provision to parents at all stages; the education of healthcare professionals; the set-up of a plan for stored data; and guidance on unsolicited findings.

3.2.2 Rethinking genetic testing services in the Arab Gulf region

The large number of consanguineous marriages is responsible for the high frequency of genetic diseases in the Gulf countries. According to the authors of an article published in the Journal of Human Genetics, due to the lack of infrastructure in these countries, molecular diagnostic testing of the samples are often sent to other countries (93). The returning results often come back as negative or inconclusive, which the authors state may be because the novel mutations and different common mutation observed in this population, are different compared to population of different countries. This has propelled authors to call for restructuring genetic testing programs in the Arabian Gulf. While though Saudi Arabia and Qatar have launched large scale genome sequencing programs, the authors believe that more needs to be done. They recommend investing in better infrastructure and a parallel research program in order to provide care that is customized to their population.

3.2.3 International Recommendations for Undiagnosed patients

A number of international umbrella patient advocacy groups have joined forces to submit a list of recommendations to address the specific needs of patients without a diagnosis urging all stakeholders to recognize undiagnosed patients as a specific population within the rare disease community (94). In doing so, undiagnosed rare disease patients provide specific care to promote their chances of receiving an accurate diagnosis in as efficient and timely way as possible, while ensuring that, until a diagnosis is made, they nevertheless receive the best possible health and social care. These recommendations also highlight the importance of promoting ethical and responsible international data sharing to help inform a clinical diagnosis, accelerate research into novel conditions and provide insights into disease mechanisms.

3.2.4 FDA finalizes guidances to accelerate the development of reliable NGS tests

The FDA has issued two guidances that will provide regulatory oversight for the use of NGS based tests (24). The guidances provide specific recommendations to accelerate the development and the validation of tests using NGS- based tests, allowing to follow the development of new innovations. As such the FDA set out to provide an adequate and flexible framework to collect data needed to support the FDA's review of NGS-based tests. The policies

are set to give developers new tools to support the development and validation of such technologies. The primary aim of the FDA is to adapt regulatory review in order to make innovative and accurate testing technologies available to patients.

3.3 Rare Diseases Research and Development – Therapies (Goal 2)

3.3.1 HHS takes steps to provide more information about clinical trials to the public

Access to more information on clinical trials is good for rare disease patients. In trying to make information on trials more readily accessible to the public, the United States Department of Health and Human Services has issued specific requirements for registering clinical trials and submitting summary results information to ClinicalTrials.gov (95,96). The new rule expands the legal requirements for submitting registration and results information for clinical trials involving FDA-regulated drug, biological and device products. The National Institutes of Health has also issued a policy for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded trials.

3.3.2 FDA guidance document on communication between pharmas and FDA during drug development

Continuous interaction between the biopharmaceutical industry and regulators is essential in the drug development process. In order to set out clear, transparent recommendations for these interactions, the FDA has published a guidance document that describes the best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and FDA at critical junctures in drug development, which may facilitate earlier availability of safe and effective drugs to the American public (97). The report describes the timely and continuous interaction, the scope of interaction, the types of advice, the expectations of the process, best practices of communication methods.

3.3.3 Report on the multi stakeholder for regulation of advanced therapy medicines

Advanced therapy medicinal products (ATMPs), encompassing gene therapies, tissue engineered products and somatic cell therapies, have the promise to reshape the treatment of a wide range of conditions, including orphan drugs. In order to explore possible ways to foster the development of ATMPs, and to enlarge patient's access to these products, the EMA published a report on the multi-stakeholder meetings that were held on this topic (98). Important topics include the need for early interaction and guidance from regulators, more transparency and information sharing, greater harmonization between Member States on various aspects of the ATMP legislative framework and measures to tackle inequalities in patient access to ATMP treatments.

3.3.4 Guidelines to settle biopharmaceutical industry and patient advocacy organizations partnership challenges

Patient involvement in drug development is key, but guidance is needed to optimize the relationships between patient advocacy organizations and pharmaceutical companies. A study focuses on the development of specific guidelines by an independent expert panel compared of patient advocacy organizations and biopharmaceutical industries leaders, highlighting ways to ensure an effective collaboration between them and addressing ethical and legal issues that may arise in the entire research and medical development (99). One of the main challenges is to add transparency to these types of collaborations in the contexts of drug development for rare diseases, thus enabling them to overcome the complexity of their partnership, and to provide therapeutics with meaningful input for patients. Those guidelines are crucial to facilitate the cooperative work between the two stakeholders.

3.3.5 Analyzing the ability of fulfilling the obligations of conditionally approved drugs in Europe

Since the introduction of conditional marketing authorization by the European Medicines Agency in 2004, patients have gained faster access to drugs which fulfill an urgent and unmet need. Examination of whether the conditionally approved drugs manage to obtain comprehensive evidence confirming that the risk-benefit balance is positive to obtain full marketing authorization and the time taken to reach it (100). On average, the median time for conditional approvals to finish their obligations and switch to regular marketing authorizations was five years, noting delays, discrepancies and lack of information on some of these drugs. From the data gathered the authors caution that the conditionally approved drugs without fully established clinical value are in the market for long periods and question whether the public health advantage outweigh the risks of limited clinical information.

3.3.6 Health Technology Assessment in rare diseases: a dynamic process

Rare diseases are often heterogeneous in their progression and response to treatment, and they come with the challenge that only a small population is available for studies and clinical trials, hence leading to difficulties in evidence generation. Challenges for evidence generation to support HTA are especially profound in the case of rare disease drugs, thus requiring novel research methods. Discussion with an expert panel presented explored differential approaches for HTA evidence generation for rare disease treatments (101). The experts informed, providing examples of case studies, that adaptive trial designs, trials analyzed using Bayesian techniques, and disease specific patient reported outcomes as well as qualitative research to elicit patients' perspectives are all of immense value to generate evidence for HTA. The authors emphasize the importance of international consensus and collaboration to agree on the how the value of products to treat rare diseases will be assessed in HTA.

3.3.7 An analysis of orphan designations and authorizations in Europe and United States

What is the status of products with orphan drug designation that have not (yet) obtained market authorization? In an article published in Orphanet Jounal of Rare Diseases, the status of these products was analyzed (102). To date, the United States has more designations as well as approvals than the Europe (around three times more). Regarding therapeutic needs, oncology is the most represented while a majority of rare genetic diseases has still an unmet therapeutic need. In addition, despite the interest and the need for drugs approved for children, about half of the drugs approved in the EU and US for a rare disease affecting children was not granted a pediatric indication. The authors concluded that, by merging all the existing approvals, patients would benefit of substantial advantages in both geographic areas. Efforts and cooperation between EU and US seem the only way to expedite the development and marketing of drugs for rare diseases.

3.3.8 Creating a sustainable environment for orphan drug development

The costs of many rare diseases drugs are large, and as such a debate continuous to be held on the price tags related to orphan drugs. An article in the Journal of Clinical Pharmacology discusses whether the high price associated with them are feasible, and if a system can be set up which will ensure sufficient return of investment (103). The authors discuss the legislations passed in the United States, European Union, Japan and Australia which has led to orphan drug development to be financially viable with more marketing authorizations in the subsequent years. The authors are aware of the public apprehension about the high pricing of orphan drugs and the fact that the high drug prices associated with low cost-effectiveness could limit reimbursement.

3.4 Rare Diseases Research and Development – Access (Goal 3)

3.4.1 Report: United Nations Secretary-general's High-level panel on Access to medicines

In 2016, the United Nations Secretary-General Ban Ki-moon commissioned a High-Level Panel on Innovation and Access to Health Technologies. This panel reviewed solutions to overcome the gaps between the rights of inventors, international human rights law, trade rules and public health in the context of health technologies, which were published in a report (104). Several aspects are of interest for the rare disease community, such as the recommendation to initiate negotiations for a binding Research & Development Convention that de-links the costs of research and development from end prices to promote access to good health for all. Furthermore, the report includes a recommendation to governments requiring that the unidentified data on all completed and discontinued clinical trials should be made publicly available in a format that is internationally recognizable.

3.4.2 EURORDIS: Position paper on access to therapies

EURORDIS-Rare Diseases Europe published a position paper on compassionate use, which is calling for the adoption of measures to revolutionize patients' access to new medicines through Compassionate Use Programs (105). According to the EU Regulation on Pharmaceuticals (106), compassionate use is 'making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening, and who cannot be treated satisfactorily by an authorized medicinal product'. In the position paper, EURORDIS puts forward several policy proposals as possible solutions to improve compassionate use across Europe. The position paper also sets out recommendations to patient organizations, industry, EU Member States and European authorities on how to advocate for, create and manage Compassionate Use Programs.

3.4.3 A call for registries independent of the industry for post-authorization assessment of orphan drugs

The EU regulations on orphan drugs have created an increase in the development of orphan drugs, however, the unsustainability of the high cost of orphan drugs along with lack of clarity on its effectiveness has been a concern of many rare disease stakeholders. The authors of a commentary in Lancet believe that the system of post-authorization assessment for orphan drugs needs to be reformed to address these problems (107). They illustrate the pitfalls in the post-authorization studies of agalsidase alfa that is recommended for the treatment of Fabry Disease to explain their case. To change the systems that are currently in place the authors propose the launch of collaborative registries that are independent from the pharmaceutical industry based on the features mentioned below, to promote appropriate use of orphan drugs and management of costs and to conduct adequate post-authorization assessment of orphan drugs.

3.4.4 Commission Expert Group on Rare Diseases: Recommendations to support the incorporation of rare diseases into social services and policies

The Commission Expert Group on Rare Diseases (CEGRD) has recently published recommendations to support the incorporation of rare diseases into social services and policies, developed within the EU Committee of Committee of Experts on Rare Diseases (EUCERD) Joint Action (108). These recommendations mainly focus on empowering health services' attempt to facilitate integrated care provision to enable them to play the role they need to play in supporting the incorporation of Rare Diseases specificities into mainstream social and support services, within a holistic and person-centered approach and a human rights perspective.

3.4.5 Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases

Currently, many different factors play a role in orphan drug uptake, but this is complicated tby the lack of pricing and reimbursement clarity. In order to improve this process, the European Working Group for Value Assessment and Funding Processes in Rare Diseases deliberated on this topic and have provided a set of recommendations which are published in Orphanet Journal of Rare Diseases (109). These principles fall into four priority areas of the orphan drug pricing and reimbursement process in Europe which include OMP decision criteria, OMP decision process, OMP sustainable funding systems and European co-ordination.

4. Trends (September 2015-June 2018)

4.1 Rare Diseases Research and Development – General

4.1.1 Outlook of patient-centered outcomes research in the United States

Patient-centered outcomes research helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. In an article describing patient-centered outcome research in the United States in the current context, the authors state that there is a large body of medical evidence which does not reach clinical practice in many cases (110). The authors believe that in order to generate better health outcomes, evidence has to be put in the hands of the clinician, and into practice. To address this concern, the Affordable Care Act to the Agency for Healthcare Research and Quality has earmarked USD 100 million to disseminate and implement patient-centered outcomes research evidence. The authors believe that the Agency will rely on its vast experience and long history in both generating new knowledge and facilitating research finding uptake.

4.1.2 Incorporating Patient Perspectives in Health Technology Assessments and Clinical Practice Guidelines

A study published in Research in Social and Administrative Pharmacy reports on a study done in Finland on the different ways patients can be involved in health technology assessments (HTA) and clinical practice guidelines (CPGs) processes and their challenges, as well as on the approaches that can be used to inform patients about this topic (111). While multichannel communication on CPGs and HTAs was seen as essential, the authors also outlined a wide variety of communication channels such as internet/social media, patient organization, health care professionals and media. This included incorporating patient representatives in the different stages of HTA and CPG groups. The authors especially note the important role of patient organizations for ensuring the involvement of patients during decision making as well as providing up to date information of the HTA and CPG decisions, and ensuring that all patients are informed.

4.1.3 View of rare disease patients and families on data sharing

What are the views of rare disease patients and their caregivers on data sharing. A study published in the European Journal of Human Genetics aimed “to optimize the information and consent process to meet participants’ expectations,” on the background of the context of compiling a European leukodystrophies database (112). The authors observe that the patients/families willingly engaged in data sharing, which they believed was a collective and an altruistic mission. The authors also report that the participants have a high level of trust in the

constitution and use of the database by researchers but were equally vigilant over the conditions use of the database. They wanted to be assured of compliance with the constitution and initial consent. The authors write that they also wanted to be kept abreast with current information especially with regard to potential partnership with the pharmaceutical industry for access to the database. The authors report the reluctance of respondents with pharmaceutical partnerships, “even though they recognize that such a partnership are valuable for therapeutic advance”, expressing concerns over their motive to work for profit rather than for the benefit of the patients.

4.1.4 Data Sharing from Clinical Trials - A Research Funder's Perspective.

In order to maximize the data generated from clinical trials, a number of research funders committed to ensuring that the data from published clinical trials can be accessed by researchers so they can validate key findings, stimulate further inquiry, and ultimately deliver lifesaving results (113). While there is an overall, worldwide consensus that clinical trial results should be shared, also supported by the joint statement of the World Health Organization, there is a need to overcome some of the challenges around data sharing, such as resources, equity and incentives, in order to realize this vision. To tackle data sharing concerns, funders need to support technical solutions to help researchers to access and (re)use data, but also continue to ask them to include data management plans in their research proposals. However, the biggest challenge to overcome, being that researchers believe sharing can be disadvantageous to them, funders must demonstrate the value of data sharing as well as other outputs by taking them into account in the grant review process.

4.1.5 Blockchain to enable medical data to be stored and transmitted safely and effectively

An article published by the European Commission highlights a European Commission funded project entitled ‘My Health My Data’ (MHMD) (114). This project foursome the creation of a platform relying on the BlockChain technology, a system that aims to ensure data visibility to the entire network of stakeholders and limit fraudulent usage. The platform gives the opportunity to allow, deny or revoke data access depending on the uses and preferences. MHMD goal is to ensure safe transfer and storage of medical data between organizations and individuals (giving patients the possibility to share their health data anonymously), thereby also allowing for an easier access for patients and research institutions.

4.1.6 23andMe will resume selling health data

Previously, the Food and Drug Administration (FDA) had told the genetic testing company 23andMe to stop presenting health data. In late 2015, 23andMe has announced that, with FDA approval, it will begin providing customers with health information again, though in different format as before (115). The company provides carrier tests that relates to the risk of passing certain inherited diseases to one’s children, presuming the other parent has a

mutation in the same gene and the child inherits both mutated genes. According to 23andMe they have information on 36 diseases, including cystic fibrosis, sickle cell anemia and TaySachs.

4.1.7 The ethics of uncertainty in genomic medicine

Genomic medicine comes with a level of uncertainty. In BMC Medical Genomics, the authors drafted a conceptual and ethical response to the question of how to conceive of and respond to this uncertainty (116). The authors suggest that genomic testing should not be offered merely as a means to reduce uncertainty; nor should uncertainty necessarily be framed negatively or as something that should always be eradicated. Instead, they recommend that the process of genomic testing should include an explicit consideration of uncertainty, both before and after testing. This should not involve mere education to reduce uncertainty, but encompass a richer engagement involving appraisal, adaptation and complex communication.

4.1.8 Implementation of rare disease patient coding across member states

In order to analyze the level of implementation of rare disease patient coding across European member states, a survey was conducted. The results take into account the responses of 21 member states. Even if there is only a small number of countries who have already implemented strategies to produce statistics on rare diseases at a national level, many have identified it as a priority. The survey indicates that rare disease patients are mostly coded in health information systems by using a general coding system for morbidity/mortality, namely ICD-10. However, the Orphanet nomenclature emerge as the main coding system dedicated to rare diseases in both inpatient and outpatient clinics.

4.2 Rare Diseases Research and Development – Diagnosis (Goal 1)

4.2.1 An algorithm to choose a diagnostic test for Mendelian disorders

Next-generation sequencing is changing the paradigm of clinical genetic testing, with numerous tests available for clinicians to choose from. An article published in Genetics in Medicine described the problems faced by the rampant implementation of NGS technology and the current limitation in variant interpretation capabilities (117). The authors emphasize that offering NGS as either “stand-alone or first-choice diagnostic approaches” may not be advisable before its full potential is addressed. The authors thus propose an algorithm to help clinicians opt for the most appropriate molecular diagnostic tool for each scenario. This testing algorithm, provided in the form of a flow diagram in the paper, may help increase the clinical sensitivity of molecular testing and reduce the overall testing cost and time to a diagnosis for patients.

4.2.2 Long tail economics and rare disease research: the impact of next generation sequencing for rare mendelian disorders

An article published in Genetics Research discusses how next generation sequencing (NGS) based research on rare diseases has come a long way and the effect of long tail economics on rare diseases research (118). The authors believe that the trend observed in rare disease research, especially in terms of the developments in NGS, can benefit from the two themes derived from long tailed economics - increased access and reduced cost. They also detail the developments in bioinformatics that has led to the development of this enormous amount of data which in turn required better curative and sharing efforts. The authors refer reduced cost to the reduction of overhead costs by centralizing resources where the curative and sharing efforts come in play. They also address the issue of reimbursement that comes with the rising cost of sequencing.

4.2.3 Rethinking variant information linked to rare diseases

Large-scale reference data sets of human genetic variation are essential for the interpretation of DNA sequence changes. In an article in Nature, one of the largest catalogues of human protein coding region variants containing data from around 60,000 individuals, performed by the Exome Aggregation Consortium is presented (119,120). They have identified more than 7.4 million variants and utilize the catalogue to calculate objective metrics for pathogenicity. Additionally, the article reports that variants linked to rare diseases show up at a rate implausibly common rate in the population. In fact, variants that supposedly cause rare Mendelian disorders rarely supported pathogenicity. Thus, the authors of the article believe that the tool developed by them acts as a "powerful filter for analysis of candidate pathogenic variants in severe Mendelian diseases".

4.2.4 Participation in interdisciplinary meetings on genetic diagnostics

Collaboration is taught to be advantageous for obtaining the best genetic diagnosis, however, which factors are of most importance. An article published in the Journal of Human Genetics describes how interdisciplinary collaboration between various services can contribute to the success of NGS diagnostics (121). It highlights factors that could contribute to successful interdisciplinary activities, namely coordination, pooling of resources, individual learning and role blurring. The article concludes, following linguistic analysis of transcripts of interdisciplinary meetings, that improved communication is necessary to improve the efficacy of these meetings.

