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Manuel Posada de la Paz
Domenica Taruscio
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Rare Diseases Epidemiology: Update and Overview

Second Edition

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Preface

The Power of one and the Power of Many: Patient Advocacy and its Influence on Rare Disease Research – Evolutionary and Revolutionary Factors

In this updated book, the Editors have invited John Forman to discuss patient advocacy in rare diseases through the actual history of a family affected by a rare disease. The Preface provides experiences and accomplishments of one family with heightening the awareness of a rare disease, mucolipidosis type III (ML3), following the birth of their first child. The necessity of the individual and the family to meet the needs of a family member has led many individuals to become the leader in the field to develop a research emphasis and provide information to the public on a specific rare disease. The role of patient advocacy in promoting research into rare diseases, like most aspects of our society, has changed over time. From volunteering, as largely passive subjects in studies, or donating samples for research, there have been evolutionary changes through many stages of development. Loose collections of families coalesced into support organizations and engaged with health professionals and researchers to promote disease knowledge, clinical care improvements, and a search for effective treatments or cures. Alongside this evolutionary growth in capacity and involvement, revolutionary changes spurred the impact of patient advocacy into new levels. One such change was the impact of human rights in society and the flow-on effect this had in the health field, with patients gaining explicit rights in consent in health care and research, plus rights to consultation on public policy.

The communications revolution from the 1990s meant patients could connect and share more easily with each other and build more effective advocacy groups while also gaining unprecedented access to medical and research information that had been effectively locked away from them. The move from passive recipients to active partners took some years to achieve. But this combination of evolutionary and revolutionary forces made it a present-day reality. The momentum continues, as patient advocacy moves from subject to participant, to partner, and then to financial supporter and leader in rare disease research. This Preface addresses a range of these issues in the context of one patient advocate's long-term commitment to research and better care for the very rare disease two of her children have. It offers

a message of hope and encouragement that much more can be achieved through additional contributions by more patient advocates.

Introduction. When invited to write this Preface, I referred to the first edition where authors associated with NORD, the US National Organization for Rare Disorders, wrote about patient advocacy and research against a backdrop of the remarkable and inspirational work of Abbey Myers, the founder and first chief executive of NORD. I considered extending this theme by addressing some other high-profile advocates and their organizations and the far-reaching impact they had on research into a wide range of rare diseases. But many of those stories are likely well known to most readers of this chapter. Instead, I decided to focus on the work of just one patient advocate who is not so widely known, but has achieved significant accomplishments over the past 30 years. I believe her story is important as a recognition of what she has done largely "under the radar" for so long and the wide range of impacts her work has achieved. It is also important as a source of inspiration to others who may wish to work toward similar aims, but feel perhaps daunted by the tasks or uncertain about their ability to make a difference in such a challenging and often mysterious area of activity. This could be especially so, if they do not have access to large sources of funds or lack knowledge of medical or scientific terms. She is, in my view, a fine example of what can be achieved with focus and determination and with very limited resources. I believe her story will also offer reassurance and support to many patient advocates who are operating at various points along the spectrum of advocacy activities. Not every advocate can aspire to nor reach the highest levels of achievement in research on their disease. The work of thousands who do unsung work at different levels remains vitally important to successfully progress in rare disease research.

In the Beginning. The parenting world of Jenny Noble and her husband Paul, living at the time in Nelson, New Zealand (NZ), had a very typical beginning with the birth of their first child Hayden, in 1981. What is still quite typical for many on the journey into the world of rare diseases was true for them too. Symptoms of a possible problem began when Hayden was just 5 years old, by which time Hayden had a brother David and a sister Sarah. The surprising fact for those times was the quick delivery of an accurate diagnosis after those first signs. Within 2 years, a correct diagnosis of mucolipidosis type III (ML3) was given, and as so often happens when the first child is diagnosed with an inherited disease, Sarah was soon found to be affected by the disease also, while David was not affected.

Lack of information and isolation were significant problems. There was no other family in New Zealand with the same disease, and in the pre-Internet age, it was very challenging to get information. In 1989, faced with significant surgery indicated and a range of other symptoms presenting, Jenny and Paul decided to borrow against their house and travel to an international meeting on MPS and related diseases (the closest umbrella gathering for ML3 families, researchers, and clinicians), to learn as much as they could about the disease and meet experts in the condition.

Making Connections and Finding Information. Finding at that meeting the doctor who first described this condition and, on that journey, finding others who had managed patients with the disease gave them important information about

surgical options and risks, plus information about other complications to be expected with ML3. Some of this unpublished information was vital to the surgery facing their family and allowed Jenny and Paul to effectively engage with the treating doctors to ensure the best outcomes for Hayden and Sarah. These connections were maintained and these experts regularly consulted by the family and their doctors back in NZ, though there were sometimes challenges regarding the acceptance of information found by them. Throughout the 1990s, both Sarah and Hayden had several major surgeries, and the work done to connect with relevant experts in different countries undoubtedly led to much better outcomes for both of them.

It was in these early times on the journey that Jenny committed to sharing the knowledge gained by networking with other families here and overseas, and throughout the 1990s, she worked closely with families, health professionals, and researchers in the disease and began building connections for related diseases too. This task was greatly assisted by the Internet which began spreading from the mid-1990s and by Paul's unwavering support. By the turn of the century, improving disease knowledge for health professionals and families, and ensuring best medical care and optimal social support systems, became her unpaid career.

Building the Networks. In 1999, my role as a parent of twins with a related disease, alpha-mannosidosis, led to my path crossing with Jenny, and we joined forces on the development of Lysosomal Diseases New Zealand (LDNZ), as an umbrella support group for all lysosomal diseases, to give structure to efforts to support and inform affected families and to work to improve scientific research, medical care, and social support. We knew from our experience that research had to go beyond basics of the disease-causing mechanism. Research into best clinical care for our children was a vital need for ours and many other affected families. Families also need help to navigate the complexities of social support programs. Jenny took on the role of field officer for LDNZ, and after several years of operating without funds, we managed to scrape together the first grants to pay her modestly, for her significant contribution.

Within the next 2 years, Jenny played a pivotal support role in the development of the New Zealand Organisation for Rare Disorders, which I set up, and soon after she accepted a board role alongside me, with ISMRD, the International Advocate for Glycoprotein Storage Diseases, based in the USA. Through these roles, Jenny could make a contribution to information, research, and policy relating to rare diseases in NZ, as well as attend to the needs of the very rare subset of lysosomal diseases under the umbrella of ISMRD. Seventeen years later, she is still actively working in these roles.

Doing the Business. Since 2000, Jenny has participated in and often led significant efforts toward research on her children's disease and on related diseases. In addition, she has worked hard to influence policy for all rare diseases – all of this with no formal training in science or medicine. Starting as a secretary in the insurance company where she met Paul, she has worked hard to develop an extensive lay knowledge of the diseases and their needs, so she could advocate effectively for them and support research and clinical care for them.

Patient Advocacy Role. In 2000, she gave evidence to NZ's Royal Commission on Genetic Modification to describe her family's experience and to successfully advocate for the continuation of experiments that might lead to treatments for mucolipidosis and other rare diseases.

Scientific Conferences and Workshops. In 2002, she coauthored "The osteodystrophy of mucolipidosis type III and the effects of intravenous pamidronate treatment" (J Inherit Metab Dis 25 (2002) 681–693). She has since presented at family and scientific meetings on the results of this research from 2005 to 2015. She has been the central fundraiser and program organizer of four ISMRD conferences in the USA and is working on another later this year, 2017, in Europe. Each of these is designed to bring the scientists, health professionals, and families together to share experiences and learn from each other. Numerous research efforts had their genesis through connections made at these events.

In 2003 and again in 2008, she did the fundraising and central organizing role for a family and scientific conference in NZ for all lysosomal diseases. The 2008 meeting included a special workshop she organized for expert consideration of bone disease in mucolipidosis, and several research projects have sprung from this discussion.