4.2.5 Ethical debates: newborn screening in the private or public domain?

Newborn screening is the process of systematically testing newborns just after birth for rare and inheritable diseases. A study published in the Journal of Bioethics discusses issues and viewpoints in the literature about voluntary and mandatory NBS program (122). According to the literature, soft impacts are assigned to the private domain when hard impacts are considered worthy of policy concern and delegated to the public domain. The authors highlight the added burden for parents regarding the difficult task of determining what is best

for their children's health. The study shows that not enough support is provided to parents and that NBS does not give enough evidence to help them make an informed decision in most cases. The authors therefore encourage notions of solidarity, care, and trust as part of the expansion of the NBS programs to help respect the distinction between public and private domain as the responsibility of the decision remains in the hands of parents.

4.3 Rare Diseases Research and Development – Therapies (Goal 2)

4.3.1 The success of crowd funding campaigns

Are different ways of funding for developing rare disease drugs possible and successful? A short study conducted by authors of an article published in The Lancet shows that crowd funding - funding directly from the public through the internet - might represent a valuable avenue to finance randomized control trials (123). The authors assessed the success rate of the top online English crowd funding websites. Their results demonstrate that most crowd funding projects reached their target, in fact even unsuccessful campaigns were able to raise some funds, albeit a small percentage of their target goal. According to the authors this strategy might be "especially useful for pilot or phase 1 studies because funding from national public agencies is insufficient or very competitive."

4.3.2 Patient-Funded Trials: Opportunity or Liability?

Patients are often involved in different aspects of drug development, including the funding of the clinical trials. A review on patient funded trials published in Cell Stem Cell reviews the challenges and opportunities, and argues that these patient-funded trials in its current form need reform (124). Patient-funded trials (PFT), refers to studies funded directly by patients seeking to enroll in trials as participants. The author believes that "left unchecked, these interests can threaten the ability of research to advance biomedical progress." In PFTs, patient sponsors are strongly motivated by the short-term goal of access to new interventions and the profit motive shifts from the sponsor to PFT clinics, which generate revenue directly from the enrolment of participants increasing patient exposure to the risks of unproven interventions. The authors provide some key recommendations to policy makers to improve the situation for PFT such as a creating a mechanism for scientific and ethical oversight of PFTs and consider whether accreditation requirements for health care facilities could be used to encourage entities conducting PFTs.

4.3.3 Orphan drug designations and approvals in the United States, the European Union, and Japan

A comprehensive study published in Drug Discovery Today provides a review of orphan drug designations and approvals since the implementation of orphan drug legislation in the United States, the European Union and Japan (125). The authors provide a list of designated and

approved orphan drugs in the three regions, which they show has steadily increased over the years, demonstrating the leverage of the orphan drug legislation. The authors also provide comprehensive data on the type of applicants that have received designations, their therapeutic classifications (ATC code) and drug type - small molecules have the highest number of designations across regions. The authors also demonstrated that 800 designations overlapped in the ~5000 designations granted in the three regions, the largest contributions coming from the U.S, followed by the EU and Japan.

4.3.4 Profitability and market value of orphan drug companies

The high costs of orphan drugs las led people to wonder about the generosity of the incentives for orphan drug development and associated company profits. A study published in PLOS One has analyzed the profitability of companies producing orphan drugs in Europe and the United States (126). The study found that companies receiving marketing authorization for orphan drugs were more profitable and had a higher return on assets, commanding a higher market value compared to non-orphan drug companies. According to authors, these companies receive many incentives due to the orphan drug legislation, spend lesser for research and development, have non-orphan indications and are priced at a level that is 6 times higher than non-orphan drugs. The authors believe that "that policies directed towards incentivizing orphan drug development have worked to the extent that companies are profiting excessively."

4.3.5 Precision medicine: how is it changing for patients?

Precision medicine describes prevention, diagnosis and treatment that take into account variability between people. An article published in the Journal of American Medical Association highlights precision medicine current practice based on personalized genetic profiling for diagnosis, risk assessment, and using evidence-based medicine (127). The study aims to show that precision medicine diagnosis and risk assessment is moving medicine towards a deeper understanding of health and disease, which personalized genetic profiling and adapt the course of action for a patient. The main challenge for precision medicine is to be able to expand the individualized knowledge that can confidently be brought together, moving beyond genomics and proteomics to include way-of-life and environment.

4.3.6 Should ultra-rare diseases drugs be treated separately: an HTA perspective?

Many of rare diseases are in fact so-called "ultra-rare." In an article published in the Orphanet Journal of Rare Diseases, this distinction is assessed between ultra-rare and more prevalent rare disease drugs from a health technology assessment viewpoint (128). In a case study they compared submissions made to the Canadian Agency for Drugs and Technologies in Health and found that ultra-rare diseases drugs were more likely 'to be biologics, to have been studied in uncontrolled clinical trials, to have a higher annual treatment cost per patient, to have less robust evidence'. They were also 'less likely to include data from at least one double-blinded randomized controlled trial and have smaller patient cohorts in clinical trials'. Finally,

the authors found that ultra-rare diseases drugs were less likely to receive a positive reimbursement recommendation, and therefore the authors believe that ultra-rare diseases drugs could be viewed as a separate subgroup from an HTA perspective in order to reduce the negative reimbursement recommendation.

4.4 Rare Diseases Research and Development – Access (Goal 3)

4.4.1 Compassionate use of drugs and medical devices in the United States, the European Union and Japan

Different geographies have different compassionate use programs. A paper published in Regenerative Therapy reviews the current compassionate use mechanisms, of the United States, the EU and Japan (129). The authors have provided and exhaustive assessment of the usage of expanded access to drugs, medical devices and biologics in these countries. While the U.S and the EU have mechanisms to be able to provide unapproved products. Japan lacks such schemes and the drugs are mostly provided at the discretion of the physician, but the authors state that they will be introducing a compassionate use program for the usage of unapproved products for which patients are unable to enter into a clinical trial.

4.4.2 Possible reimbursement models for gene therapies

Gene therapy is generally a one-time treatment and in cases of rare diseases may pose a one-time cost, which is perceived to be very high. As an example, the first gene therapy Glybera, was priced at around US$1 million per patient but had the potential to be an efficacious treatment and thus possibly cost-effective, but is meanwhile withdrawn from the market. An article published in Regenerative Medicine the authors discuss the challenges associated with gene therapies and provide payment models for sustainable reimbursement (130). The payment models described by the authors include up-front payment, annuity-style payment, intellectual property-based payment, fund-based payment. They recommend annuity-style payment models for highly priced gene therapies as it "ensure(s) widespread patient access, award innovation, spread costs and, if linked appropriately to health or social outcomes, limit financial risk. However, they acknowledge that changes will need to be made to implement this kind of payment model in the current reimbursement system.

4.4.3 Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers

In the Orphanet Journal of Rare Diseases is an article studying what is “considered of value when choosing between hypothetical therapeutic options and to quantify both their benefit-risk preferences and the influence of disease context (131).” After studying a variety of rare disease

patients and informal caregivers the authors found that respondents attributed most importance to drug response, risk of serious side effects, and the ability to conduct usual activities when choosing a hypothetical treatment in contrast to attributes related to treatment modalities. They were also willing to accept risks depending on the severity of their disease and access to therapeutic options.

4.4.4 Getting to the root of high orphan drug prices

The Commonwealth Fund, a private foundation that does research on healthcare issues, published a report on issues related to high prescription drug prices and the actions that should be taken to fix them and assure affordable access to medication (132). One of the drug types it investigates are orphan drugs. The report shows that high prices of orphan drug medication are the result of market exclusivity protections that give drug manufacturers time to recoup the costs of developing treatments and to enable them to achieve a return on investment. The Commonwealth Fund report suggests different solutions that could help patients with a rare disease to have access to affordable prices for orphan drugs.

4.4.5 Health Related Quality of Life among adults with rare disease

Most rare diseases related research is focused on etiology, treatment and care, with limited research on Health-Related Quality of Life (HRQL). A study published in the Orphanet Journal of Rare Diseases shows the limitation of HRQL research for patients with diverse rare disorders (133). The study compares validated measures from the general population and people with common chronic diseases. According to the study, creating a social support network where rare disease patients can exchange and meet may improve patients' quality of life by increasing their knowledge on their disease and making them feel less isolated. At the moment, only a few organizations prioritize HRQL as a social support in their patient care management. The authors' examination is that HRQL should be included in health agencies and rare disease organizations' funding priorities to help improve HRQL for patients' care. The study states that it is an important challenge for the wellbeing of rare disease patients, as they might not be cured during their lifetime, so it remains crucial to also focus on their quality of life as well as new therapies.

5. Infrastructures (September 2015-June 2018)

5.1 BBMRI-ERIC recommends the development of biobank-based Expert Centers

The Biobanking and BioMolecular Resource Research Infrastructure (BBMRI) has published a review in the European Journal of Human Genetics on the rationale and the advantages of setting up Expert Centers as "key intermediaries between public and private sectors performing the analysis of biological samples under internationally standardized conditions (134)." In Europe, BBMRI was awarded the Community legal framework for a European Research Infrastructure Consortium (ERIC). According to the review, BBMRI-ERIC is a key resource as the life science industry can rely on the samples provided by them throughout the process from the early research stage up to preclinical research as well as further clinical development.

5.2 ELIXIR survey to address infrastructure needs of the rare disease community

ELIXIR, an intergovernmental organization that brings together life science resources from across Europe, addresses the infrastructure needs of the rare disease community as part of their work packages, aiming to help create and maintain sustainable ELIXIR resources in the long term. As part of this effort, they investigated the current usage and needs of the community in terms of infrastructure (135). The investigation is focused on prioritizing the most important bioinformatics tools, what needs to be improved, and will ultimately lead to better ELIXIR services adapted to the requirements of the community.

5.3 The EuroBioBank Network: its achievements and challenges

In an article published in European Journal of Human Genetics, the EuroBioBank (EBB) is described as the "first operating network of biobanks in Europe to provide human DNA, cell and tissue samples as a service to the scientific community conducting research on rare diseases(136)." The authors describe the EuroBioBank Network Charter, its principles of partnership and conditions of entry for biobanks and biomaterials. The article reviews its achievements, recognitions, publications prepared by EBB to date and their role in helping the industry towards drug development. Participation in RD-Connect, an FP7 EU-supported platform linking RD biobanks, registries, and bioinformatics data, is also described. Furthermore, the authors highlight their role in fulfilling the objectives of IRDiRC as they provide work and expertise under its umbrella. They also reflect challenges they have yet to overcome, which include "lack of harmonization; lack of biomaterial and data sharing; lack of recognition; and lack of sustainability.

6. Transnational-International collaboration (September 2015-June 2018)

6.1 Cooperation between European Medicines Agency and Health Technology Assessment bodies creates synergies

In 2010, the EMA and EUnetHTA initiated a collaboration based on a mandate of the High-Level Pharmaceutical Forum 2008. The objective of this collaboration is to identify and undertake specific steps to improve the efficiency of the processes and conditions for patients' timely access to an effective medicine. In 2012-2015, the collaboration worked on a joint work plan, for which the outcomes are now published in a report (137). The report reviews the organization of regular meetings of EMA and EUnetHTA representatives, the creation of synergies between both organizations, the sharing of experiences, and the efforts undertaken to increase transparency. The authors note that collaboration of both organizations through the life cycle of development and management of pharmaceuticals already brings added value in terms of finding concrete synergies in the processes.

6.2 Worldwide collaboration for orphan drug designation

In the United States, the European Union and Japan, incentives have been set out for the development of treatments for rare diseases. In a review in Nature Reviews Drug Discovery, the collaborations that the EMA has with other regulators, the FDA and PMDA, to designate orphan drugs is described (138). Since the inception of the possibility of joint applications with the EMA and the United States in 2007, the two agencies have worked together to understand areas of similarity at the time of submission for an orphan drug designation.
The EMA also collaborates with the PMDA, with some similarities with the scientific submission, and some evidence of medical plausibility can be interchangeably used even though the prevalence threshold in Japan is different to the one required in Europe. The authors hope for an increase in the global approach towards orphan medicine, as it would mean greater benefits for rare disease patients.

6.3 The importance of international collaboration for rare diseases research – a European perspective

In order to advance rare diseases research, international collaboration is of vital importance. Over the last two decades, awareness of the importance of international collaboration has risen and important contributions were made at national, European and international levels to foster collaboration in rare diseases research and development. In an article in Gene Therapy, the authors emphasize these contributions, and highlight several examples such as coordination of funding agencies, academic researchers, companies, regulatory bodies, and patient advocacy organizations and partnerships with European infrastructures (139).

Together, these collaborations are key to improve the life of rare disease patients, by maximizing the impact of global investments in rare diseases research.

6.4 NORD-FDA collaborate to collect natural history data on rare diseases

Natural history studies are essential for the better understanding of rare diseases, and vital to orphan drug development. In a collaboration between the FDA and the National Organization for Rare Disorders (NORD), grants are awarded for the development of natural history studies for 20 rare diseases (140). According to NORD President and CEO Peter Saltonstall, this project will "tackle one of the greatest needs and an inherent challenge of the rare disease community: having enough longitudinal data to help medical researchers better understand how these diseases develop and progress over time." As part of the grant, NORD, the FDA and patient groups will work together to develop a registry toolkit containing best-practice tools and templates that will aid future organizations to initiate and conduct natural history studies.

6.5 EMA and FDA reinforce collaboration on patient engagement

Partnering with patients in orphan drug development represents a relatively new way of working that has inherent benefits throughout the research and development life cycle. In order to expand further on patient engagement, the EMA and FDA have set up a new working group to exchange best practices (141). This working group will provide a forum to share experiences and best practices on the way both agencies involve patients in development, evaluation and post-authorization activities related to medicines. This is especially important for rare diseases who show a high level of engagement in providing real life experiences, expertise as well as contributing to scientific discussion, of which rare disease patients are a typical example.

6.6 New collaboration between Orphanet and NIH-NCATS Genetic and Rare Disease Information Center

In 2016, Orphanet and the NIH Genetic and Rare Diseases Information Center (GARD), formally established a partnership. The aim of this partnership is to mutualize efforts so as to provide the audiences of both sites with the most complete and up-to-date information on rare diseases. In a first step, the Orphanet and GARD nomenclatures are being aligned, so as to allow cross-referencing between the two resources. In a second step, summary texts from Orphanet (along with a link to the relevant Orphanet disease page and the Orphanet logo) are being included in GARD for the diseases for which GARD does not have a text (142,143).

This cross-Atlantic partnership will improve the visibility of both initiatives on the other sides of the ocean.

6.7 Shire, Microsoft and EURORDIS–Rare Diseases Europe formed a Global Commission to accelerate the time to diagnosis for children with rare diseases

In order to address the diagnostic challenges for children living with a rare disease, a strategic alliance “The Global Commission to End the Diagnostic Odyssey for Children” was set up as partnership between Shire, Microsoft and EURORDIS-Rare Diseases Europe (144). This initiative is a multi-disciplinary group of experts with the creativity, technological expertise and commitment required to make a major difference in the lives of millions of children and their families. The Global Commission set out to develop an actionable roadmap to help the rare disease field to reduce the multi-year diagnostic journey.

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Part 2: Statistics of research project and clinical trials 2010-2017

1. Introduction

The aim of this document is to provide an overview of the rare disease research landscape in terms of research projects and clinical trials funded during the period 2010-2017. The intention of this document is to be descriptive, so as to provide a picture of what type of research, in which medical domains and for which diseases has been funded during the period. This period starts with the creation of IRDiRC and ends with a specific data collection performed towards members of IRDiRC funding research, at a moment IRDiRC set up its new goals for the next decade. By doing that, this description will give a glimpse on trends and gaps of research on rare diseases.

2. Methods

2.1. Sources:

This document is based on three kinds of sources:

1. The Orphanet database
2. The World Health Organisation (WHO) ICTRP database of clinical trials
3. A proactive collection of research data from IRDiRC Funders members

1. The Orphanet database of resources related to rare disease research: Orphanet offers, amongst a range of expert resources on rare diseases, a catalogue of research projects and clinical trials collected, qualified and curated by members of the Orphanet network in their respective countries according to Standard Operating Procedures. Orphanet is the only research projects and trials database that is specific for rare diseases. A data extraction was performed to obtain the research projects and CTs from January 2010 to December 2017 included.
2. In order to complete its database of clinical trials (CTs) related to rare diseases both in countries of the Orphanet network and funded by members of IRDiRC, a collaboration has been established between Orphanet and WHO, aiming at automatically retrieving CTs specific for rare diseases by using the Orphanet nomenclature of rare disorders; CTs are submitted for curation, qualification and validation to the Orphanet team to produce an added-value database of CTs for rare diseases.
3. As many IRDiRC members are not located in a country covered by the Orphanet network, a specific data collection campaign was conducted so as to have a complete list of research projects and CTs financed by IRDiRC members. It was conducted by the IRDiRC Scientific Secretariat in 2018 to cover the years from 2010 to 2017 included. 29 IRDiRC funding members have provided data on research projects and 20 on clinical trials.

2.2. Data and metadata production:

Data was compiled and deduplicated. Metadata were produced including, for research projects:

- The fact that the project is national or multinational
- Funded by an IRDiRC member of not
- The category of research project (excluding clinical trials),[1] which was secondarily used to derive four large categories:
    - Basic research
    - Pre-clinical research
    - Clinical observational studies
    - Other types of research (Health economics, sociological, epidemiological studies, for instance)
- The disease(s) targeted by the project, using the Orphanet nomenclature, diseases non-rare in Europe but rare in other parts of the world and present in the Orphanet database for extra-European rare disease-related activities representation purposes.
- The dates of start and end
- The fact the project is ongoing or terminated
- The funding body
- The country
- The amount of total funding.

For clinical trials (CTs), meta-data include:

- The fact that the trial is national or multinational
- Funded by an IRDiRC member of not
- The category of the CT (drug development; medical device development, vaccine development, interventional trial, protocol trial)
- The phase of the CT
- The disease(s) targeted by the project, using the Orphanet nomenclature, diseases not rare in Europe but rare in other parts of the world and present in the Orphanet database for extra-European rare disease-related activities representation purposes.
- The name of the medical compound/drug being tested in the CTs
- The dates of start and end
- The fact the trial is ongoing or terminated
- The fact it is recruiting or not
- The sponsor

[1] Categories include : Gene search, Mutation search, Gene expression profile, Genotype-phenotype correlation, In vitro functional study, Animal model creation/study, Human physiopathology study, Pre-clinical gene therapy, Pre-clinical cell therapy, Pre-clinical drug development/drug delivery, Pre-clinical vaccine development, Diagnostic tool/protocol development, Biomarker development, Medical device/instrumentation development, Epidemiological study, Observational clinical study, Health sociology study, Health economics study, Public health study (excluding health economics), Induced pluripotent stem cells (iPS) creation/study, Natural history study, Drug repurposing, Small molecule screening, Biotechnology innovation, Ontology/bioinformatics study, Outcome measures development, CRISPR-Cas9 study, Biorepositories development/creation, Databases & Registries development/creation

- The country
- The amount of total funding.

Research projects and CTs metadata requires the access to project's abstracts and CTs detailed data

2.3. Limitations:

Data collected in each Orphanet country cannot be considered as perfectly exhaustive despite the best efforts to achieve maximum comprehensiveness, for it relays on the willingness of data sources and of investigators to share and update their data. As seen above, not all IRDiRC members have provided their data, and therefore research funded by the whole consortium could not be represented.

Qualifying and quality controlling data from countries outside the Orphanet network was performed by one full-time person in IRDiRC Scientific secretariat working with Orphanet. However, data coming from the NCI (National Institute of Cancer) couldn't be analyzed because of the number of projects was too large to be analyzed in the timeframe of the preparation of this report: whereas NCI research projects were included for total research projects counts, they had to be excluded from all the other analyses. However, clinical trials funded by the NCI have been included for analysis.

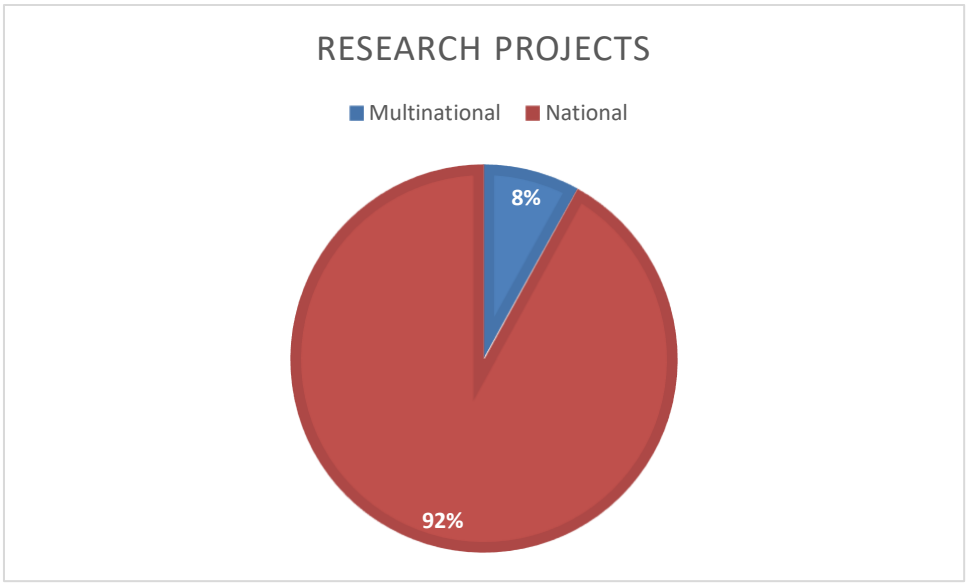
Start and end dates collection was inhomogeneous and did not allow for a proper analysis of research over the time. No such an analysis is provided in this document.

Data on amount of funding was lacunar and difficult to exploit (several currencies, heterogeneity of reporting methods amongst the funders). No financial analysis was performed.

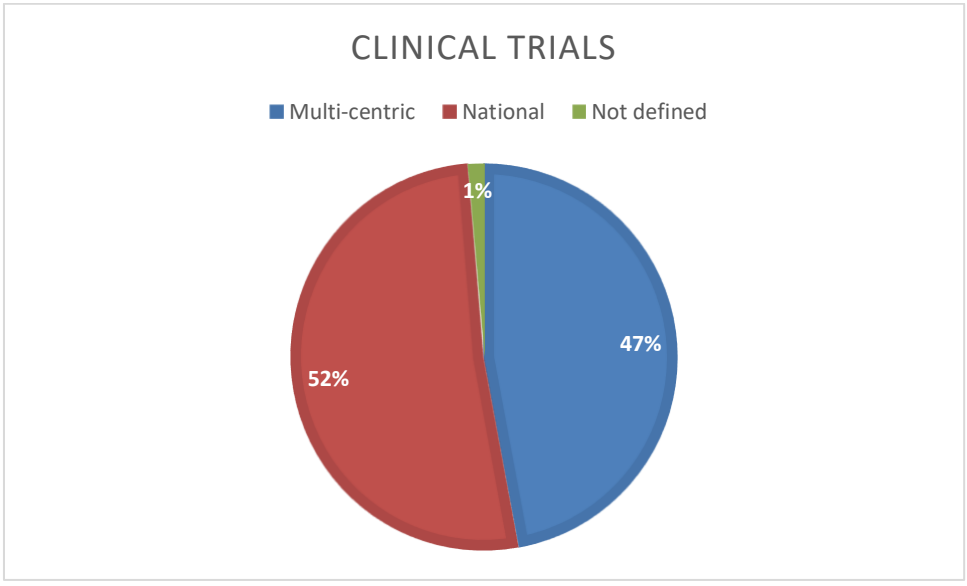
3. Results

3.1. Data selected.

11294 research projects were collected, of which 4566 were funded by the NCI and could only be counted for the medical domain analysis. For the reasons exposed above, they had to be excluded for further analysis. 6728 research projects from 31 countries were kept for analysis after curation once the NCI is not taken into account. 92% of them were national, multinational projects representing only 8% of them. Thirteen percent were funded by IRDiRC members.



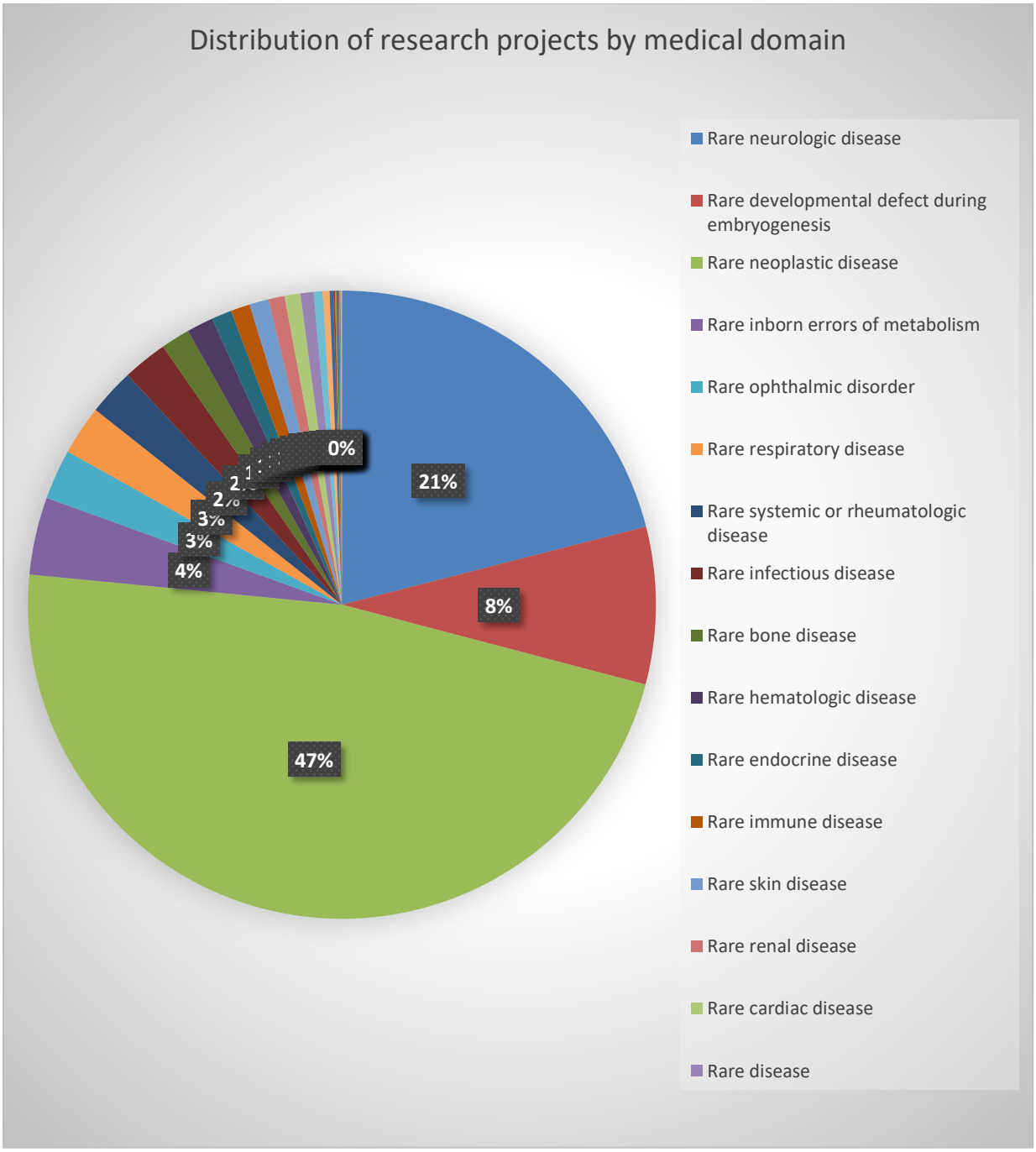
4871 clinical trials were collected from 35 countries. Forty-seven were multicentric and 52% were national, this information was lacking for 1%. Eighty-two percent were funded by funders that are not members of IRDiRC. IRDiRC members funded 18% of CTs.



3.2. Analysis of research projects

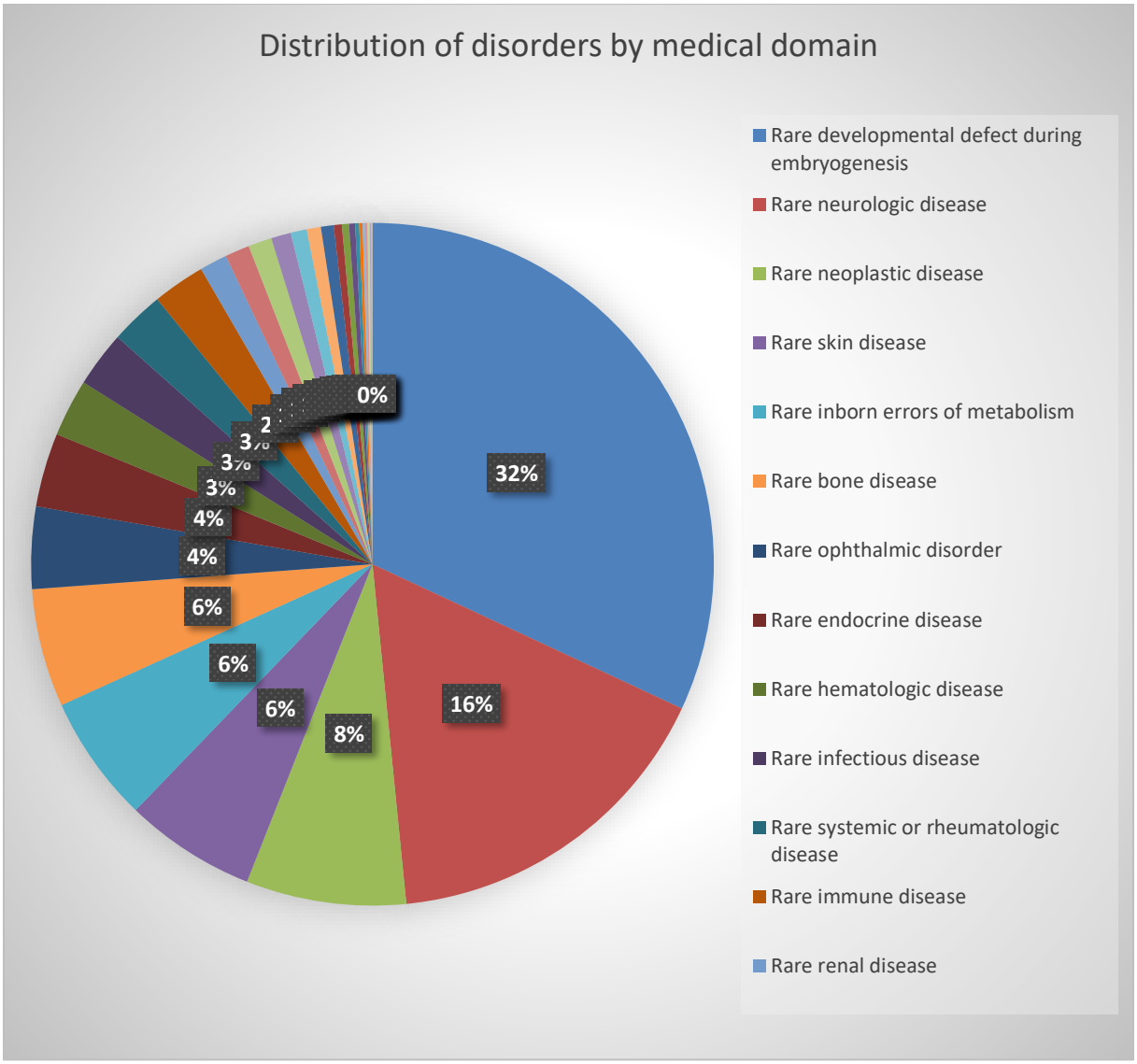
3.2.1. Distribution by medical domain

When including the NCI to the analysis, the first medical domain for which research is conducted is oncology (47%), followed by neurology (21%) and developmental defects (8%).



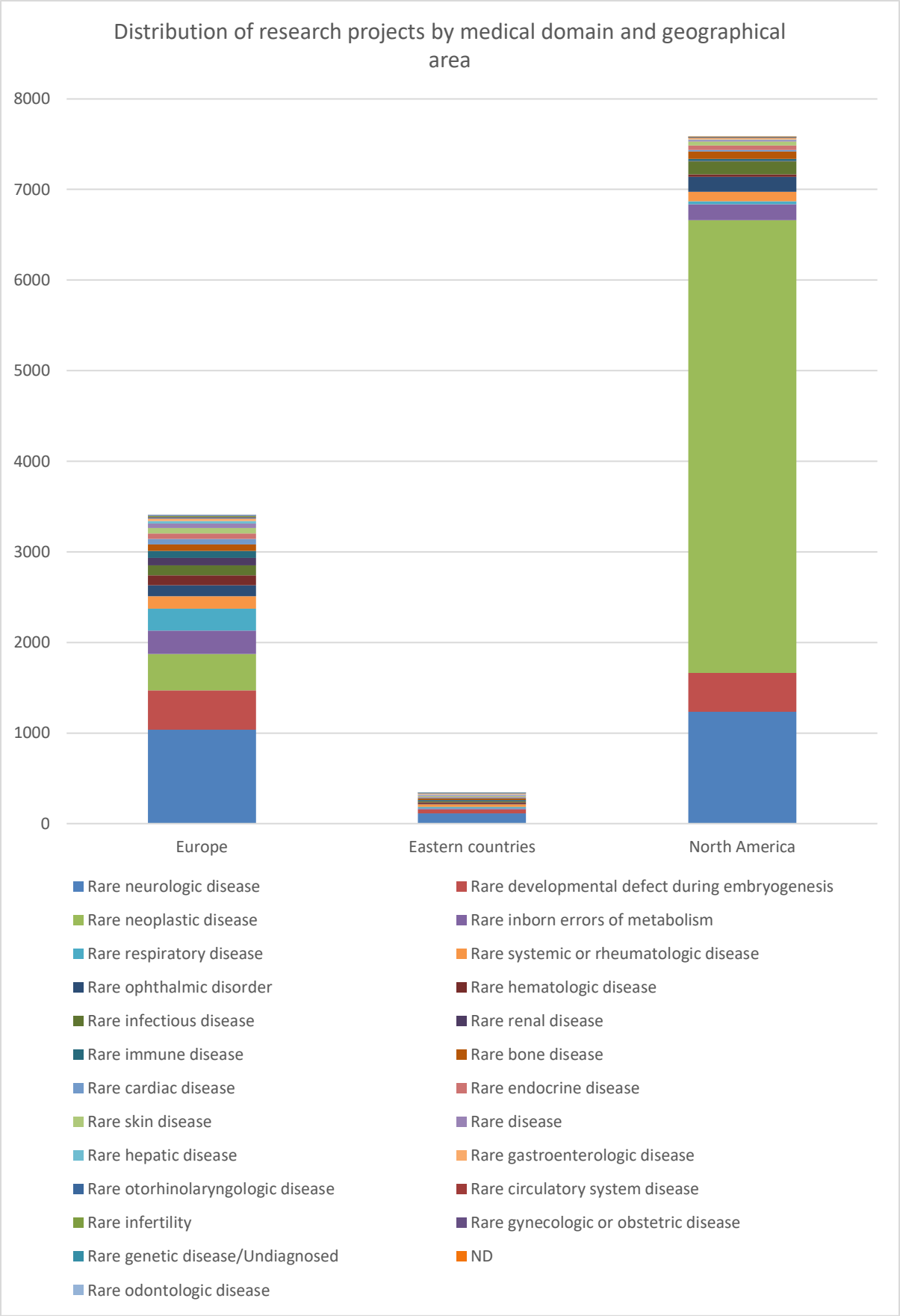
In comparison, the pie below represents the percentage of all rare diseases by medical domain: 32% of all RD are developmental anomalies, 16% are neurological diseases and 8% are rare cancers. Overall, about half of all RD research projects concentrates on a domain that represents

8% of all RD. The coverage of rare diseases globally and by medical domain is analyzed at the end of this section.