In 2010, she repeated these fundraising and organizing roles for the International MPS Conference held in Adelaide, South Australia.

Support for Basic Research. Through fundraising efforts that Jenny has led, LDNZ has been able to support NZ researchers. We funded a study on treatment outcomes for patients with Gaucher disease and funded teams studying animal models of lysosomal diseases. Our small grants have provided important bridging to larger grants for work on Batten disease in sheep and Sanfilippo A disease in huntaway dogs. These research projects have made significant progress toward the development of therapies for both diseases.

Research Partnerships. In 2013 and again in 2016, Jenny's central role in ISMRD's fundraising efforts led to a partnership with other advocacy groups and foundations to provide a grant of $40,000 in 2013 for research into heart issues in mucolipidosis, and a sum of $150,000 was raised in 2016 funding exploratory gene therapy for the disease in cell culture and animal models and a separate study into potential therapy for the bone problems in the disease.

Clinical Care. On several occasions over these years, Jenny has worked closely with me on problems with clinical care coordination for those with complex and chronic diseases, especially those who leave the relatively well-organized world of pediatric care and graduate into the "black hole" of adult services. Case studies have been used in conjunction with the Pediatric Society, health officials, district health boards, and the Health and Disability Commissioner (HDC), to identify failings and make improvements. Success in this work is frustrated by the tendency of adult specialists and their hospital managers to slip back into their traditional methods of "silo" delivery and to lose sight of the collaboration and coordination that is indicated by the patient needs and which is in fact their right under our HDC Code of Rights. These experiences highlight the related need for research into health service delivery, which this work has contributed towards.

Natural History Study. In 2005, Jenny provided leadership and fundraising support for the development of a natural history study into the nine glycoprotein diseases in partnership with a US medical center, from which mutation discoveries, genotype/phenotype correlations, nomenclature changes, transplant outcomes, and diagnostic techniques have been published. And she's not finished yet!!

The Broader Context of Rare Disease Research. Patient advocates can contribute to research in many ways, including as passive participants and donors, as partners with clinicians and researchers in specific studies, as planners of conferences to build interest in disease research, by influencing legislators and funding agencies about rare disease research, by raising funds to make research happen, by developing biobanks and registries, by funding natural history studies, by sitting "at the table" when plans and priorities are devised, by influencing clinical trial design and consenting processes and how research is evaluated by regulators, by debating research priorities, and by influencing screening and diagnosis policies and practices.

Individual advocates may be daunted by the tasks and the scale of work needed. But all can make a meaningful contribution in some way or another. It is not necessary to aim to be in the top echelon of movers and shakers. Start with what you know and what you can do. Every contribution is valuable. Build a network of like-minded people. Network with the scientists and clinicians at conferences. Ask questions and seek answers. Don't be scared to show the limits of your knowledge. If you have anxieties about this, remember that I personally have asked the most naïve question ever asked by any patient advocate at a scientific and medical conference. Remember that the experts are invariably helpful and considerate, and they will value your experience of dealing with the practical aspects of the disease on the day-to-day life of patients and families. Your experience is something they don't know enough about, and they are keen to learn from you.

Conclusion. Personal stories provide a compelling angle to this discussion, I believe, and I have used Jenny Noble's story because I see it as a very informative example of what can be achieved by an individual with commitment and determination for the cause and a willingness to be in it for the long haul. She has been involved in many areas relevant to rare disease research, but not all of them. She played to her strengths and did what she could. She learned more when she needed to. But she did not aim to become a medical geneticist or research scientist. She did more at her level than she could likely have achieved if she had gone down that path. She deserves great recognition for her commitment for the cause, but perhaps the greatest accolade for her would be that her story has inspired patient advocacy readers to feel motivated to do more to support research and to feel comfortable that getting started at a level they feel confident with will be welcomed and valued. The power of one can be multiplied many times over, if we all do our bit.

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Personal Gratitude

On a personal note, it is important to acknowledge and recognize our spouses, children, and grandchildren who have provided the opportunity and emphasis to sustain our continued commitments to the rare diseases community with hopes of enabling rapid and accurate diagnoses and providing ready access to available treatments.

To my wife Mercedes and our children and grandchildren because I love them. They encourage me to continue living, and also they promote and facilitate my work aimed to people affected by rare diseases. I owe my life to them because of the love they give me every day.

To my husband Alberto, my parents Antonietta and Francesco, my parents-in-law Adriano and Marina, and my brothers and sister Giovanni, Fernando, and Franceschina, to their families, and to our nephews, the little ones and the grown-up. I am grateful for their love, understanding, and continuous support and interest toward my work and research, so exciting as well as so challenging. To the worldwide community of patients and their families and to their relentless efforts in order to achieve better health, rights, and dignity.

To my wife Jan Groft and our children. I remain grateful for their continued understanding of the significant unmet needs of patients and families when confronting a rare disease. Their unending support and encouragement sustain our hopes and beliefs of better care and an improved quality of life for the hundreds of millions of patients in the world, along with their families and caregivers who each day renew their commitments to help uncover the mysteries of their known or undiagnosed rare disease.

Acknowledgments

With the second edition of this book, we want to acknowledge the numerous advances that have occurred due to the strength, dedication, sacrifice, and efforts of millions of patients, families, and caregivers throughout the world who are living with rare and undiagnosed diseases. These patients continuously and tirelessly serve as research partners with basic, clinical, and translational research and regulatory scientists in their quest for an accurate diagnosis and treatment for their disorders. We are also very happy to recognize the significant contributions of the biopharmaceutical and medical device industries as partners in our quest for appropriate diagnostics and treatments for rare diseases throughout the world. These are expanding global efforts of the rare diseases community to join forces with the philanthropic foundations and patient advocacy groups who provide daily support and direction for patients, their families, health-care providers, and the public about rare diseases.

Our acknowledgment, admiration, and gratitude go also to all rare disease patients that have passed away but helped health-care providers and researchers gain a better understanding of their diseases. It is the deepening of this knowledge from the lives of these patients that will be translated into a better quality of life and advanced medical care for the millions of patients now living and those to be born with rare diseases and many more who will acquire a rare disease after birth and during their lifespan.

Disclaimer

This book presents independent results, reviews, and scientific opinions. The views expressed are those of the Editors and authors and not necessarily those of their institutions.

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About the Editors

Dr. Manuel Posada de la Paz, Dr. Domenica Taruscio, and Dr. Stephen C. Groft have shared experiences, knowledge, and research resources during 20 years of program and collaborative research efforts. They have participated and led international efforts on patient registries; natural history studies; patient recruitment for clinical trials; bio-specimen repositories; clinical trial design for studies with small patient populations; global research consortia and networks; education and training programs for researchers, health-care providers, and the patient advocacy communities; and expanding the role of the patient and the patient advocacy group as research partners.

The second edition of our text, *Rare Diseases Epidemiology*, is proudly introduced as a research resource for the numerous partners in the rare diseases community. It has been an extremely challenging effort for us, the editors, and the numerous chapter contributors from global collaborators to present the updated information from rapidly changing approaches to orphan product development, rare diseases research activities, and epidemiology methods to reveal the extent of the occurrence of rare diseases around the world. We trust the extensive information provided in the text will prove to be useful to the reader and lead to expanded knowledge about rare diseases and application of knowledge gained to drive policy decisions in both the public and private sectors.

Manuel Posada de la Paz is a specialist in internal medicine and in public health and preventive medicine. He has considerable expertise in areas such as multivariate analyses, medical statistics, and research methodology. In his current position as director of the Institute of Rare Diseases Research (IIER), Institute of Health Carlos III, he leads a broad range of rare diseases activities in Spain in areas such as epidemiological and public health research. Dr. Posada is also the director of the National Rare Diseases Biobank (ISCIII) and the Patient Rare Diseases Registry. Dr. Posada has been assisting as an independent expert of the Commission Expert Group on Rare Diseases (CEGRD), European Commission, and a member of the Advisory Board of the European Platform on Rare Diseases Registration. He is currently the president of the International Conference on Rare Diseases and Orphan Drugs (ICORD).