When dividing the countries in three geographical areas (North America, Europe and Eastern countries) we observe the following distribution by medical domain:

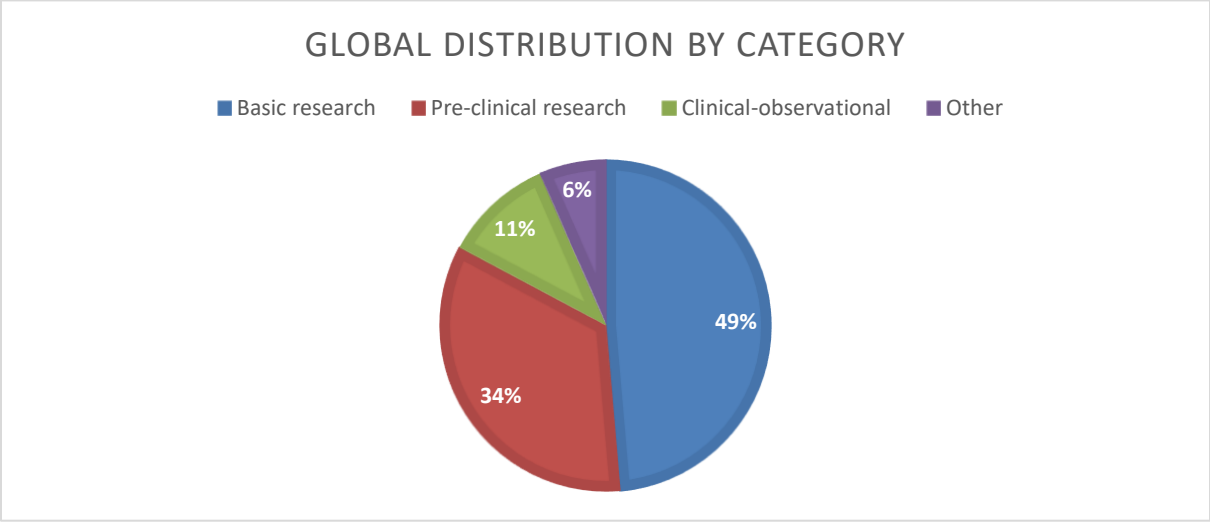
In North-American countries (US and Canada) rare cancers come in the first place when the NCI is considered, whereas in Europe and in Eastern countries the two first studied medical domains are neurology and developmental anomalies (dysmorphology). However, when excluding the NCI, North-American countries follow the same distribution than in Europe: neurology comes first (41%), then dysmorphology (14%) and oncology (13%). Inborn errors of metabolism is the fourth sector in Western countries. Eastern countries show a slightly different distribution: if neurological diseases and developmental anomalies are the two most studied domains, the third one is rheumatic and systemic diseases. No research project on rare cancers has been mapped in Eastern countries within the funding bodies studied.



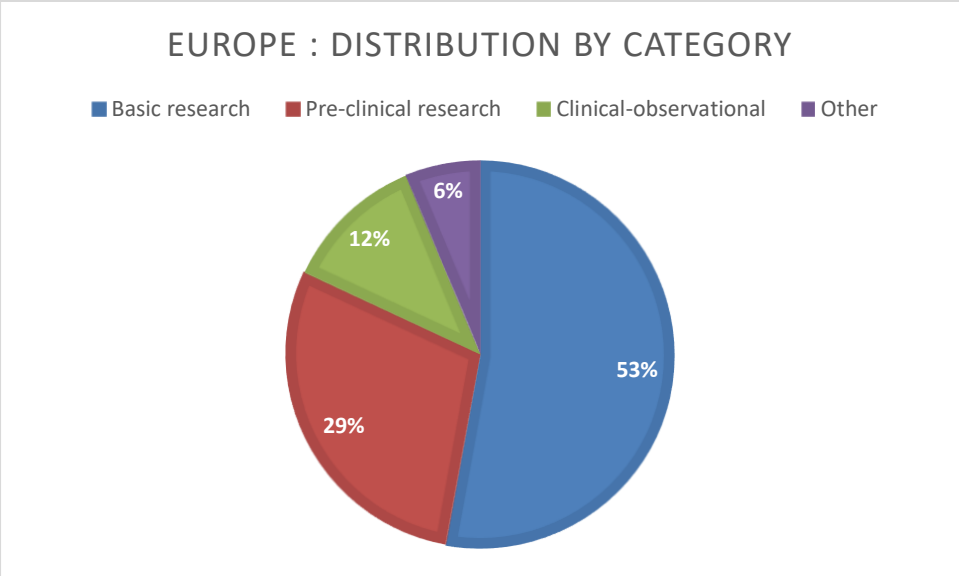
ND is used to designate projects on conditions not related with. Particular medical domain (i.e. on consequences of transplantation)

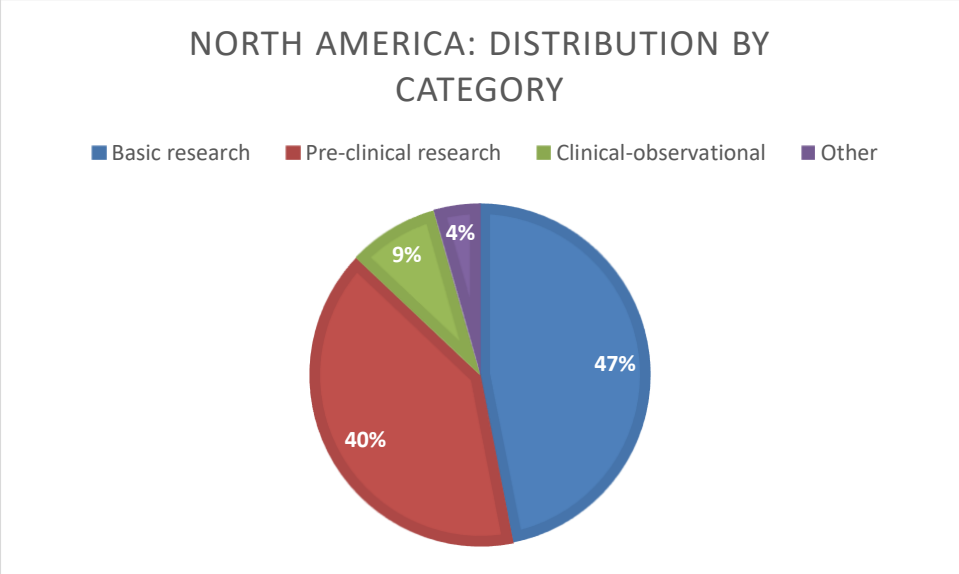
3.2.2. Distribution by type of research

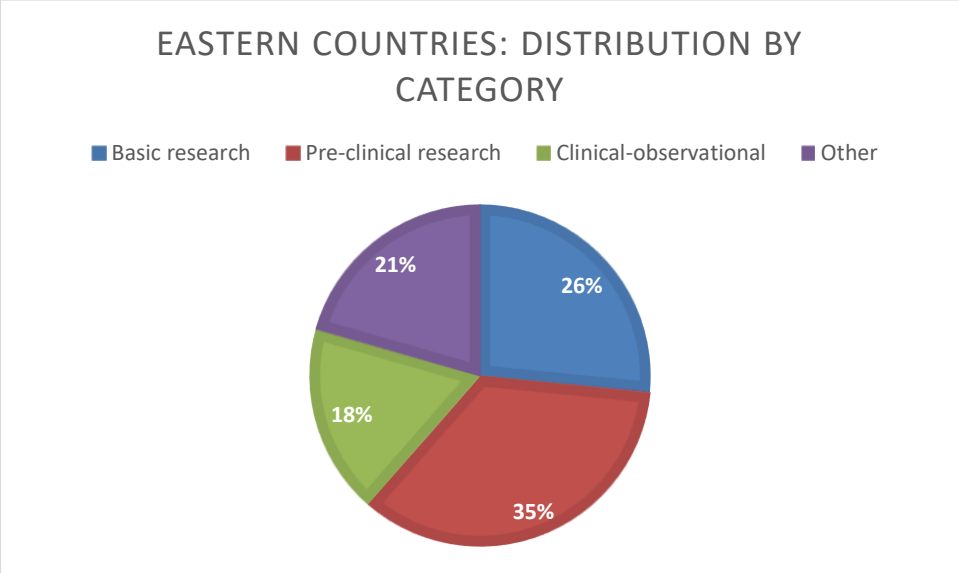
Globally, almost half of the research projects were basic research. This encompasses genes and mutations search, functional studies, physiopathological studies, animal model creation or study, basic research conducted to develop biomarkers, iPS creation or study and on use of CRISPR-Cas9 techniques. 2380 projects (34%) were pre-clinical research projects, including gene or cell therapy pre-clinical studies, drug development or drug repurposing, small molecules screening, vaccine development, medical devices development, diagnostic tools/methods, and biotechnology innovation. 11% of the projects were observational studies or natural history studies, whereas 6% encompasses epidemiological, public health, health sociology, health economics studies, databases/registries/repositories creation or development, studies on ontologies or bioinformatics and outcome measures development.



When comparing geographical areas, some differences can be observed as shown in the pies below:

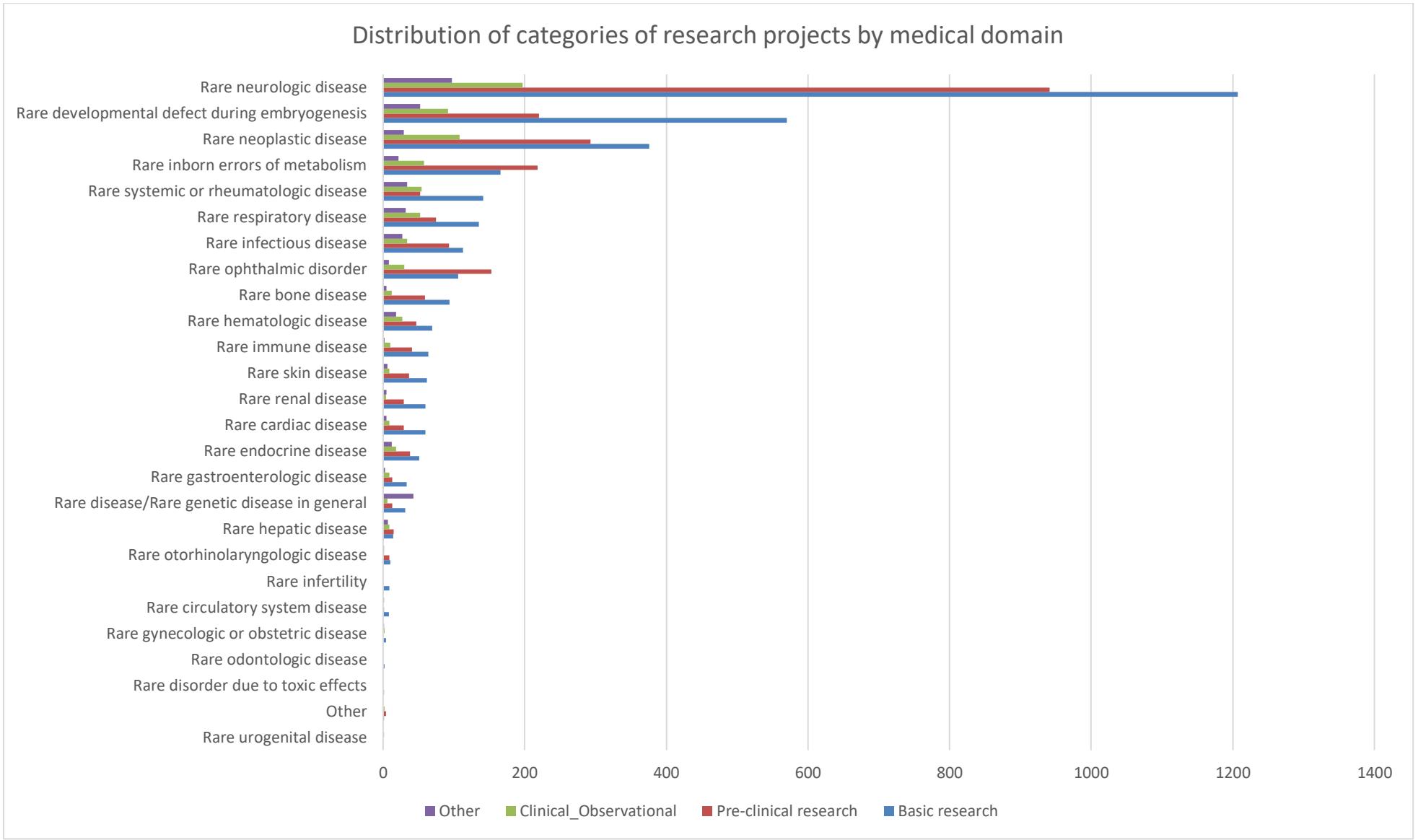

EUROPE : DISTRIBUTION BY CATEGORY
Basic research
Pre-clinical research
Clinical-observational
Other
6%
12%
53%
29%

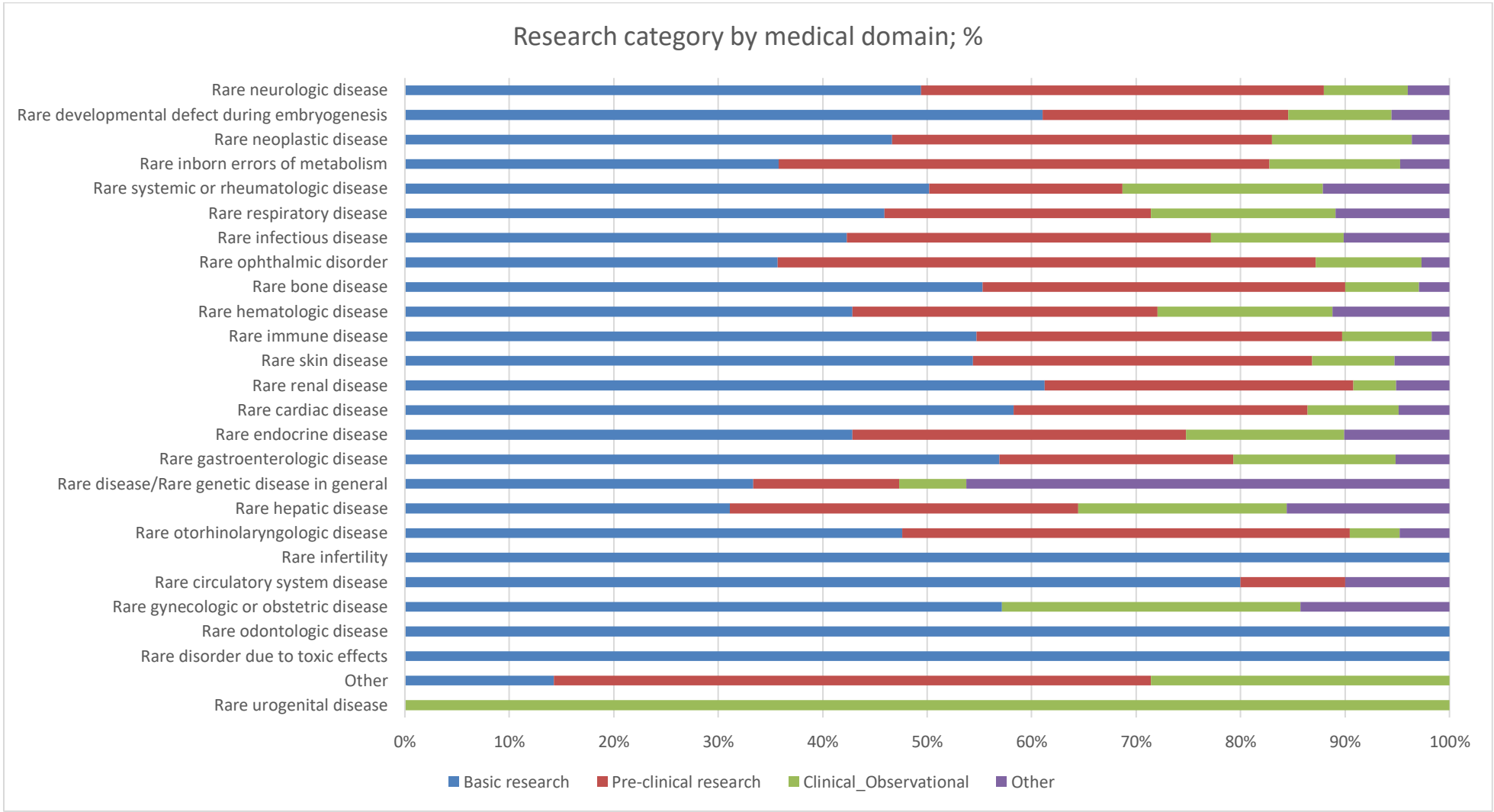

NORTH AMERICA: DISTRIBUTION BY CATEGORY
Basic research
Pre-clinical research
Clinical-observational
Other
4%
9%
47%
40%


EASTERN COUNTRIES: DISTRIBUTION BY CATEGORY
Basic research
Pre-clinical research
Clinical-observational
Other
21%
26%
18%
35%

3.2.3. Type of research projects by medical domain

In most medical domains, most of the research is basic research. However, a significant part of funded research is pre-clinical research for neurological, neoplastic, infectious and endocrine diseases, whereas in ophthalmology and in inborn errors of metabolism pre-clinical research is predominant.


Distribution of categories of research projects by medical domain
Rare neurologic disease
Rare developmental defect during embryogenesis
Rare neoplastic disease
Rare inborn errors of metabolism
Rare systemic or rheumatologic disease
Rare respiratory disease
Rare infectious disease
Rare ophthalmic disorder
Rare bone disease
Rare hematologic disease
Rare immune disease
Rare skin disease
Rare renal disease
Rare cardiac disease
Rare endocrine disease
Rare gastroenterologic disease
Rare disease/Rare genetic disease in general
Rare hepatic disease
Rare otorhinolaryngologic disease
Rare infertility
Rare circulatory system disease
Rare gynecologic or obstetric disease
Rare odontologic disease
Rare disorder due to toxic effects
Other
Rare urogenital disease
0
200
400
600
800
1000
1200
1400
Other
Clinical_Observational
Pre-clinical research
Basic research


Research category by medical domain; %
Rare neurologic disease
Rare developmental defect during embryogenesis
Rare neoplastic disease
Rare inborn errors of metabolism
Rare systemic or rheumatologic disease
Rare respiratory disease
Rare infectious disease
Rare ophthalmic disorder
Rare bone disease
Rare hematologic disease
Rare immune disease
Rare skin disease
Rare renal disease
Rare cardiac disease
Rare endocrine disease
Rare gastroenterologic disease
Rare disease/Rare genetic disease in general
Rare hepatic disease
Rare otorhinolaryngologic disease
Rare infertility
Rare circulatory system disease
Rare gynecologic or obstetric disease
Rare odontologic disease
Rare disorder due to toxic effects
Other
Rare urogenital disease
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Basic research
Pre-clinical research
Clinical_Observational
Other

3.2.4. Disease coverage.

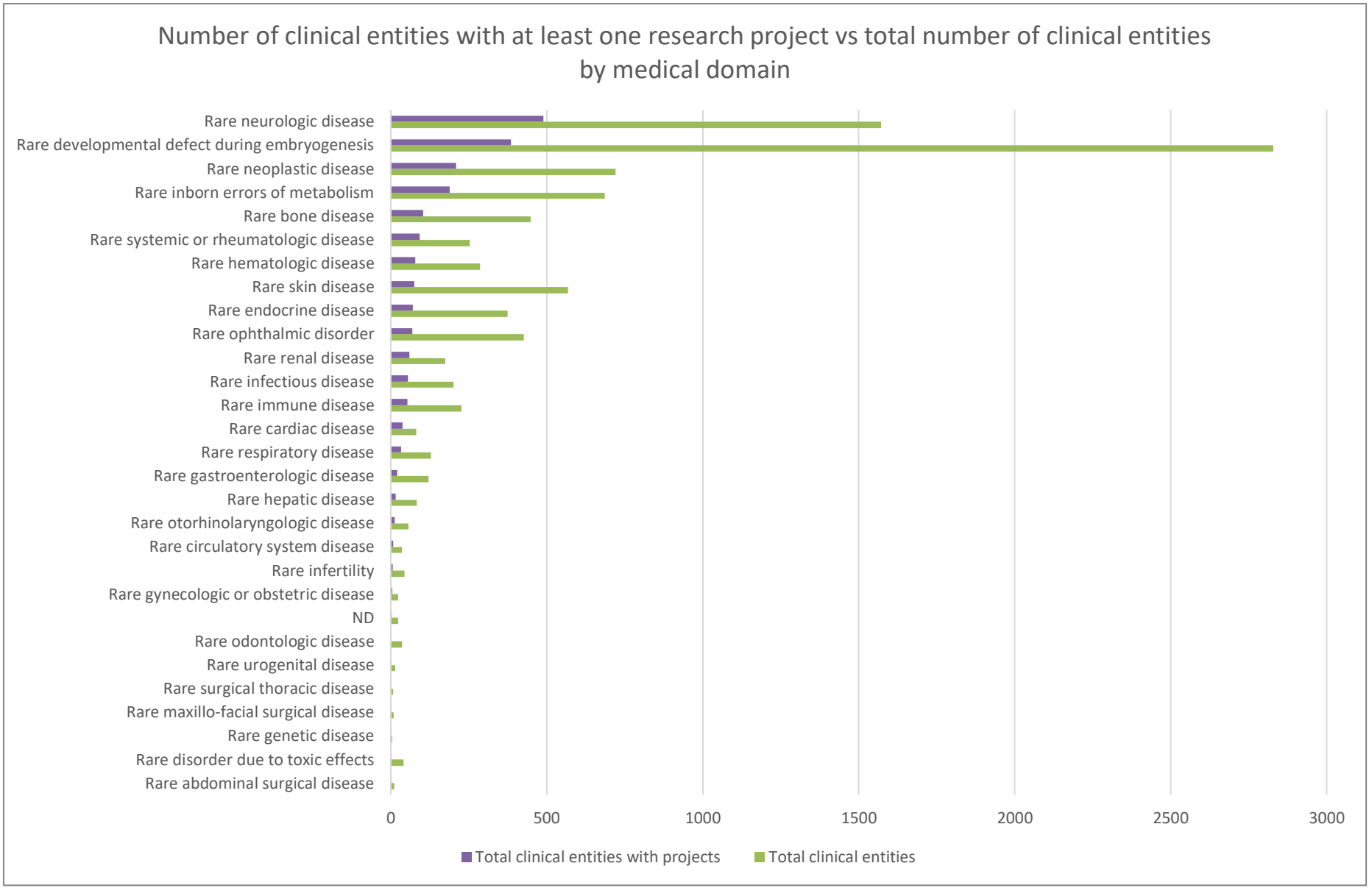
For the analysis of disease coverage, clinical entities (groups, disorders and sub-types) were considered indifferently, the procedure for linking rare disorders being that the most granular level should be chosen. Projects linked to groups are, in general, not meant to be projects specific for each one of the diseases included in the group, but on the group globally. As far as only one research project by clinical entity is considered for this indicator, and the total number of clinical entities is taken as the denominator, the eventual bias of this mode of calculation on the results is minimized.

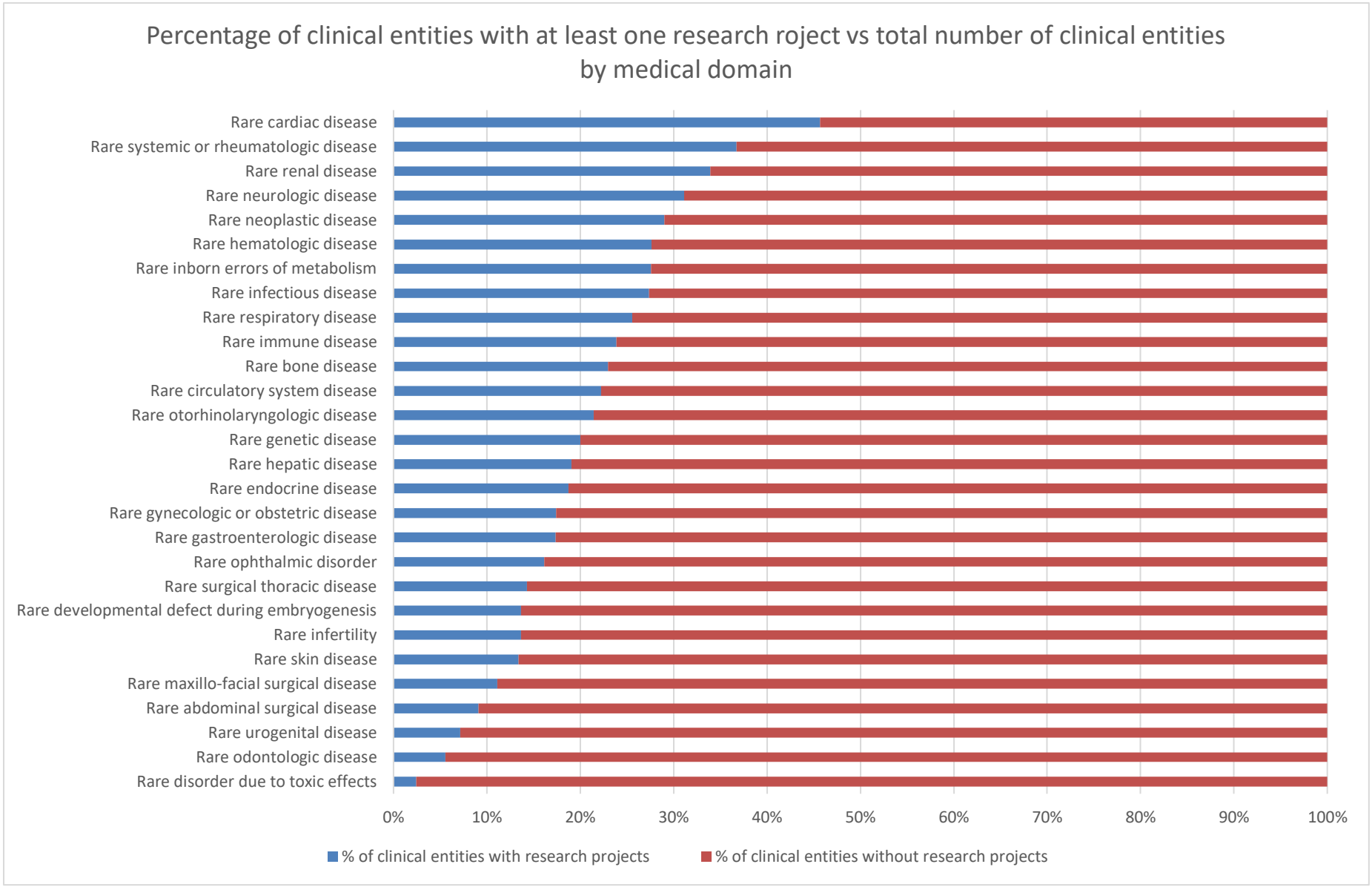
Only 22% of all clinical entities are covered by research projects. The proportion of clinical entities covered per medical domain varies considerably from between medical domains: research on rare cardiac diseases (which represent 0,7% of all rare diseases) is 47%, whereas only 13.6% of rare developmental defects (counting for 32% of all rare diseases) are covered. Neurological diseases are covered at 31%; they count for 16% of all rare diseases, and are the second most numerous groups of rare diseases after developmental defects.

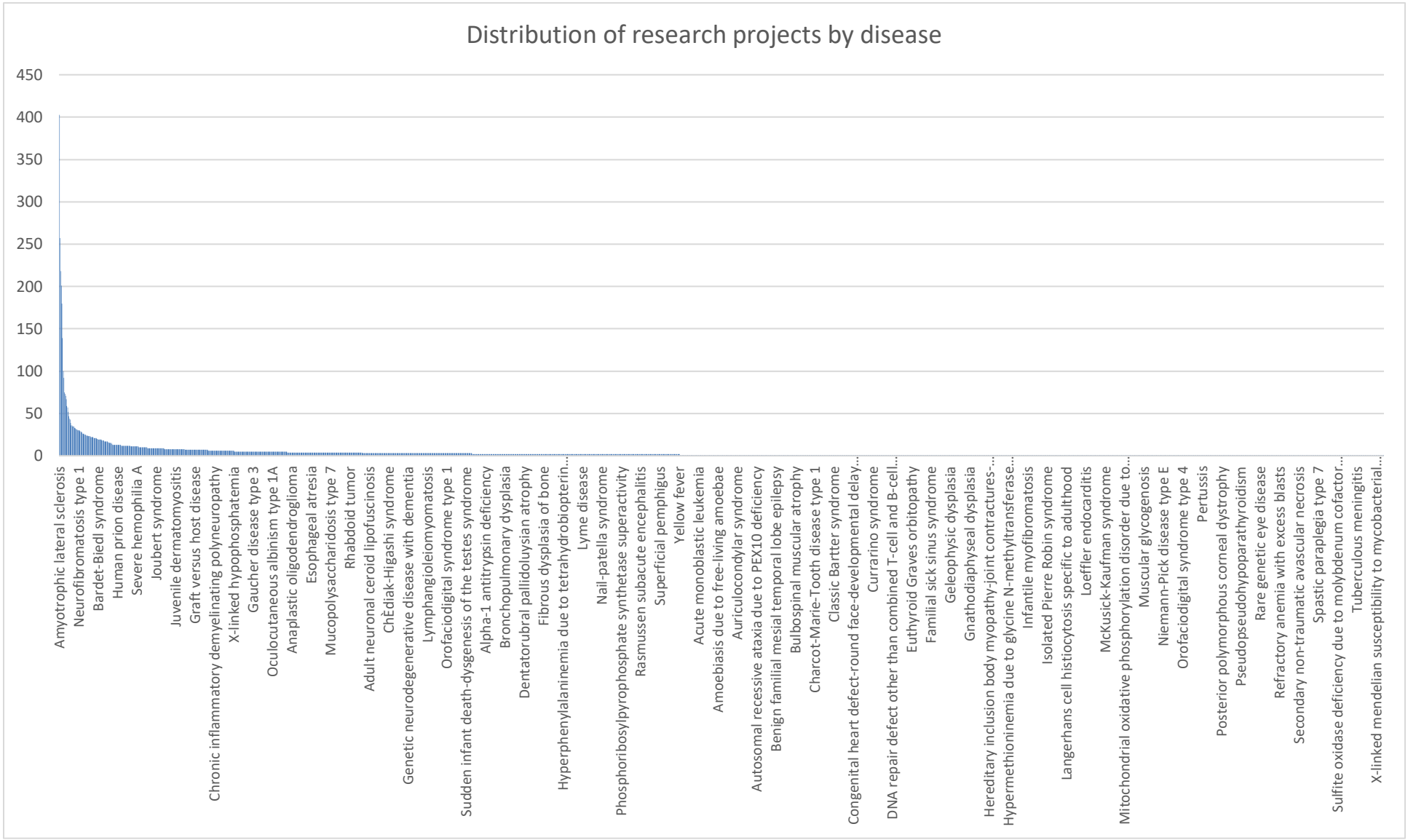
Distribution of research projects by disease is long-tail, with some diseases concentrating up to 403 projects and others as little as 1.

Globally, the five diseases for which the research projects are more numerous are, in decreasing order: amyotrophic lateral sclerosis, Huntington disease, Duchenne muscular dystrophy, Cystic fibrosis and glioblastoma.

When comparing geographical areas, the top-five diseases re, for Europe, Cystic fibrosis, Amyotrophic lateral sclerosis, Huntington disease, Duchenne muscular dystrophy and retinitis pigmentosa. For North-American countries, they are: Amyotrophic lateral sclerosis, Huntington disease, glioblastoma, Duchenne muscular dystrophy and retinitis pigmentosa. For Eastern countries, the five diseases with funded research are Amyotrophic lateral sclerosis, Duchenne muscular dystrophy, rare diseases in general (including registry creation and undiagnosed, rare and intractable diseases research programs), Multiple systemic atrophy and retinitis pigmentosa.


Number of clinical entities with at least one research project vs total number of clinical entities by medical domain
Rare neurologic disease
Rare developmental defect during embryogenesis
Rare neoplastic disease
Rare inborn errors of metabolism
Rare bone disease
Rare systemic or rheumatologic disease
Rare hematologic disease
Rare skin disease
Rare endocrine disease
Rare ophthalmic disorder
Rare renal disease
Rare infectious disease
Rare immune disease
Rare cardiac disease
Rare respiratory disease
Rare gastroenterologic disease
Rare hepatic disease
Rare otorhinolaryngologic disease
Rare circulatory system disease
Rare infertility
Rare gynecologic or obstetric disease
ND
Rare odontologic disease
Rare urogenital disease
Rare surgical thoracic disease
Rare maxillo-facial surgical disease
Rare genetic disease
Rare disorder due to toxic effects
Rare abdominal surgical disease
0
500
1000
1500
2000
2500
3000
Total clinical entities with projects
Total clinical entities

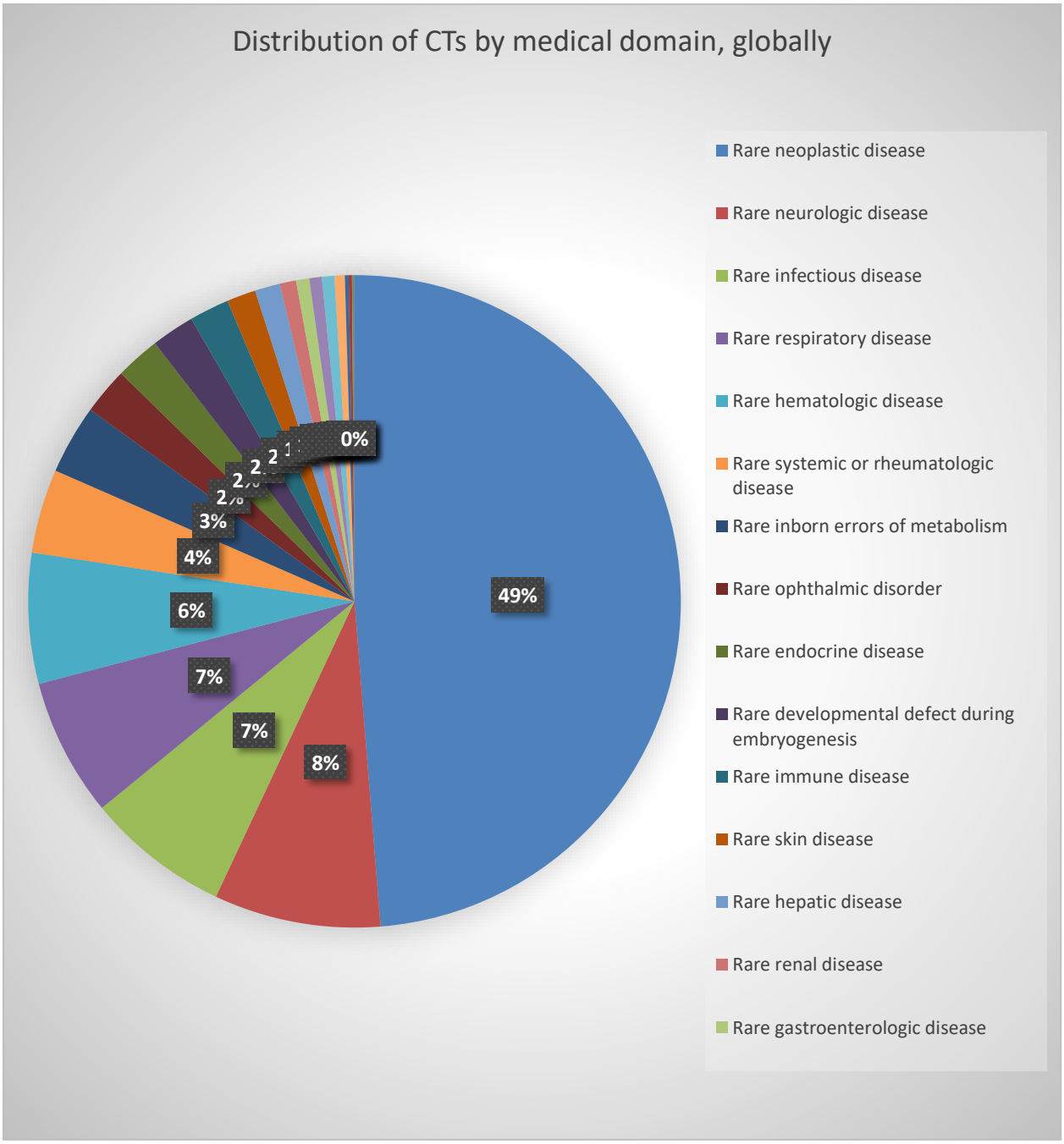

Percentage of clinical entities with at least one research roject vs total number of clinical entities by medical domain
Rare cardiac disease
Rare systemic or rheumatologic disease
Rare renal disease
Rare neurologic disease
Rare neoplastic disease
Rare hematologic disease
Rare inborn errors of metabolism
Rare infectious disease
Rare respiratory disease
Rare immune disease
Rare bone disease
Rare circulatory system disease
Rare otorhinolaryngologic disease
Rare genetic disease
Rare hepatic disease
Rare endocrine disease
Rare gynecologic or obstetric disease
Rare gastroenterologic disease
Rare ophthalmic disorder
Rare surgical thoracic disease
Rare developmental defect during embryogenesis
Rare infertility
Rare skin disease
Rare maxillo-facial surgical disease
Rare abdominal surgical disease
Rare urogenital disease
Rare odontologic disease
Rare disorder due to toxic effects
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
% of clinical entities with research projects
% of clinical entities without research projects


Distribution of research projects by disease
450
400
350
300
250
200
150
100
50
0
Amyotrophic lateral sclerosis
Neurofibromatosis type 1
Bardet-Biedl syndrome
Human prion disease
Severe hemophilia A
Joubert syndrome
Juvenile dermatomyositis
Graft versus host disease
Chronic inflammatory demyelinating polyneuropathy
X-linked hypophosphatemia
Gaucher disease type 3
Oculocutaneous albinism type 1A
Anaplastic oligodendroglioma
Esophageal atresia
Mucopolysaccharidosis type 7
Rhabdoid tumor
Adult neuronal ceroid lipofuscinosis
ChÈdiak-Higashi syndrome
Genetic neurodegenerative disease with dementia
Lymphangioleiomyomatosis
Orofaciodigital syndrome type 1
Sudden infant death-dysgenesis of the testes syndrome
Alpha-1 antitrypsin deficiency
Bronchopulmonary dysplasia
Dentatorubral pallidoluysian atrophy
Fibrous dysplasia of bone
Hyperphenylalaninemia due to tetrahydrobiopterin...
Lyme disease
Nail-patella syndrome
Phosphoribosylpyrophosphate synthetase superactivity
Rasmussen subacute encephalitis
Superficial pemphigus
Yellow fever
Acute monoblastic leukemia
Amoebiasis due to free-living amoebae
Auriculocondylar syndrome
Autosomal recessive ataxia due to PEX10 deficiency
Benign familial mesial temporal lobe epilepsy
Bulbospinal muscular atrophy
Charcot-Marie-Tooth disease type 1
Classic Bartter syndrome
Congenital heart defect-round face-developmental delay...
Currarino syndrome
DNA repair defect other than combined T-cell and B-cell...
Euthyroid Graves orbitopathy
Familial sick sinus syndrome
Geleophysic dysplasia
Gnathodiaphyseal dysplasia
Hereditary inclusion body myopathy-joint contractures-...
Hypermethioninemia due to glycine N-methyltransferase...
Infantile myofibromatosis
Isolated Pierre Robin syndrome
Langerhans cell histiocytosis specific to adulthood
Loeffler endocarditis
McKusick-Kaufman syndrome
Mitochondrial oxidative phosphorylation disorder due to...
Muscular glycogenosis
Niemann-Pick disease type E
Orofaciodigital syndrome type 4
Pertussis
Posterior polymorphous corneal dystrophy
Pseudopseudohypoparathyroidism
Rare genetic eye disease
Refractory anemia with excess blasts
Secondary non-traumatic avascular necrosis
Spastic paraplegia type 7
Sulfite oxidase deficiency due to molybdenum cofactor...
Tuberculous meningitis
X-linked mendelian susceptibility to mycobacterial...