Domenica Taruscio is the director of the Italian National Center for Rare Diseases at the Italian National Institute of Health and of the National Rare Diseases Registry. She is a specialist in histopathology and carried out postdoctoral studies in human genetics at Yale University (CT, USA) and in bioethics. For decades, her efforts have been mainly directed to face the many and complex challenges posed by rare diseases, and she has addressed them from various facets: from science to society, from experimental research to public health, and from training health professionals to the empowerment of patients and their families – having always at heart the quality of life of rare disease patients and of their families serving in the European Commission as an independent expert in the European Rare Diseases Task Force, European Union Committee of Experts on Rare Diseases (EUCERD), Commission Expert Group on Rare Diseases (CEGRD), Health Research Advisory Group, and European Platform on Rare Diseases Registration; is Italian member of the Committee for Orphan Medicinal Products (COMP) at EMA (2000–2009); and is past president of the International Conference on Rare Diseases and Orphan Drugs (ICORD). Dr. Taruscio has been a member of the Management Board of the European Molecular Genetics Quality Network (EMQN). She has been the scientific coordinator of several national, European Union, and international projects on rare diseases: European Project for Rare Diseases National Plans Development (EUROPLAN), European Platform for Rare Disease Registries (EPIRARE), RARE-Bestpractices, and EU Tender on newborn screening. She is a work package leader in several EU projects such as RD-Connect, Advance-HTA, BURQOL-RD, E-RARE, EUROCAT Joint Action, JARD, and RD-Action. Currently, she is co-chair of the Interdisciplinary Committee of the International Rare Disease Research Consortium (IRDiRC) and scientific co-coordinator of the Undiagnosed Diseases Network International (UDNI).

Stephen C. Groft is currently a senior advisor to the director of the National Center for Advancing Translational Sciences at the NIH, USA. He assisted in establishing the Office of Orphan Products Development at FDA in 1982 and served as the director of NIH's Office of Rare Diseases Research (ORDR) from 1993 to 2014 stimulating rare diseases research and developing information for patients, health-care providers, research investigators, the biopharmaceutical industry, and the public about rare diseases, ongoing and completed research and clinical trials, and patient advocacy groups. Numerous initiatives were established in this role including the establishment of the Genetic and Rare Diseases Information Center, the International Rare Diseases Research Consortium, the International Conference on Rare Diseases and Orphan Drugs, and the Rare Diseases Clinical Research Network. He assisted in the development of the Undiagnosed Diseases Program at NIH and the global Undiagnosed Diseases Network International and developed common data elements for patient registries. ORDR co-sponsored numerous scientific conferences to assist in identifying research priorities and developing research agendas for the investigation of rare diseases.

Part I
Introduction

Chapter 1
Rare Diseases: Joining Mainstream Research and Treatment Based on Reliable Epidemiological Data

Stephen C. Groft and Manuel Posada de la Paz

Abstract Despite growing acceptance of patient registries and natural history studies to provide useful information, the rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of most rare diseases in national and global populations. Likewise, the patients and health care providers lack adequate information on the pathophysiology of rare diseases and expected outcomes of these disorders. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions. To replace many of the perceptions with realities, several global efforts have been implemented to sustain and increase the reported progress with the thousands of rare diseases. The first efforts is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Next, is the continued identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups (PAGs), research investigators, the biopharmaceutical and medical devices industries, and the government research and regulatory agencies for a specific rare disease or group of related diseases. Gaining access to information about rare diseases, patient advocacy groups, ongoing and planned research studies and products in research protocols continue to improve the lives of patients and their families. Many basic, clinical and translational research investigators, public and private sector funding organizations, patient advocacy groups, foundations, and the pharmaceutical, biotechnology, and medical devices industries are committed to translating research discoveries that will be useful in the treatment and care of

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patients with rare diseases over their lifespan. Evidence from well-constructed epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare diseases.

Keywords Rare diseases • Clinical research networks • Epidemiology • Information systems • Patient advocacy groups • Orphan drugs • Orphan products

1.1 Introduction

The rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of rare diseases in the national and global populations to support additional public health measures to address these tremendous needs. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions. Translation of basic research discoveries and information gained from patient registries and natural history studies continues to occur at a relatively rapid rate and is leading to research hypotheses generation in clinical research studies and trials of products for rare diseases. Despite this increased emphasis by the private and public sectors and successful research accomplishments leading to increased regulatory approval for orphan products, approximately 95% of rare diseases lack an adequate intervention. Reluctance to become involved in research and development efforts is frequently attributed to the need for more reliable information about the rare diseases from epidemiological and natural history studies. Significant efforts have been made by the rare diseases community to develop procedures and methods to enable rare diseases to enter mainstream research and provide better information for treatment options.

The majority of rare diseases are inherited conditions but a significant number are acquired through various interactions including the effects of environmental factors. As perceptions are replaced by reliable data and information from the community we can address these needs more appropriately. We know there are an ever increasing number of disorders falling under the term rare disease. The exact number of rare diseases remains unknown. Estimates approaching and exceeding 8000 conditions have been expressed. As sophisticated analytic capabilities continue to improve to identify genetic variability, more and more diseases will be subcategorized into distinct rare disorders and conditions. The proposed International Classification of Diseases -11 from the World Health Organization provides the opportunity to increase the number of Rare Diseases with specific classification codes to approximately 5400 in their nomenclature [2, 31, 32]. Expanded genomic analyses will explain many of the phenotypic differences observed in patients. Frequently, those involved with larger numbers of patients in their practice or in their research protocols recognize the phenotypic expression of a rare disease varies from patient to patient. In many instances, it is the active patient advocacy group leader who

describes the differences in patients. Data from appropriate epidemiologic studies are required to confirm the opinions offered by clinicians, patients, and families.

The discussions that follow address many of the perceptions, barriers and the successful activities responding to these needs. The lack of access to appropriate information to aid in the informed decision making process remains a major barrier to an improved quality of life for patients and their families, and caregivers. High costs of products to treat rare diseases are now viewed as a barrier to ready access to care. When no interventions are available for treatment, most patients and families with rare diseases are extremely happy to have a product available regardless of the costs of the products. They are often reluctant to voice concern about the costs of treatments for rare diseases. Collaborative research efforts involving academic investigators, government research and regulatory scientists, the biopharmaceutical industry and patient advocacy groups are vital in all phases of research for rare diseases.

1.2 Very Few People Have the Rare Condition

One of the first issues a patient encounters at the time of obtaining a diagnosis is the conclusion presented that very few patients are diagnosed with their disease. The response is usually based on the publication of results in very narrowly defined populations from a single or a few studies. Unfortunately, most of the results published do not include a sufficiently large population to draw realistic conclusions about the incidence or prevalence of a particular disorder. Only after an individual or a family becomes aware of the availability of services from a patient advocacy group or a link to a social media group with other families are they convinced there are many others living with the same disease. These patients frequently provide vital information about the symptoms and anticipated outcomes of the disease and how best to live with their condition. The lack of ready access to patient advocacy groups is troubling to many patients who are lacking such representation. These connections help eliminate the stigmatization that frequently occurs, whether they are developmental, psychological or physical expressions of the disease. Stigmatization of children with rare diseases remains a major concern. In recent years, we are seeing a reduction of the problem due to the willingness of the families, patients, or parents to address the disease openly and to educate the public about their disease.