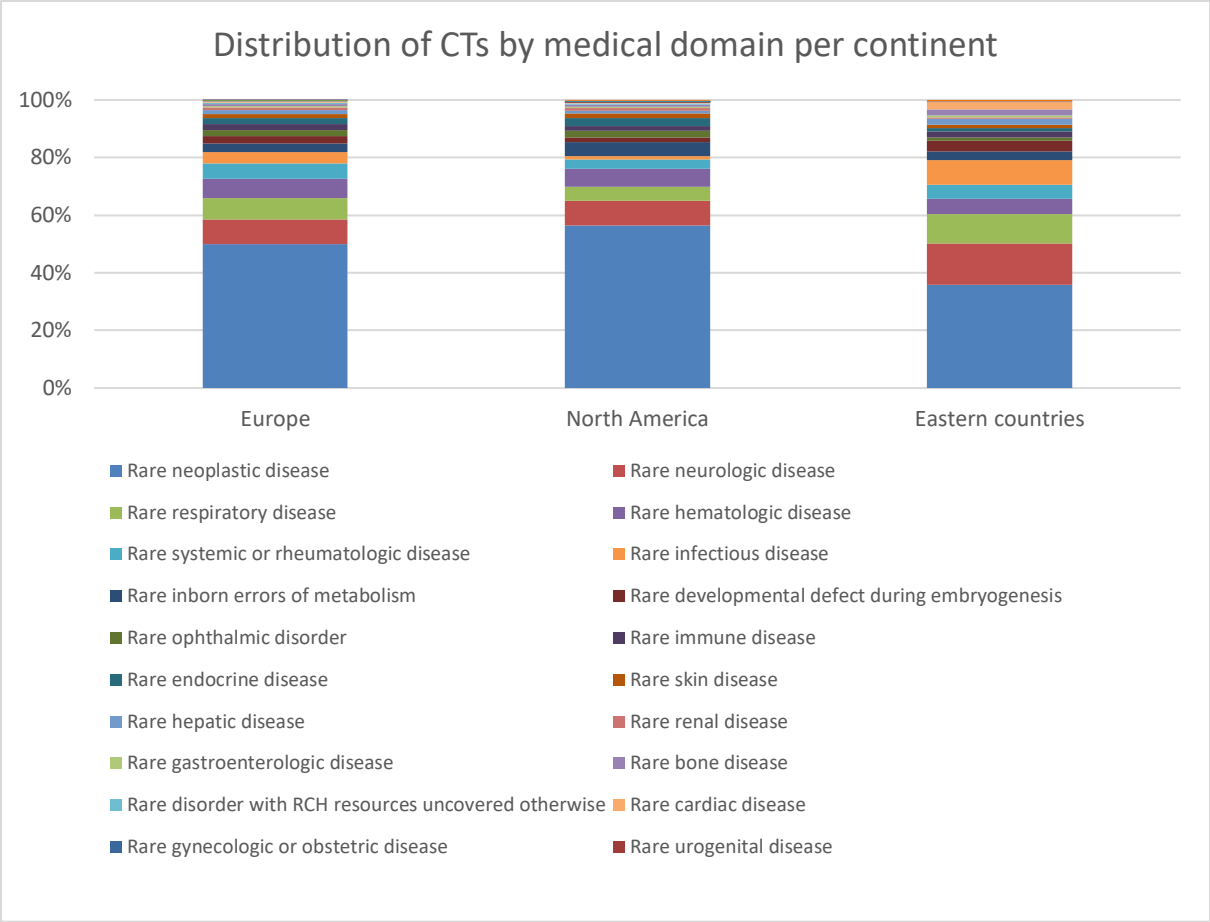
3.3. Analysis of clinical trials

3.3.1. Distribution by medical domain

About half of all CTs (49%) involve rare cancers, the other half being distributed amongst the rest of clinical domains. Rare neurological diseases and rare respiratory diseases come far behind, with 8% and 7% of all CTs respectively.

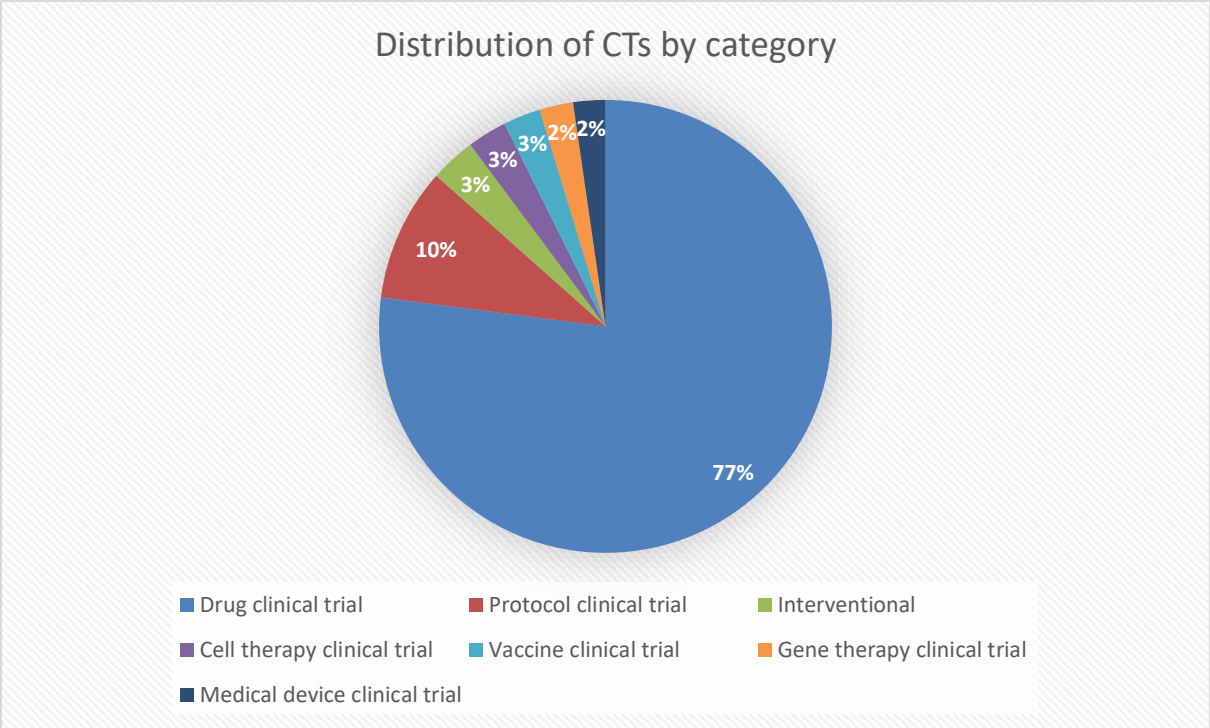


The same trend is observed in the three geographical areas studied, as shown in the figure below:

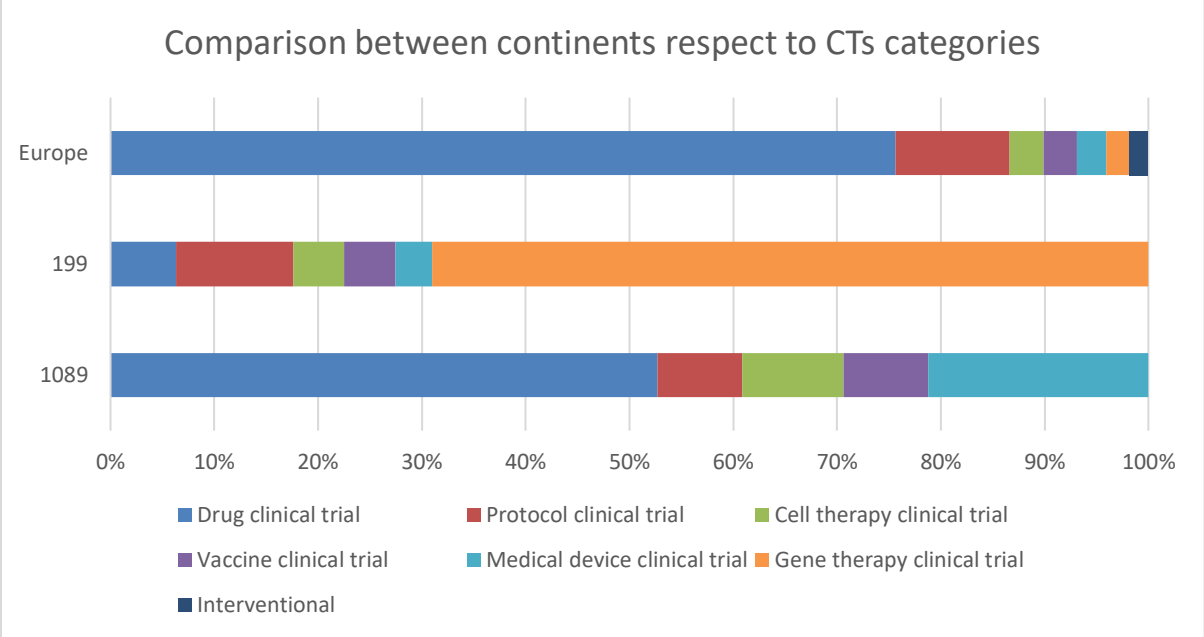


3.3.2. Distribution by type and phase of clinical trials

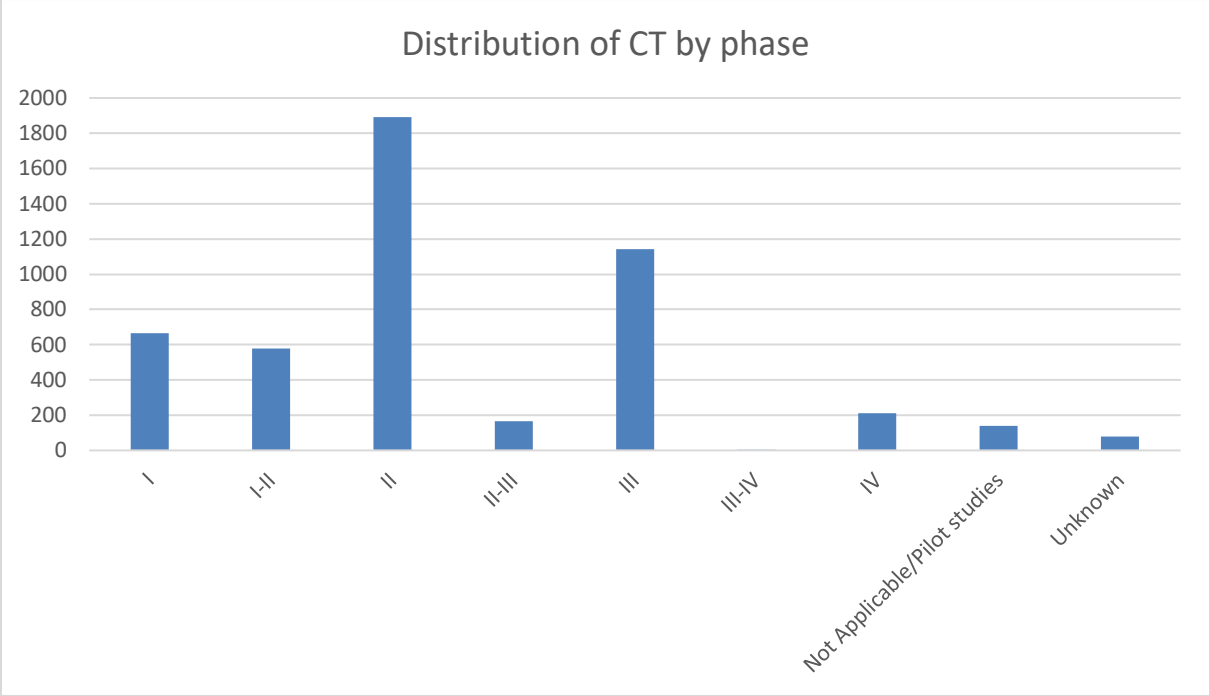
The vast majority of clinical trials were conducted for testing drugs, followed by those comparing treatment protocols. Other kinds of interventions, trials on cell therapy or vaccines represented 3% of all CTs each, gene therapy and medical device being the focus of 2% of all CTs each.



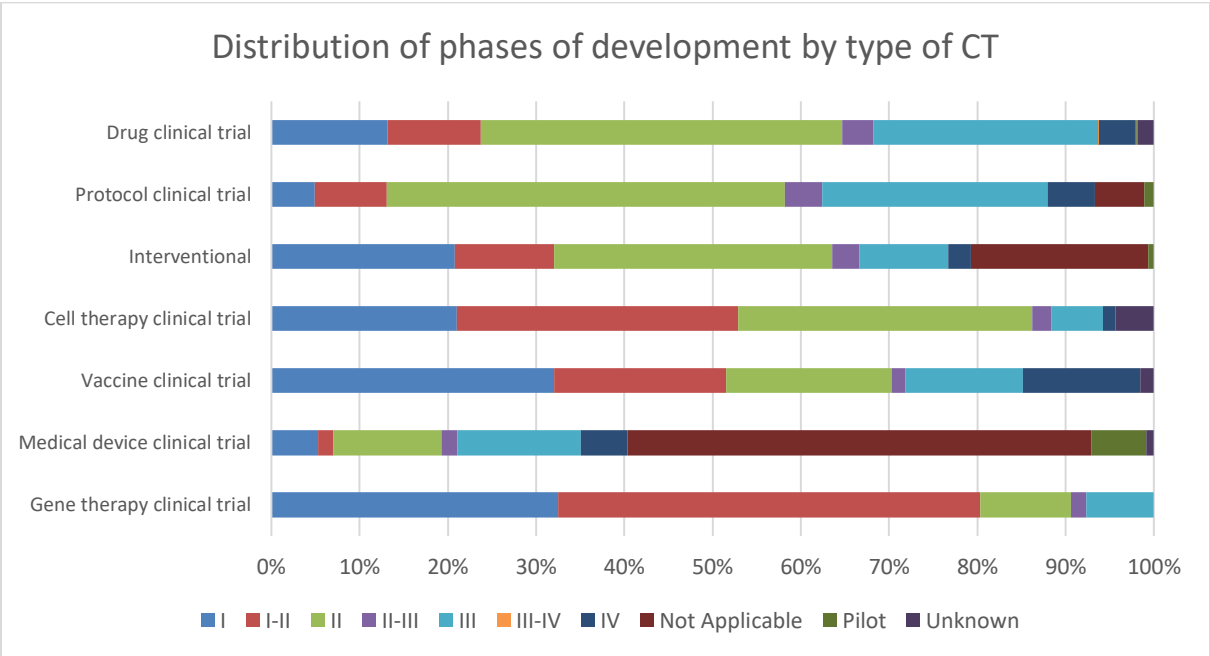
When comparing geographical areas, the predominance of drug CTs is confirmed in all of them, the only important difference being a larger number of interventional CTs in Eastern countries.



Most CTs were in the intermediate phases of development (II and III) as shown in the figure below. Less than 5% of all CTs are in advanced phases of development.