One of the major barriers to removing the stigmatization is the lack of adequate incidence and prevalence data for the thousands of rare diseases. Estimates of between 6% and 8% of the population may experience a rare disease [29]. In the USA, an estimated 25–30 million patients have a rare disease. Estimates from the European Union are even higher of between 27 and 36 million people due to a larger population base. Global estimates have been reported as high as 350 million people with a rare disease. When a multiplier of 3–4 people who are affected significantly by rare diseases including family members or caregivers, the number of people directly affected by rare diseases begins to approach and may even exceed 100 million people in both the USA and the European Union and approximately 1.05 to 1.4 billion people worldwide.

Most rare diseases do not recognize geographical, historical or political borders. However, some diseases may occur more frequently in selected populations or in individual countries. The possible occurrence of different inherited conditions points to the need for families to establish and maintain an extensive family history of the health and illnesses of their family members through multiple generations. In the absence of information from longitudinal or natural history of diseases studies, extensive family history studies and environmental exposure studies may be very good predictors of the occurrence of genetic and acquired disorders until the time when large data sets of information from significantly larger patient cohorts can be mined for more reliable information [10]. One of the confounding issues is the occurrence of co-morbidities affecting patients with rare diseases. This can contribute to the increased difficulty to obtain the correct diagnosis.

If a diagnosis is obtained through genetic testing, whole genome or exome sequencing, it is critical for the individual and the family to receive adequate interpretation of the results and an explanation of the health implications for the individual, related family members, and future generations. Access to genetic counseling services is essential to maintain emotional and psychological well-being of the family members whether affected by the genetic disorder or not. Counseling services should be made available prior to the decision of whether or not to have the diagnostic procedure done and after the results are received regardless of the outcomes. Each individual and family must be considered separately and the resulting decision must be respected by other members of the family and the health care providers.

1.2.1 Precision or Personalized Medicine

Genomic Information and Genomic Medicine is now an integral part of patient recruitment and enrollment in clinical trials and study design. This integration of data has led to the development of compounds with a greater likelihood of success in selected patient populations. In Precision Medicine, it is important to engage in research with each product and patient as an individual. Development of specific clinical endpoints and appropriate bio-markers and companion diagnostics is leading more quickly into the full integration of research and product development. Major pharmaceutical breakthroughs continue to facilitate the development of precision medicine products for the care of individuals with rare diseases and conditions. NIH has provided significant resources to develop research partnerships and infrastructure to implement a Precision Medicine Initiative (PMI) emphasized by former USA President Barack Obama [1, 20]. Funds have been provided for cohort projects and to include a Data and Research Support Center to gain access and help organize access to information from more than 1 million Americans. There will also be a Participant Technologies Center to support enrollment of patients in the study. Current product approvals such as for Vertex's Lumacaftor and Ivacaftor suggest the level of specificity of products for patient populations with specific genetic variability. With the sophistication of information presented to patients, a greater

understanding of the principles behind genetics and genomics and precision medicine will require a greater public education effort to increase science and health literacy in the global populations [27].

1.2.2 International Classification of Diseases

One of the persistent requests from the rare disease community has been the need for appropriate classification of rare diseases in standard diagnostic coding resources. Having this information readily available is a key to many of the uncertainties related to an absence of reliable prevalence data. These codes are available and utilized by the health care providers and are essential for reimbursement from third-party payers and national governments after establishing medical necessity. A Rare Diseases Technical Advisory Group for the World Health Organization's (WHO) efforts assisted in the revision of the International Classification of Diseases (ICD). Obtaining an appropriate ICD classification and coding will assist in determining the prevalence of rare diseases. Adopting these codes and integrating them into medical records system will increase the ability to obtain useful data from summary information in patient records and particularly from those using an electronic health record format. Adequately designed natural history studies of rare diseases should also benefit from the improvements to be offered in coding revisions. However, the difficulty of obtaining the correct diagnosis may require several years of visits to practitioners, clinics, and hospitals. In many cases, coding of symptoms of a disease may continue until an agreed upon diagnosis is obtained. At the time of obtaining the correct diagnosis, clinicians need to have a diagnostic code to address the uniqueness of individual patients. The assignment of an appropriate code for rare diseases is also crucial if we are to monitor global health trends by the use of reliable statistical data as mentioned previously. As mentioned previously, a Beta version of ICD – 11 is available for public review and comment at the website of the WHO.

1.3 Gaining Access to Available Information About the Rare Disease or Condition

With ready access to the Internet and World Wide Web and social media connections, patients and their families now have ready access to the extensive collection of information available from numerous sources including disease-specific PAGs. Even though there are significant sources of educational materials available to most people in the developed nations, lack of ready access to these resources remains a major need for millions of individuals and families in the developing nations around the world. Developing methods to convey the increased body of knowledge available from groups around the world is a key to increasing access to the

ever-increasing, reliable and useful information developed by numerous sources. These sources include the National Institutes of Health, the National Library of Medicine, the Office of Rare Diseases Research, the Genetic Alliance, Global Genes, the National Organization for Rare Disorders (NORD), Eurordis, Orphanet, Office of Orphan Products Development (OOPD) at the United States Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMEA), patient organizations, industry, foundations, health care provider organizations, and other government sources.

Extensive use of data sources is sought by the public MEDLINE/PubMed. The NLM's database recorded almost a 2.8 billion searches in FY 2015. On an average day in April 2015, approximately 3.5 million searches were performed on the PubMed Web site. (9) [14] An additional 5.2 million searches were done by scripts, e.g., by application programming interfaces (APIs).The NLM indexes 5618 biomedical journals for the MEDLINE/PubMed database to assist users in identifying articles on specific biomedical topics. A combination of staff, contractors, and cooperating USA and international institutions indexed 806,000 articles in FY2015, bringing the total number of MEDLINE citations to over 22 million. A growing number of Medline citations contain an active link to the free full text articles contained in Pub Med Central or other sites such as the publisher of the articles. Many of these articles may be freely available depending upon the publisher's access requirements. Considerable information on rare diseases is readily available to those with access to the world-wide-web from the Genetic and Rare Diseases Information Center and Orphanet [8, 23].

The most recent figures from the Genetic and Rare Diseases Information Center supported by the ORDR/NCATS and NHGRI reveal that information has been made available for over 6800 rare and genetic diseases to requests from 120 countries in their 14 year history. Orphanet, located in France's INSERM, continues to provide useful and reliable information to the European Union member states and worldwide from multiple sources for over 5600 different rare diseases. Recently, GARD and Orphanet announced plans to share information gathered from their resources to increase the amount of information readily available from their websites [3].

New sources of useful information appear regularly from help-lines established by individual countries and organizations to supplement currently available information. Traditional sources of information continue to expand their information base as improved search engines enable the identification and collection of more information from many sources and presented in a more systematic fashion to potential users. For some rare diseases, it is not a lack of information, but information overload that can be overwhelming to patients and their families. It is important with multiple sources presenting information to the patients or their families to remain aware that not all patients are capable of accepting and absorbing the same amount of information and at the same pace as others. Facilitating or guaranteeing access to useful information is a major step to assist and to enable patients to understand their disease better, to live with their disease, and to learn about the numerous aspects of their disease on their time schedule. When accomplished on each indi-

vidual's own schedule, it is expected to improve the understanding and acceptance of the disease with or without available treatments.

Types of information generally recognized as significant for patients and health care providers are available from numerous other sources such as academic centers, patient advocacy groups and foundations, the biopharmaceutical industry, health care providers, and information services, hotline and social media resources with individual and group interactions. Lack of ready access to information frequently leads to other misunderstanding about the disease and anticipated outcomes. The information falls into several major categories and include but are not limited to information about the disease, expected cause of the disease, prognosis, inheritance potential, available treatments approved by regulatory agencies or products in investigational status, and ongoing or planned research studies. As more clinical trials and natural history studies are completed, results from completed studies presenting both positive and negative results in understandable terms to patients and families are helpful. Gaining access to knowledgeable health care providers or specialty clinics is essential, Availability of links to patient advocacy groups and social media organizations provide real life or real world experiences with a rare disease are beneficial to patients and families and treating physicians and other health care providers. Results from Phase 4 or post marketing surveillance studies conducted by biopharmaceutical industry sources are required more frequently by regulatory agencies as part of the regulatory approval of products prior to entering the marketplace. This information is extremely useful to monitor safety and efficacy in larger patient populations.