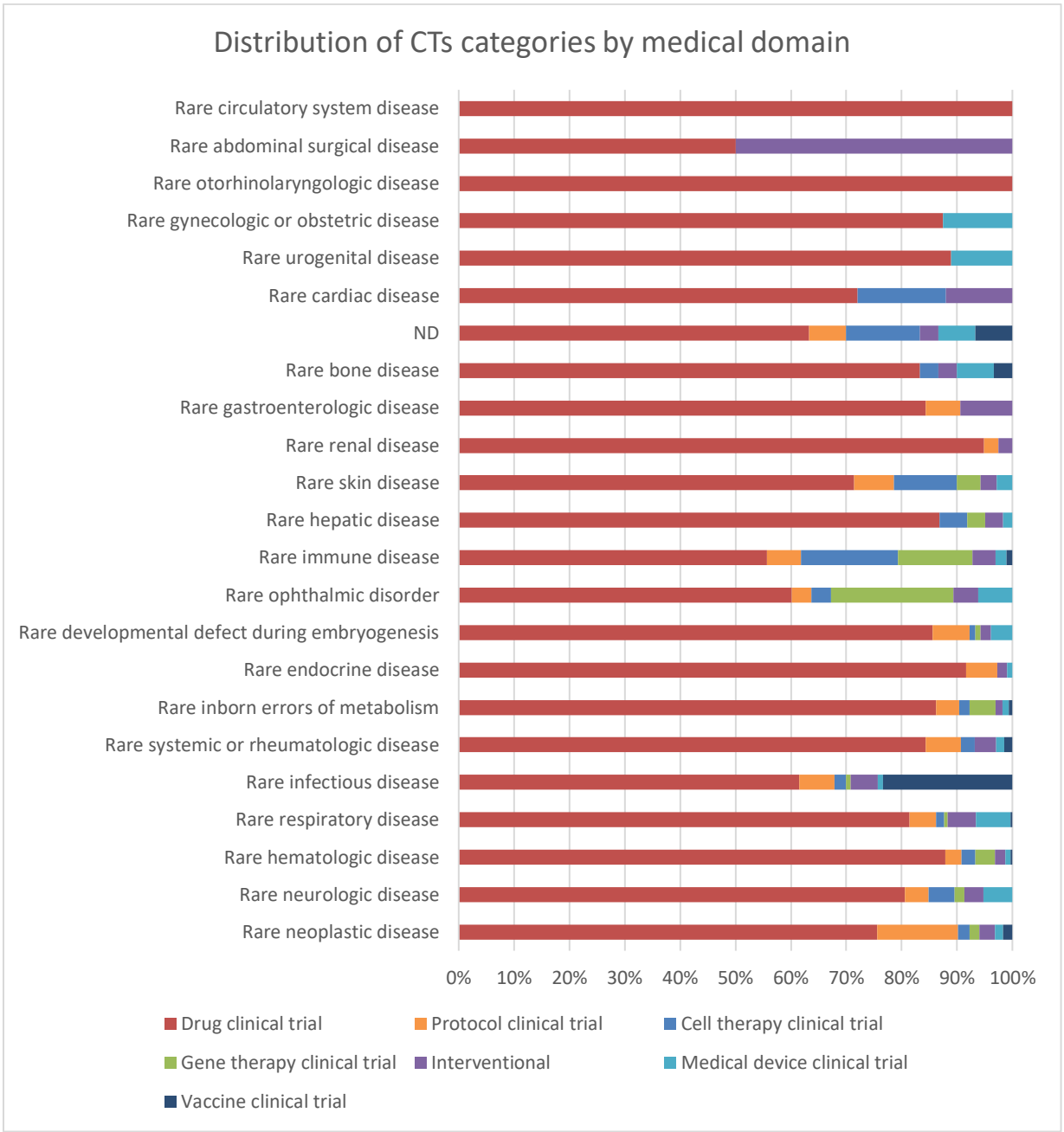


When comparing the phases of development of treatments versus the type of treatment (type of CT), we see that gene therapy is, overall, in early phases of development (I-II) (up to 80% of CTs), cell therapy achieving phase II studies in the considerable number of cases (33%). Most drug and protocol CTs are in phase II (41% and 45% respectively) and phase II-III or III of development (29% and 30% respectively).



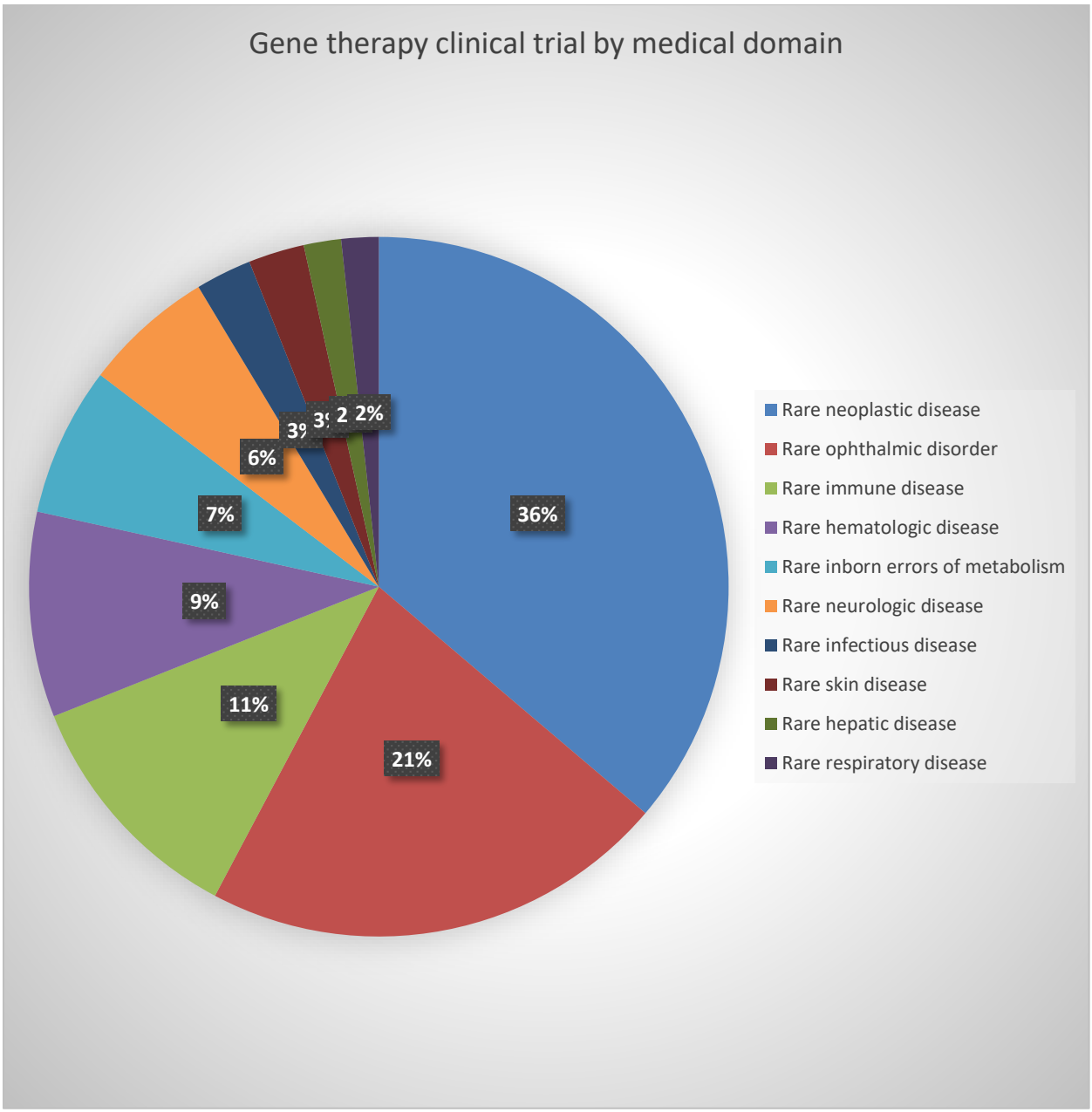
3.3.3. Types of CTs by medical domain

The graphic below shows the distribution of categories of CTs per medical domain. Not surprisingly, drug clinical trials and protocol CTs represent the vast majority of trials in all the domains.

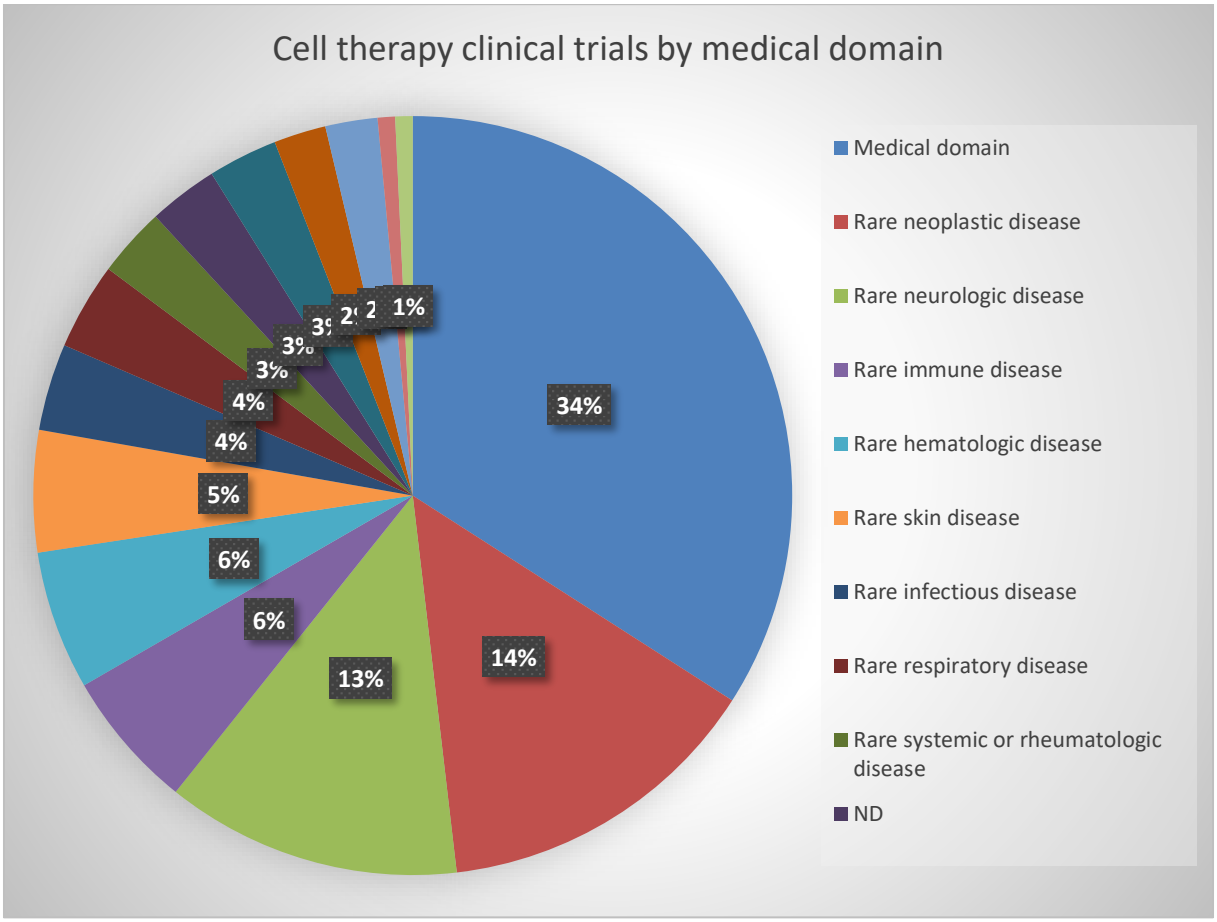


In order to identify the areas in which innovative therapies are being tested in clinical trials, we analysed the CTs by medical domain for the categories “gene therapy” and ‘cell therapy”.

CTs on gene therapy are conducted for rare cancers (in 36% of cases), followed by rare ophthalmic diseases (21%) and rare immune diseases (11%), as shown in the figure below:



Thirty-four percent of cell therapy CTs are conducted for rare cancers, followed by rare neurological diseases (14%) and rare immune diseases (13%).



3.3.4. Disease coverage.

CTs' disease coverage is defined as number of clinical entities (disorders, groups or sub-types) for which there is at least one CT. For the analysis of disease coverage, clinical entities (groups, disorders and sub-types) were considered indifferently, the procedure for linking rare disorders being that the most granular level should be chosen. CTs were linked to groups when no detailed inclusion criteria were given in terms of specific diseases covered. As far as only one CT by clinical entity is considered for this indicator, and the total number of clinical entities is taken as the denominator, the bias of this mode of calculation on the results is minimized.

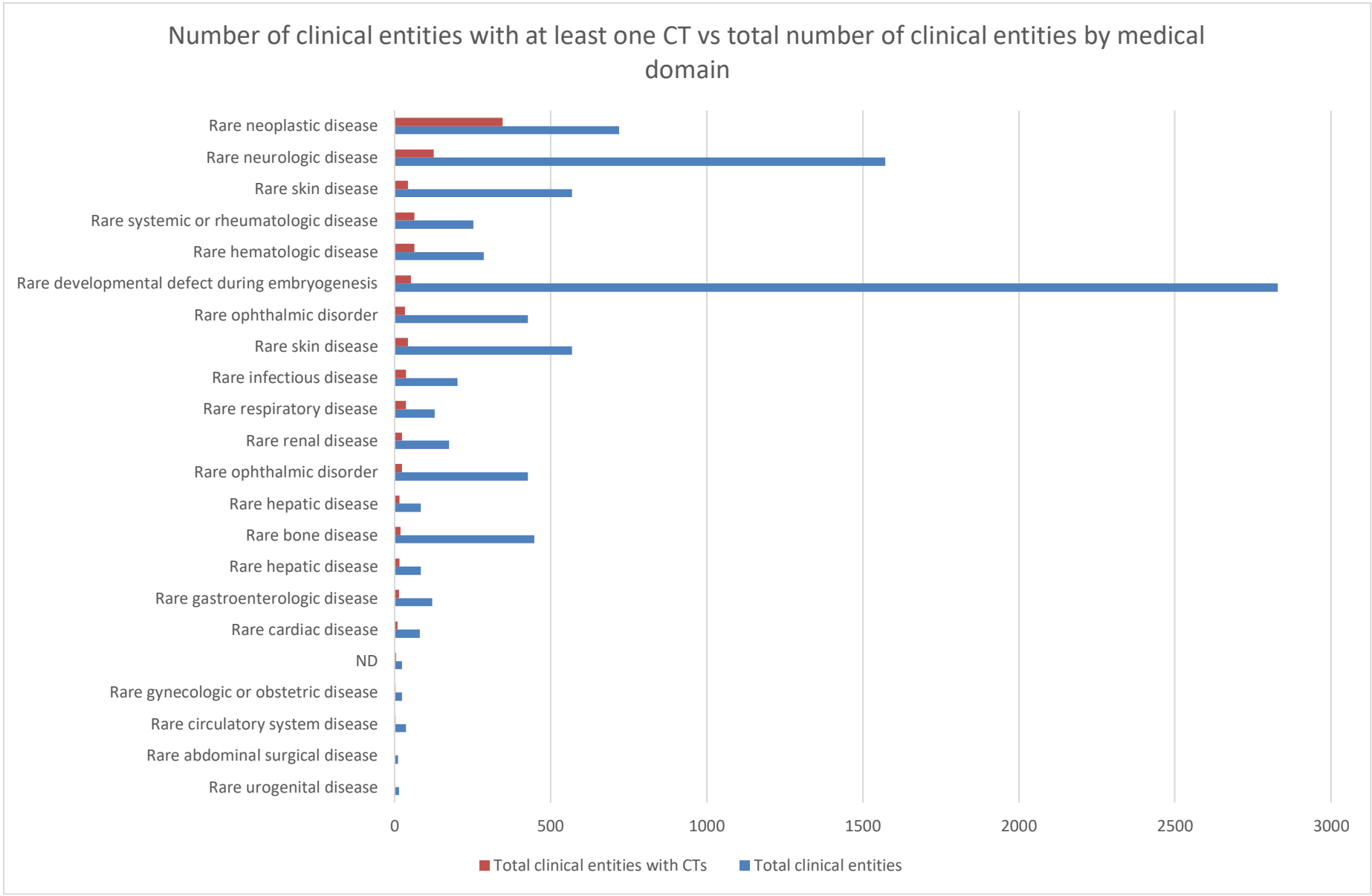
Only 10.8%% of all clinical entities are covered by clinical trials. The proportion of clinical entities covered per medical domain varies considerably between medical domains: CTs on rare cancers (which represent 7,6% of all rare diseases) is 48%, whereas only 1.9% of rare developmental

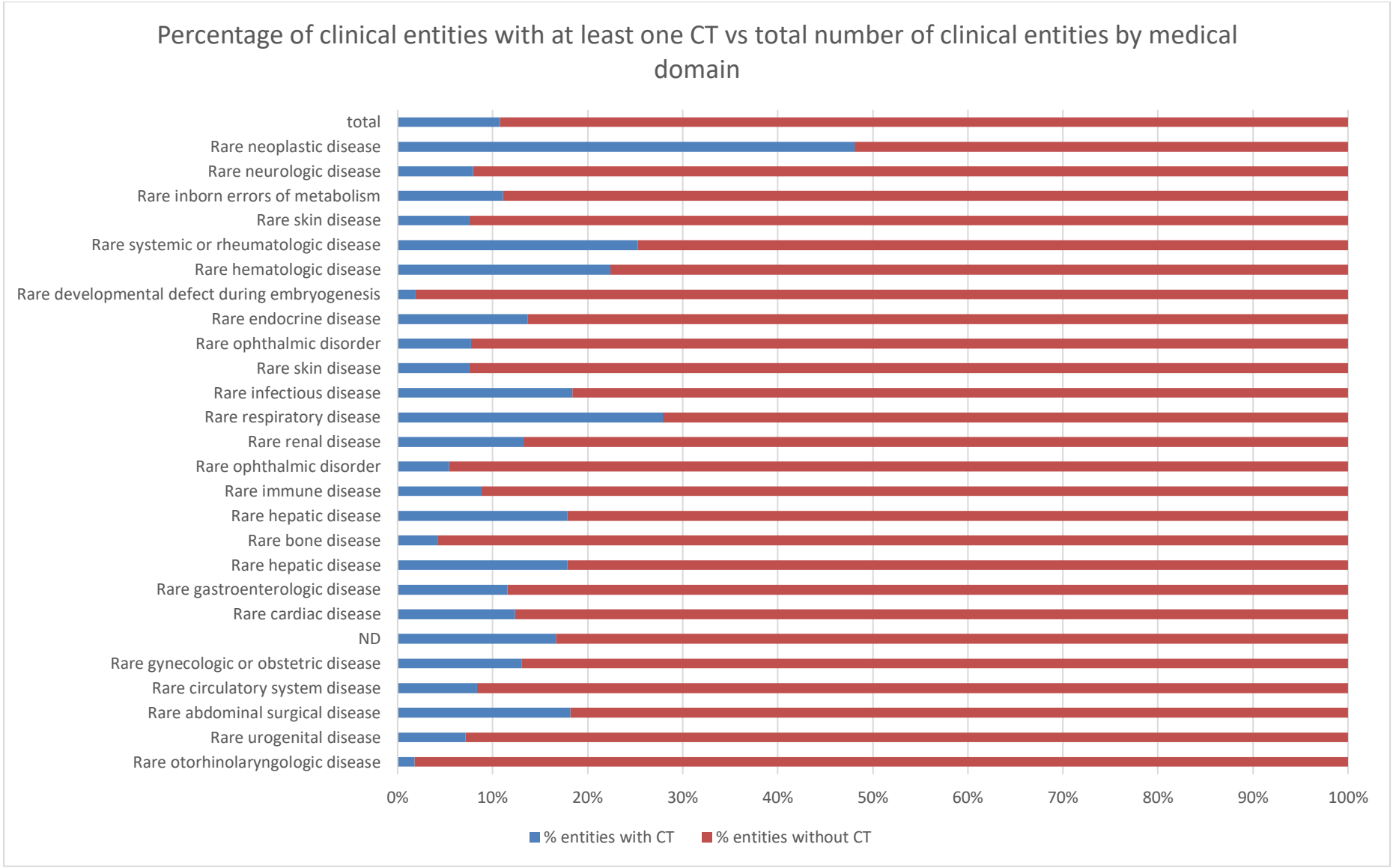
defects (counting for 32% of all rare diseases) are covered. Hematological diseases are covered at 22,4%; they count for 4,5% of all rare diseases.

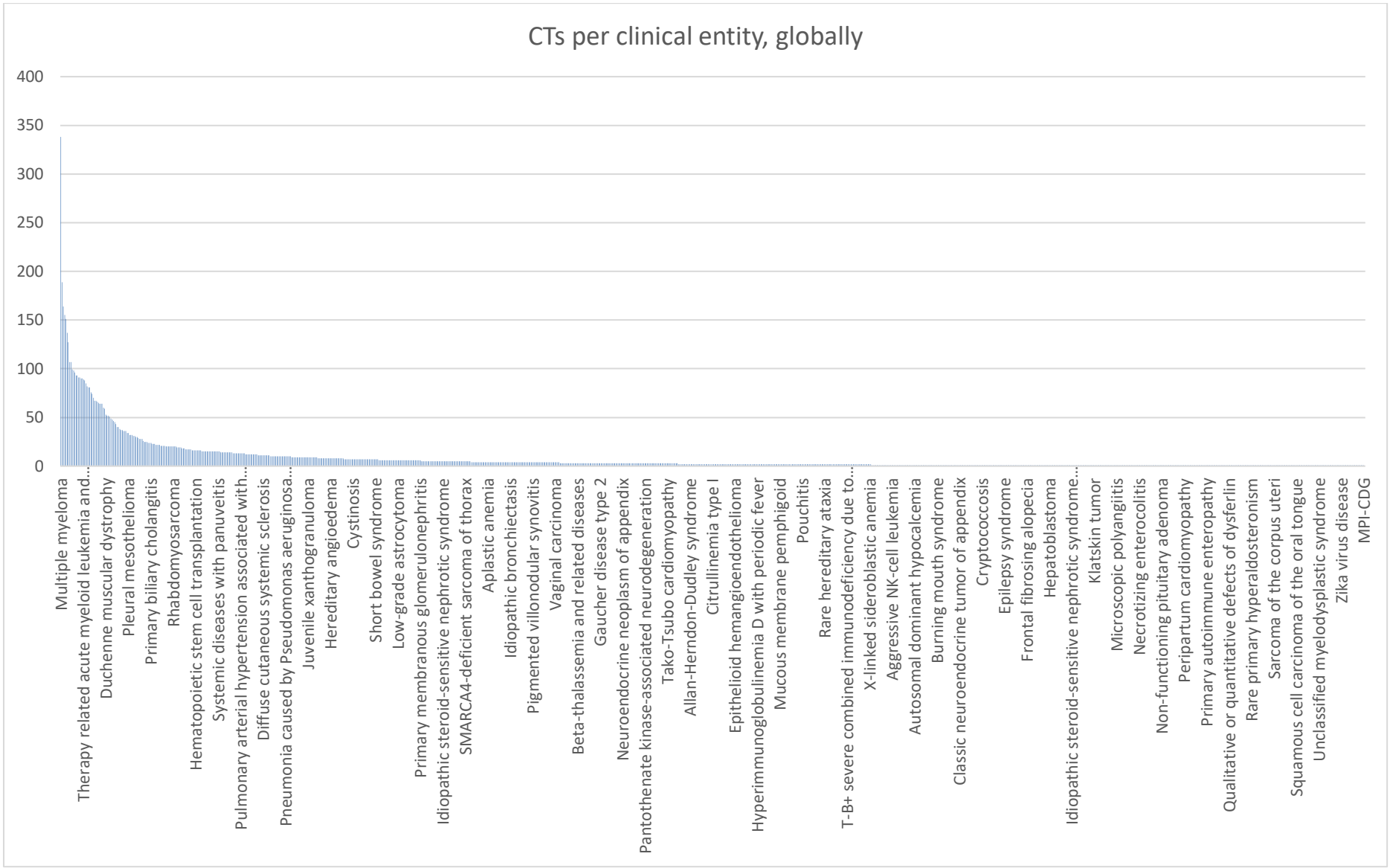
Distribution of CTs by disease is long-tail, with some diseases concentrating up to 338 CTs and others as little as 1.

Globally, the five diseases for which the CTs are more numerous are, in decreasing order: Multiple myeloma, Acute myeloid leukemia, B-cell chronic lymphocytic leukemia, Glioblastoma and Diffuse large B-cell lymphoma. Cystic fibrosis follows at the 6th position.

When comparing geographical areas, the top-five diseases are, for Europe, the same than those listed above, Cystic fibrosis being the first non-neoplastic disease and appearing at the 6th place (95 CTs). For North-American countries, they are: Multiple myeloma, Acute myeloid leukemia, Glioblastoma, Diffuse large B-cell lymphoma and Malignant tumor of Fallopian tubes. Again, the first non-neoplastic disease is cystic fibrosis, appearing at the 9th position (29 CTs). For Eastern countries, the five diseases with funded CTs are Acute myeloid leukemia, Multiple myeloma, cystic fibrosis, malaria and Chronic myeloid leukemia.


Number of clinical entities with at least one CT vs total number of clinical entities by medical domain
Rare neoplastic disease
Rare neurologic disease
Rare skin disease
Rare systemic or rheumatologic disease
Rare hematologic disease
Rare developmental defect during embryogenesis
Rare ophthalmic disorder
Rare skin disease
Rare infectious disease
Rare respiratory disease
Rare renal disease
Rare ophthalmic disorder
Rare hepatic disease
Rare bone disease
Rare hepatic disease
Rare gastroenterologic disease
Rare cardiac disease
ND
Rare gynecologic or obstetric disease
Rare circulatory system disease
Rare abdominal surgical disease
Rare urogenital disease
0
500
1000
1500
2000
2500
3000
Total clinical entities with CTs
Total clinical entities


Percentage of clinical entities with at least one CT vs total number of clinical entities by medical domain
total
Rare neoplastic disease
Rare neurologic disease
Rare inborn errors of metabolism
Rare skin disease
Rare systemic or rheumatologic disease
Rare hematologic disease
Rare developmental defect during embryogenesis
Rare endocrine disease
Rare ophthalmic disorder
Rare skin disease
Rare infectious disease
Rare respiratory disease
Rare renal disease
Rare ophthalmic disorder
Rare immune disease
Rare hepatic disease
Rare bone disease
Rare hepatic disease
Rare gastroenterologic disease
Rare cardiac disease
ND
Rare gynecologic or obstetric disease
Rare circulatory system disease
Rare abdominal surgical disease
Rare urogenital disease
Rare otorhinolaryngologic disease
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
% entities with CT
% entities without CT

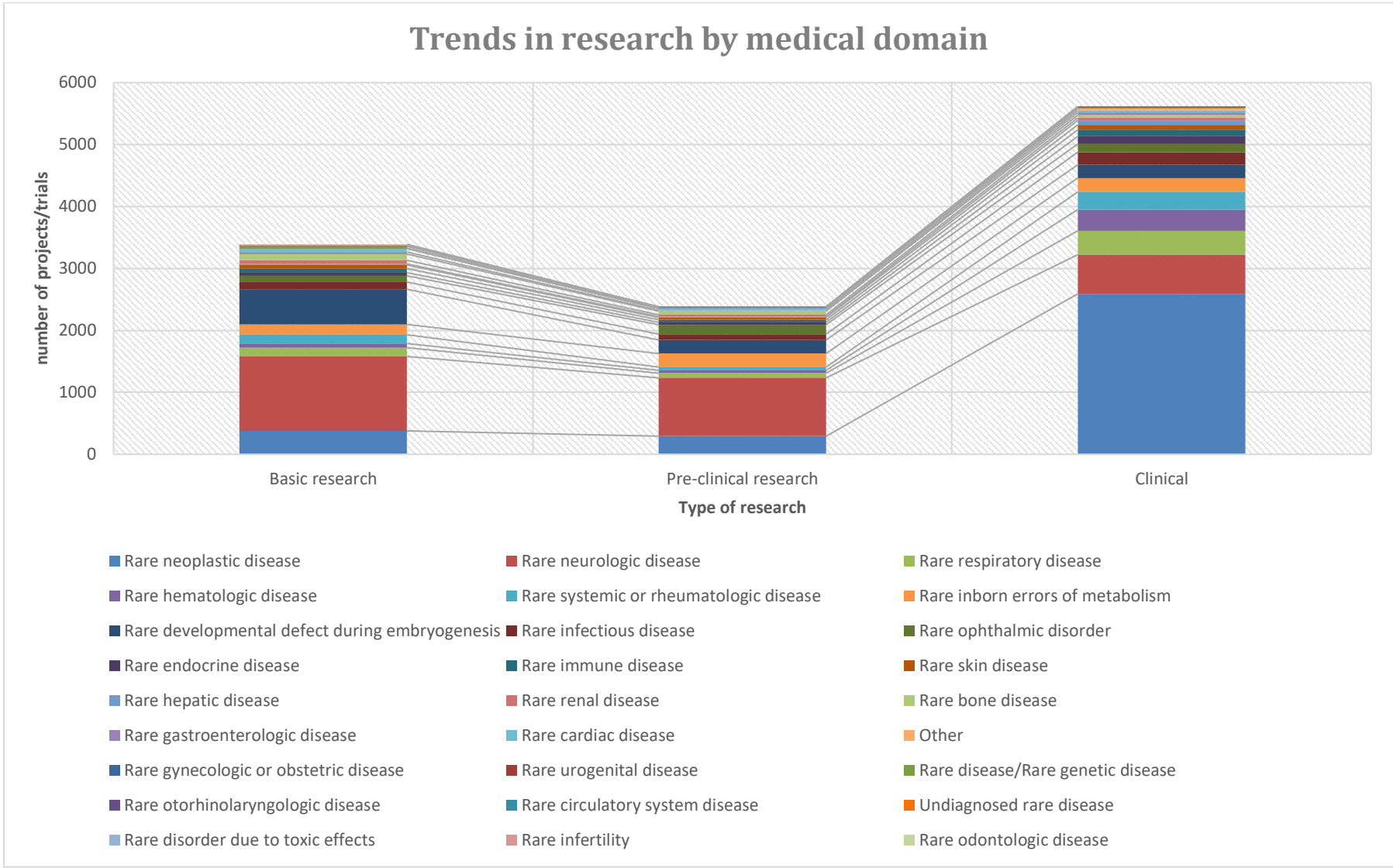

CTs per clinical entity, globally
400
350
300
250
200
150
100
50
0
Multiple myeloma
Therapy related acute myeloid leukemia and...
Duchenne muscular dystrophy
Pleural mesothelioma
Primary biliary cholangitis
Rhabdomyosarcoma
Hematopoietic stem cell transplantation
Systemic diseases with panuveitis
Pulmonary arterial hypertension associated with...
Diffuse cutaneous systemic sclerosis
Pneumonia caused by Pseudomonas aeruginosa...
Juvenile xanthogranuloma
Hereditary angioedema
Cystinosis
Short bowel syndrome
Low-grade astrocytoma
Primary membranous glomerulonephritis
Idiopathic steroid-sensitive nephrotic syndrome
SMARCA4-deficient sarcoma of thorax
Aplastic anemia
Idiopathic bronchiectasis
Pigmented villonodular synovitis
Vaginal carcinoma
Beta-thalassemia and related diseases
Gaucher disease type 2
Neuroendocrine neoplasm of appendix
Pantothenate kinase-associated neurodegeneration
Tako-Tsubo cardiomyopathy
Allan-Herndon-Dudley syndrome
Citrullinemia type I
Epithelioid hemangioendothelioma
Hyperimmunoglobulinemia D with periodic fever
Mucous membrane pemphigoid
Pouchitis
Rare hereditary ataxia
T-B+ severe combined immunodeficiency due to...
X-linked sideroblastic anemia
Aggressive NK-cell leukemia
Autosomal dominant hypocalcemia
Burning mouth syndrome
Classic neuroendocrine tumor of appendix
Cryptococcosis
Epilepsy syndrome
Frontal fibrosing alopecia
Hepatoblastoma
Idiopathic steroid-sensitive nephrotic syndrome...
Klatskin tumor
Microscopic polyangiitis
Necrotizing enterocolitis
Non-functioning pituitary adenoma
Peripartum cardiomyopathy
Primary autoimmune enteropathy
Qualitative or quantitative defects of dysferlin
Rare primary hyperaldosteronism
Sarcoma of the corpus uteri
Squamous cell carcinoma of the oral tongue
Unclassified myelodysplastic syndrome
Zika virus disease
MPI-CDG

4. Final remarks

This document was intended to depict the research landscape on rare diseases between 2010, date of the creation of IRDiRC, and 2017, year in which IRDiRC adopted its new goals at the horizon 2027. It gives an insight on the fields in which the investment is more important, and as a consequence, reveals the enormous gap still to fill in research: there are only 11% of rare diseases for which clinical trials are conducted, and 22% of rare diseases for which there is some kind of research, from basic, to pre-clinical, observational or other types of studies).

The comparison of medical domains with regards to the big categories of research: basic, pre-clinical and clinical, shown in the figure below, allows for the detection of medical domains in which research is turned on understanding diseases and searching for causes (like in developmental defects) and those in which an active pre-clinical research is perhaps ready for translational approaches, like neurology. Others, like oncology, are more oriented to find or improve therapies and protocols through clinical trials.

It is out of the scope of this document to analyze disease by disease, group by group, what is going on in research. However, it gives a taste of how could it be possible to dissect diseases and groups, to unveil the promises and the dead-ends. This should be made possible by providing data and tools to perform fine-grained analysis.


Trends in research by medical domain
6000
5000
4000
3000
2000
1000
0
number of projects/trials
Basic research
Pre-clinical research
Clinical
Type of research
Rare neoplastic disease
Rare neurologic disease
Rare respiratory disease
Rare hematologic disease
Rare systemic or rheumatologic disease
Rare inborn errors of metabolism
Rare developmental defect during embryogenesis
Rare infectious disease
Rare ophthalmic disorder
Rare endocrine disease
Rare immune disease
Rare skin disease
Rare hepatic disease
Rare renal disease
Rare bone disease
Rare gastroenterologic disease
Rare cardiac disease
Other
Rare gynecologic or obstetric disease
Rare urogenital disease
Rare disease/Rare genetic disease
Rare otorhinolaryngologic disease
Rare circulatory system disease
Undiagnosed rare disease
Rare disorder due to toxic effects
Rare infertility
Rare odontologic disease

Annex I: Overview of members that submitted information on research projects and clinical trials

Organization	Project data received	Clinical trial data received
Western Australian Department of Health	Not Sent	NA
Rare Voices Australia	NA	NA
European Organisation for Treatment & Research on Cancer, EORTC	NA	OK
Canadian Institutes for Health Research, CIHR	OK	NA
Genome Canada	OK	NA
Canadian Organization for Rare Disorders, CORD	NA	NA
BGI	OK	NA
Chinese Organization for Rare Disorders, CORD	NA	NA
E-Rare Consortium	OK	OK
European Commission - DG Research and Innovation	OK	OK
Rare Diseases Europe-EURORDIS	NA	NA
Agence Nationale de la Recherche, ANR	OK	NA
Academy of Finland	OK	NA
French Muscular Dystrophy Association, AFM-Téléthon	OK	OK
French Foundation for Rare Diseases, FMR	OK	NA
Lysogene	NA	OK
Children's New Hospitals Management Group	OK	NA
Federal Ministry of Education and Research, BMBF	OK	Not Sent
I-ORD	NA	NA
ORDI	NA	NA
Shire	NA	Not Sent
Chiesi Pharmaceutici	NA	OK
Istituto Superiore de Sanità, ISS	OK	NA
Telethon Foundation	OK	OK
Japan Agency for Medical Research and Development, AMED	OK	OK
Advocacy Service for Rare and Intractable Diseases' multi-stakeholders in Japan, ASrid	NA	NA
National Institutes of Biomedical Innovation, Health and Nutrition, NIBIOHN	Not Sent	NA
Saudi Human Genome Project	OK	NA
Netherlands Organisation for Health Research and Development, ZonMw	OK	OK

Rare Diseases South Africa	NA	NA
Korea National Institute of Health, KNIH	OK	NA
National Institute of Health Carlos III, ISCIII	OK	NA
Roche	NA	OK
Ultragenyx	NA	OK
Loulou Foundation	OK	NA
National Institute for Health Research, NIHR	OK	OK
Cydan II	NA	NA
Food and Drug Administration, FDA	OK	OK
Genetic Alliance	NA	NA
Sanofi - Genzyme	NA	Not Sent
Global Genes	NA	NA
Ionis Pharmaceuticals	NA	Not Sent
National Organization for Rare Diseases, NORD	NA	NA
NIH - National Cancer Institute, NCI	OK	OK
NIH - National Center for Advancing Translational Sciences, NCATS	OK	OK
NIH - National Eye Institute, NEI	OK	OK
NIH - National Human Genome Research Institute, NHGRI	OK	OK
NIH - National Institute for Child Health and Human Development, NICHD	OK	OK
NIH - National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS	OK	OK
NIH - National Institute of Neurological Disorders and Stroke, NINDS	OK	OK
NKT Therapeutics	NA	Not Sent
Pfizer	NA	Not Sent
PTC Therapeutics	NA	Not Sent
Recursion Pharmaceuticals	NA	NA
Sanford Research	OK	NA

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