1.4 Generating Research Interest

Because there are so many disorders under the rare diseases umbrella, it is frequently suggested there is little research interest in a particular disease. For most of the rare diseases there continues to be a major need for increased research emphasis in both the public and private sectors. However, we are observing shifts in emphasis in research portfolios to include a focus on rare diseases and orphan products. We continue to see a growing global emphasis on research of rare diseases. For example, the ClinicalTrials.gov database, developed and made available by the NIH National Library of Medicine and the US Food and Drug Administration, presents information on approximately 234,500 planned, ongoing and completed studies for rare and common diseases reported from more than 195 countries throughout the world [15]. This database highlights completed, planned and ongoing interventional phase 1, 2, 3, 4 of drugs, biologicals and devices, surgical procedures, observational, longitudinal, behavioral, and expanded access studies. In September 2016, results from completed studies receiving support from the USA government and the pharmaceutical industry are required to be provided in a timely fashion to ClinicalTrials.gov after the completion of the clinical studies. In an effort to make information about clinical trials widely available to the public, the U.S. Department

of Health and Human Services (DHHS) issued a final rule that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug Administration-regulated drug, biological and device products. The NIH issued a complementary policy for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded trials, including those not subject to the final rule. Requirements under the final rule apply to most interventional studies of drug, biological and device products that are regulated by the FDA. The requirements do not apply to phase 1 trials of drug and biological products, or small feasibility studies of device products. The final rule specifies how and when information collected in a clinical trial must be submitted to ClinicalTrials.gov. It does not dictate how clinical trials should be designed or conducted, or what data must be collected [19, 25].

1.4.1 Access to Research Funding Sources

Evidence exists that the research community will investigate special groups of rare diseases if priority is given by funding agencies. Research efforts have been known to follow research funds. As an example, 10 research consortia requiring multiple research sites and investigators received funds from five research NIH Institutes when the Rare Diseases Clinical Research Network was first funded in 2003. In 2016, 22 consortia received support from the ORDR and ten of the research institutes of NIH (NCATS, NINDS, NIAID, NICHD, NIDDK, NIDCR, NIAMS, NEI, NIDCR and NHLBI and the Office of Dietary Supplements) [18].

The European Union (EU) through their Framework Programs 6 and 7 and through the General Directorate of Health and Consumers (DG SANCO) funded different types of networks such as fundamental research consortia, European Reference Networks (ERN), surveillance networks, and translational networks. Member States of the EU have also funded at national level several consortia on rare diseases. It is important to mention the interesting experience of E-RARE action, a consortium of international European, Australian and USA agencies for funding rare diseases projects. E-RARE has funded in their two previous calls for proposals in 2007 and 2009 13 and 16 different rare diseases consortia respectively. The current emphasis is on the repurposing of existing products for rare diseases. The significance of the benefit offered by multi-institutional collaborative efforts and an expanded role of the patient advocacy groups has gained acceptance as a model for research of rare diseases. This is a desirable method to gain access to a critical mass of research investigators and patients. Many investigators and organizations are working to direct their efforts to establishing common protocols which ultimately increase the scientific understanding of the disease and the pathophysiology of specific diseases and molecular pathways of many other disorders. It is anticipated that the future expansion of these consortia and networks will compare favorably to the

sophisticated research and treatment networks developed in oncology and infectious diseases, and other more common diseases such as arthritis, diabetes, HIV/AIDS, and hypertension.

1.4.2 Identifying Rare Diseases Research and Orphan Product Development Projects

NIH provides ready access to a coded and monitoring system for selected rare diseases and orphan drugs. The Research, Conditions, and Disease Categorization (RCDC) system can now be easily found [17]. This system provides ready access to information on basic and clinical research projects receiving support from NIH, FDA, HRSA and CDC. This information is often the starting point to developing a systematic research agenda by identifying ongoing research projects and helps individuals and organizations identify the missing gaps in research. In 2015, NIH provided funding resources for numerous research projects research on rare diseases and conditions

- Rare Diseases ~ 9400 Research Projects ($3.639 Billion USD)
- Orphan Drugs ~ 1650 Research Projects ($785 Million USD)
- Gene Therapy ~ 615 Research Projects ($238 Million USD)
- Stem Cell ~ 3900 Research Projects ($1.429 Billion USD)
- Regenerative Medicine ~ 2500 Research Projects ($862 Million USD)

The NIH Clinical Center Hospital (CCH) also provides considerable resources and support for rare diseases research through the Intramural Research Programs of the 17 research Institutes and Centers (ICs)

- Number of Rare Diseases Under Investigation – 568
- Number of Active Rare Diseases Protocols and Total Study Protocols – 799/1630
- Number of NIH Investigators with Rare Diseases Focus – 315/495
- Patients with Rare Diseases in Studies at NIH – 15,653 (65% of all CCH Patients)

One observation from the experience gained with the focus on rare diseases is the relative lack of information from natural history studies of diseases to provide a better understanding of the disease across the lifespan. Knowledge from these studies is essential for the development or research hypotheses, identification of potential biomarkers, and phenotypic variations in patients. Due to the high costs of initiating and maintaining studies for many years, there has been a reluctance to support these studies. Only in recent years has the value of these studies been accepted by the research and regulatory communities as a generator of new research hypotheses and information for research and treatment for rare diseases. The FDA now considers adequately developed and implemented Natural History Studies with appropriate analysis and interpretation of study results to be one of the most essential steps in

generating information about clinical endpoints or to identify appropriate biomarkers to be developed and validated prior to initiating a clinical trial [24].

Frequently, research of rare and common cancers leads to the development of novel approaches to clinical trial design, patient recruitment, and analyses of results for both common and rare diseases. Rare diseases research benefits from these innovative approaches as they are adapted and adopted by the research community. Rare tumors like most rare diseases provide significant financial, physical, and emotional disease burden and present unique challenges in the research and development of potential interventions. Increased knowledge of the pathophysiology at the molecular level from basic research studies leads to potential new therapeutic treatments. Newer clinical trial designs such as BASKET or umbrella trials are leading to the evaluation of multiple potential agents in one trial or multiple different but molecularly-related disorders in trials of single agents or a combination of potential treatments. There are similarities in the requirements for the evaluation of oncology therapies and in the investigation of products for rare diseases that need to be explored, considered and implemented when appropriate [5].

1.5 Limited Access to Treatments for Rare Diseases

Even with the significant emphasis placed on rare diseases research and orphan products development by national governments, drug, biological and medical devices industries and foundations, adequate treatments for approximately 95% of rare diseases do not exist. Approximately 4045 Orphan Product Designations have been made by USA FDA since 1983 with 595 approved orphan product designations made during the same period. In recent years, an increase in orphan product designations and approvals in the USA and European Union have been noticed. There were 39 approvals in 2016 and 48 approvals in 2015. This is quite different from the two approvals in 1983, the first effective year of the Orphan Drug Act in the USA. The Pharmaceutical Research and Manufacturers of America (PhRMA) reported approximately 560 Compounds in Development for Rare Diseases and 836 Compounds and Vaccines in Clinical Trials for Common and Rare Cancers. The increase in approved products is likely to continue. There were 333 designations provided in 2016 and 354 designations in 2015 Again, this contrasts dramatically with the 26 designations provided in 1983. This lack of treatment can be traced to numerous causes including high costs of research and development, the high risk of failure of most potential compounds to reach the marketplace, the large number of diseases, small patient populations for many rare diseases, better return on investment with other projects and different regulatory requirements around the world. More recent evidence from data points to a different landscape for products for rare diseases. Nearly one-third of products approved for rare diseases have annual sales greater than $1 Billion USD [6, 12, 21, 22].

In recent years, FDA and EMA have initiated novel review programs to expedite review of New Drug Applications (NDA) and Biological License (Applications

Table 1.1 Expedited programs for serious conditions – drugs and biologics (2015 = 21/45 novel drugs approved or 47% for rare diseases)

Program	Qualifying criteria: Serious condition and…	Features
Fast track (14/45 = 31%)	Nonclinical or clinical data demonstrate potential to meet an unmet medical need	Actions to expedite development and review
		E.g., meetings
	Or, QIDP (qualifying infectious disease product)	Rolling review
Breakthrough therapy (10/45 = 22%) (EU PRIority MEdicine (PRIME)	Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinical significant endpoint over available therapies	All Fast Track features
		Intensive guidance on efficient drug development
		Organizational commitment
Accelerated approval (6/45 = 13%) (EU Conditional marketing approval)	Provides meaningful advantage over available therapies	Approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit
	Demonstrates effect on surrogate or clinical endpoint that can be measured earlier than IMM (irreversible morbidity or mortality)	
Priority review (24/45 = 53%) (EU Accelerated Assessment)	Would provide a significant improvement in safety or effectiveness	Shorter review clock goal for marketing applications (6 months vs. 10 months)
	Or, other qualifying programs	
	(*27/45 = 60% Used Expedited Programs)	

(BLA). Separate programs in the USA FDA and the EMA such as Fast Track, Breakthrough Therapy (EU Priority Medicine or PRIME) Designation, Accelerated Approval (EU Conditional Marketing Approval), and Priority Review Status (EU Accelerated Assessment). Table 1.1 provides highlights of the emphasis placed on the expedited regulatory review and approval processes. These programs have increased efficiency of drug development and regulatory review approaches for serious conditions, including rare diseases and rare cancers.

1.5.1 Repurposing Drugs: Gaining Access to Treatments and Investigational Products for Rare Diseases

The rare disease community still experiences some difficulty in gaining access to possible treatments through the development of new chemical entities. Other potential compounds could be identified by a global coordinated and systematic approach to the repurposing or repositioning of products approved for other rare or common conditions that might be useful for different rare diseases and conditions. To expand existing regulatory product approval processes, it would be necessary to develop

research and regulatory pathways to identify potential new uses from astute clinical observations and a systematic review of the published literature. Information on potential uses of products other than approved products may be gathered from well-constructed patient registries and Natural History Studies and even data gathered from PAGs and social media interactions of patients and families. Clinical trials may follow if clinical improvements are noticed in patients. Adopting this approach will require expanded efforts of the traditional pharmaceutical industry research and development activities. This process will also require a much broader approach to identify potential new uses for products other than existing indications for marketed products or products of little commercial interest. The magnitude of this approach for over 8000 rare diseases requires a globalization of efforts.

Repurposing of approved products and those previously included in clinical trials could entail a collaborative pooling of research and development assets with a sharing of research results and possible sharing of benefits to a number of potential commercial sponsors in emerging niche markets for specific rare diseases. In some respect this activity requires a re-visiting to the origins of the USA Orphan Drug Act looking at drugs of limited commercial value for the prevention, diagnosis and treatment of rare diseases and conditions not from a perspective of the 1970s but of the capabilities offered in the twenty-first century. These efforts could be assisted by more robust and powerful tools from information technology advances in searching large datasets over a very short time periods to determine potential uses from larger patient population samples. These processes would also be assisted by gaining access to chemical libraries and compounds not under development or not of further interest to the members of the biopharmaceutical industry. The transfer of compounds between the inventor and a company or between two companies is dependent upon successful completion of negotiations related to intellectual property and liability issues. This approach frequently requires an analysis of the current status of the compound and the completion of the necessary studies that will meet the requirements of the regulatory agencies. Absence of information for regulatory approval will be identified as noticeable gaps of required data. To fill these gaps, collaborative efforts require expanded utilization of resources from the public and private sectors.

The estimated costs of developing new indications for the 2nd and 3rd indications would be expected to drop dramatically from the costs of developing a new molecular entity for the first approved indication. Current estimates suggest costs for developing a new molecular entity exceed $1.2 Billion USD.

1.5.2 Recruiting for Clinical Trials and Managed Access Programs

About 1.7 million people participate in 80,000 drug company-sponsored clinical trials each year. It remains an extremely difficult task to recruit and retain an adequate number of study participants to meet the needs of opening and completing the

clinical trial in a timely fashion and within the proposed budget [28]. Increasingly, patient advocacy groups and social media groups are contributing to recruitment of patients into clinical trials. Meeting recruiting goals for all clinical studies is essential if we want to draw accurate conclusions from the clinical studies and if we want to make progress in the diagnosis, prevention, and treatment of rare diseases. Changes in clinical trial design such as a crossover design have improved the likelihood of obtaining active treatment for all patients during the clinical trial. Other trials have increased the ratio of patients expected to receive the investigational intervention.

The biopharmaceutical industry has maintained an emphasis on providing individual patient access to approved interventions when they are unable to pay for the treatments. Managed Access Programs include many different programs from different pharmaceutical companies and may be recognized with terms such as Named Patient, Compassionate Use, Early Access, Expanded Access and Pre-Approval Access programs. They may be defined differently in various countries but are generally for products not commercially available or approved by regulatory agencies. These programs enable the collection of Real World Data from a wider pool of patients who may or may not be included in a clinical trial. There are indications that regulatory agencies will utilize Real World data to assist in regulatory decision-making actions in the future [11].

1.6 Gaining Access to Experienced Rare Diseases Clinicians for Diagnosis and Care

Obtaining the diagnosis is not an easy task and often represents the first frustration encountered by patients and their families. Until a diagnosis is obtained, patients will continue to face barriers to obtain adequate information and treatments for their rare disease. The appropriate diagnosis of a particular rare disease may result after numerous visits to specialists at multiple locations. The difficulty in obtaining the correct diagnosis in the presence of co-morbidities is particularly challenging. For many patients ending the diagnostic odyssey is an accomplishment and relief to finally have a name for the constellation of symptoms that frequently leads to a separation and isolation from the traditional medical care systems. In a survey of patients with a rare disease, reported by the USA National Commission on Orphan Diseases (NCOD), 15% of patients indicated it took more than 5 years to obtain the correct diagnosis. The NCOD patient study results also indicated that gaining access to appropriate care can be very difficult to obtain and adequate information and clinical expertise is often insufficient to meet the unmet needs of patients and their families [16].

Eurordis reported in 2006, the results of a survey of diagnostic delays for patients with eight diseases in 17 European countries (Crohn's Disease, Cystic Fibrosis, Duchenne Muscular Dystrophy, Ehlers-Danlos Syndrome, Marfan Syndrome, Prader-Willi Syndrome, Tuberous Sclerosis and Fragile X Syndrome) [7]. Between 5 and 30 years had elapsed between the appearances of the first symptom to obtain-

ing the correct diagnosis for 25% of the patients. 25% of the respondents traveled to a location outside of their home region to obtain the confirmatory diagnosis. A review of inquiries completed by the Genetic and Rare Diseases Information Center supported by the USA ORDR and NHGRI at NIH discovered 6% of inquires related to undiagnosed diseases.

1.6.1 Undiagnosed Diseases

The Undiagnosed Disease Program (UDP) was initiated at the National Institutes of Health (NIH) through a partnership consisting of the National Human Genome Institute (NHGRI), the Clinical Center (CC) Hospital, the Office of Rare Diseases Research (ORDR) and other NIH Institutes and Centers (ICs). Since that time, with funds provided by the NIH Common Fund, the UDP has expanded considerably and now includes the Undiagnosed Diseases Network and Undiagnosed Diseases Network International. These programs are now contributing their coordinated efforts to gather considerable information from the many organizations attempting to obtain the diagnosis for rare and common diseases [9, 13, 30].

After a diagnosis is obtained, patients and their families continue to search for specific information about their diseases. The quest for information about the cause, expected outcome, heritability, possible future manifestations, the availability of an investigational or approved treatments, learning how to live, cope and manage the condition over their lifespan is an important goal in the pursuit of optima care., Information on planned, ongoing, and completed research studies is considered essential. Recommendations from review committees in the USA and Europe have indicated the need to identify knowledgeable clinicians and locations of research and treatment centers with expertise in their disease.

1.7 Reference Centers of Excellence for Rare Diseases

In the European Union, with approval by the High Level Group on Health Services and Care, the European Rare Diseases Task Force has defined general criteria for Reference Centers of Excellence for Rare Diseases. DGSANCO designates reference centers for rare diseases. Identifying these centers should increase public awareness of possible centers of treatment and research excellence. Many research centers have transformed into treatment centers of excellence as information is gained from research and translated into clinical care as a result of having access to relatively large patient populations. Research or treatment centers of excellence frequently are considered regional or even national referral centers. Many centers of excellence provide active genetic counseling services to help educate the patient, their families, and public and health professionals about the rare diseases in their center. These research centers of excellence frequently serve as the optimal training

program for the new rare disease research investigator [4, 26]. The European Commission recently announced plans for the 24 European Reference Networks (ERNs) approved by The Commission in late December 2016. Through these networks, over 370 hospitals and nearly 1000 rare disease centers of expertise will be linked, connecting thousands of experts, researchers and doctors, across 25 EU Member States.

Resistance to the identification of reference centers of excellence is often heard due to concerns of appearances of inclusion or exclusion of one institution over another. This lack of access may impede gaining access to optimal care for many patients with rare diseases by not making information readily available to the patients in need of specialized treatments. There is recognition that due to current limitations on treatments, cures for most diseases are difficult to obtain. For many disorders, the staffs at these centers have assisted in the development of better care through a team approach to address all of the symptoms resulting from a multi-systemic disease treatments and an improvement in the quality of care of symptoms and the quality of life of patients. The patient advocacy groups have played a major role in improving the care of patients with rare diseases as well as educating health care providers about optimal care of patients. Frequently, the patient advocacy groups, utilizing their experiences with patients and health care providers, are able to identify the most skillful and knowledgeable clinicians who are able to provide the best services for their patient community. Developing and providing this information to the rare diseases community indicates the need for increased collaboration of patient advocacy groups, clinicians, and research investigators on a global basis. A major deficiency exists in identifying and addressing the needs of the many patients who do not receive benefits from the support of an organized patient advocacy effort for their diseases. Likewise, in developing nations, it has been suggested to provide centers of expertise at tertiary medical centers in each country to expand the knowledgebase for rare diseases and provide more ready access to expertise with rare diseases.

1.8 Training of Rare Diseases Research Investigators

To address the needs of training the next generation of research investigators, traditional research and training funding mechanisms from government and industry are used to foster the development of young investigators deciding on career choices or experienced clinicians who are seeking a career change. Continued emphasis on the value of research emphasis on rare diseases needs to be provided to pre-doctoral students, postdoctoral trainees and physician scientists.

Many patient advocacy organizations have found that a useful mechanism to initiate or expand research interest in their disease is to support research fellows who are seeking funds to support their continued research training or initiation of pilot projects. After receiving funding support, sufficient data can be gathered from pilot studies and proof-of-concept studies to support a grant application for an expanded research project that requires considerably more funds and more stable

funding. Generating interest with a particular disease can lead to a very rewarding career as new information is discovered and shared with others.

Consortia in the Rare Diseases Clinical Research Network supported by the ORDR/NCATS and other research ICs at NIH are required to have an active clinical research training component for new and usually younger investigators. In several of the research consortia the trainees have completed their research fellowships, moved to a different academic institution, and opened a new research site as part of the consortia.

The individual consortia are expected to offer a unique environment for clinical research in rare diseases for new investigators, post-doctoral or clinical fellows, junior faculty or established scientist investigators to re-direct their research careers to emphasize rare diseases research. Support from the academic institution or other outside organizations is allowed. The consortia are required to have two trainees in these positions at all times during the grant period. It is possible after the training period has been completed, the new rare diseases clinical research investigator assumes a position at a different institution and can join the consortia as a new research site as part of the anticipated expansion of the individual consortia. As mentioned previously, this has occurred and is an expected outcome of the research plan.

1.9 Conclusions

To establish realistic goals for the rare diseases community, numerous global efforts are required to sustain and increase the existing progress with the thousands of rare diseases.

The first is the identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups (PAGs) for individual rare diseases and umbrella organizations representing numerous PAGs such as NORD, Eurordis, Genetic Alliance, Global Genes, Faster Cures, New Zealand Organization for Rare Disorders, IORD and ORDI in India, Korean Organization for Rare Diseases, Japan Patients' Association and ASrid (Japan), Rare Voices Australia, Taiwan Foundation for Rare Disorders, China Organization for Rare Diseases, Canadian Organization for Rare Disorders, the Geiser Foundation, Rare Africa and many others. Improving communication among the PAGs will also eliminate the feelings of isolation, loneliness or stigmatization that are reported by patients around the world. Knowing there are others with the same condition and connecting these individuals regardless of language barriers is often helpful to learn to live with a rare disease and maximize the quality of the life of the individual and their families and friends.

The next requirement is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Several rare diseases organizations have discovered the value of encouraging these global interactions such as the Treat-NMD Network, Prader-Willi Syndrome Association and Progeria Research Foundation.

Many excellent research teams exist in individual countries. Expansion into global research networks will improve recruitment of patients into studies and increase the number of patients in research studies. The end result is increased access for all patients to clinical trials and the facilitation of the speedy completion of clinical trials. Partnering for Cures, Re(ACT), and organizations such as IRDiRC and ICORD are committed to expanding global and integrated research infrastructures and tools needed to meet the research needs of the rare diseases community. Activities such as those recently announced by NCATS and the Office of Rare Diseases Research such as the development of the Biomedical Translator and the Tool Kit with an emphasis on research tools are keys to future advances through research.

To provide easy access to useful and reliable information for patients, families, health care providers and the public is the goal of many government and non-government organizations. The development and dissemination of information through information centers, help lines, clearinghouses, government organizations, individual PAG, multi-disease organizations and the industry is a costly, but very helpful, process in terms of time, personnel and financial support. Excellent sources are readily available and provide information on a regular and updated basis in numerous countries. To avoid duplication of effort, organizations are encouraged to seek these sources of information and determine the usefulness of available information for their constituent members and then identify and fill in the missing gaps of information for their constituents. It is desirable to have the consolidation of information sources to ease the burden of the rare diseases community in their pursuit of information about their diseases.

Gaining access to research investigational studies frequently leads to an improvement in the quality of care available to patients from knowledge and experiences gained by the clinic staff treating many patients with rare diseases in the study. Improving communication and exchanging best practices information available between a referring physician and a rare disease specialist will increase the spread of best-care information to the local treatment facility or practitioner. It will also increase the likelihood of patients gaining access to approved treatments more quickly after approval by regulatory agencies.

For many rare diseases, the distinction between research and clinical care is very narrow and there is not always a bright line separating the two. The most novel treatments and most recent information from coordinated care efforts provided by health care teams from multiple countries and multiple medical and clinical specialties may be gained from research studies as part of the clinical care of larger populations of patients participating in clinical trials of rare diseases.

Providing ready access to the information about rare diseases practitioners knowledgeable about a particular rare disease, ongoing or planned research projects will help the patients, their families and practitioners gain a better understanding of their disease. By removing the existing misperceptions, patients and their families can adopt a realistic approach to the treatment of a rare disease that is based on the hope that others do care about their disease. Many scientists, government, private sector, and patient organizations, foundations and the pharmaceutical, biotechnology, and medical devise industries are committed to research discoveries that will

be useful in the care of patients with rare diseases over their lifespan. Evidence from well-constructed epidemiological studies will measure disease frequencies, distribution, and changes over time by identifying those affected, their location, when the diseases occur, and causes. They also will help to identify interventions that might affect outcomes and improve quality of life. Epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare disease. Perhaps our long–term goal should be incorporation of rare diseases into the mainstream of all research and development activities and not require a special emphasis to meet individual disease needs.

The future presents considerable optimism for the rare diseases community. At the heart of this optimism is data and information gathered from well-constructed patient registries, and natural history studies generating research hypotheses to be tested in clinical trials, and the continued emphasis on rare diseases research and orphan products development utilizing appropriate statistical methods and data analysis of results. Contributing to a better understanding of individual rare diseases from epidemiological studies will require collaborative efforts of all individuals and organizations involved in the public and private sectors.

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Part II
Rare Diseases Diagnosis

Chapter 2
Undiagnosed Diseases: Italy-US Collaboration and International Efforts to Tackle Rare and Common Diseases Lacking a Diagnosis

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Abstract Rare diseases (RD), according to European Union criteria, affect 5 per 10,000 persons, or 30 million people, in the EU; in the USA, RD are defined as conditions that affect fewer than 200,000 individuals in the population (320 million). Most known rare disorders are severe and chronic, with many being degenerative and life threatening. There are roughly 5000–8000 rare diseases (European Commission, DG Health and Food Safety, Public Health, Rare Diseases, Policy. http://ec.europa.eu/health/rare_diseases/policy/index_en.htm. Accessed 19 December 2016; NORD-The National Organization for Rare Diseases: https://rare-diseases.org/). Patient populations for individual RD are small and scattered; international collaborations are crucial to pool resources fragmented across individual countries for better diagnosis and treatment. Undiagnosed RD (URD) are condi-

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tions that elude diagnosis; some patients wait years for a definitive diagnosis. URD may include groups of unnamed disorders with common characteristics, phenotypically well described diseases, diseases with an unknown molecular basis, or those due to unknown, non-genetic factors.

The US NIH Undiagnosed Diseases Program arose in 2008 to provide a diagnosis for individuals who had long sought one without success; in 2013 a nationwide Undiagnosed Diseases Network was established in the United States. In 2015, the Undiagnosed Disease Network International (UDNI) was established and includes US, Australia, Canada, Japan, Italy and other European countries. Other national initiatives have also been undertaken and are in progress all over the world.

Keywords Undiagnosed diseases • Networks • Programs • Initiatives • Platforms • Databases

2.1 UDN Initiatives in the US

In 2008 The National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP) was launched to address an unmet need in the US health care system, i.e., the diagnosis of mysterious, often multisystem diseases [17]. A prime mover in initiating the program was the recognition by the NIH Office of Rare Diseases Research that it took 1–5 years to reach a proper diagnosis for 33% of patients with rare disorders and more than 5 years for 15% of these patients. Moreover, at least 6% of the inquiries to the Genetic and Rare Diseases Information Center were from individuals still seeking a diagnosis. A second critical motivation for establishing the program was to discover new diseases that would provide medically relevant insights into biochemistry, physiology, and cell biology.

Individuals whose conditions have eluded medical diagnoses may apply to become UDP participants and, if accepted, are admitted to the NIH Clinical Center in Bethesda, MD. Applications to the UDP require a summary letter from the referring clinician and complete medical records, including imaging and histologic slides of biopsy material. This material is reviewed by 1–5 consultants representing 25 different specialties, who offer opinions on the applicant's suitability for admission. Accepted patients undergo a week of diagnostic tests, and expert consultations are provided for free. The patient is examined by a multidisciplinary medical team with a deep knowledge base in the fields of both rare and common diseases. The team, drawn from various NIH institutes and centers, studies a patient's clinical and laboratory results for diagnostic clues while the patient is in the Clinical Center and in the weeks and months following their visit.

The UDP offers patients the hope of a diagnosis and the possibility of therapeutic strategies. In return, patients provide UDP researchers the opportunity to gain new insights into genetic and biochemical mechanisms of disease and into normal cell biology, biochemistry and physiology. So far, UDP researchers have encountered

patients with uncommon presentations of known disorders, multi-systemic complex disorders and new disorders that have never before been diagnosed.

UDP clinical researchers are using advances in DNA sequencing to detect defects in genes that point to known disorders. These tools offer the potential for discoveries about the role of molecular and biochemical events that can cause disease and, eventually, the development of diagnostic and therapeutic approaches for rare and common diseases [12, 13].

The caseload of the UDP is steadily growing, with more than 100 pediatric and adult patients added each year. In the period between May 2008 and May 2014 there were 9300 inquiries, 3100 applications, 750 acceptances, 700 patients seen or scheduled with an annual patient visit rate of 130. Between 25 and 50% of cases were resolved with a either a clinical, molecular or biochemical diagnosis; approximately 25% of cases were closed with no diagnosis.

Of the total number of cases applying to this program, approximately 30% were invited to proceed in the study following careful review by the program's medical team. In general, it takes 8–12 weeks for the UDP to evaluate an application, and the waiting list for admission is 2–6 months.

Diagnostic investigations include specialized, commercially available tests focused on candidate diagnoses, as well as generic studies using next-generation genetic analyses, e.g., single-nucleotide polymorphism arrays and whole-exome sequencing. UDP participants may receive consultation regarding their treatment after their evaluation, but treatment is usually not provided as a component of the program. The treatment recommendations that NIH clinicians may offer remain the responsibility of the patient and the referring clinician.

In 2013 the Common Fund of the US NIH supported a nationwide Undiagnosed Diseases Network (UDN) that was established in order to bring together clinical and research experts in centers located throughout the United States to solve the most challenging medical mysteries using advanced technologies. The aim is both help individual patients and families and to contribute to the understanding of how the human body works. The UDN is made up of a Coordinating Center, Clinical Sites, and Core Facilities. The Coordinating Center, which coordinates the work of the UDN and manages the Network's database, is loacated in the Department of Biomedical Informatics at Harvard Medical School [18].

The Clinical Sites, where UDN participants are evaluated, are at the Baylor College of Medicine, Duke Medicine, Harvard Teaching Hospitals (Brigham and Women's Hospital, Boston Children's Hospital, Massachusetts General Hospital), the National Institutes of Health (NIH) Clinical Center, Stanford Medical Center, University of California at Los Angeles Medical Center, and Vanderbilt University Medical Center. The two Sequencing Cores, where genetic testing for the UDN is performed, are at the Baylor College of Medicine and HudsonAlpha with Illumina.

The UDN Metabolomics Core offers a comprehensive array of analyses, including quantitative targeted and untargeted measurements, as well as structural determination of novel metabolites, which can be combined to generate a unique

molecular profile for each patient being evaluated. In addition, the metabolomics core works closely with the UDN Clinical Sites to integrate metabolomic and genomic data with clinical signs and symptoms, in order to generate hypotheses regarding pathophysiology that can be translated into specific clues regarding the etiology of the undiagnosed disorders being evaluated. It will provide the UDN with advanced tools to study biological markers that might be related to disease. The Model Organisms Screening Center helps the network to understand how specific genetic changes might contribute to disease by studying those changes in *drosophila* and zebrafish [18].

2.2 UDP Initiatives in Europe: Austria, Bulgaria, Hungary, Sweden, Spain, Italy

2.2.1 Austria

In Austria, the Ministry of Health has formed the National coordination point for rare diseases (NKSE) to propose a national strategy for the best possible diagnostics and treatment of rare diseases. The strategy consists of creating a communication network of local clinicians, regional healthcare institutions and national clinical centers, to provide efficient infrastructure to investigate rare diseases. Within the network, the Vienna Center for Rare and Undiagnosed Diseases (CeRUD) [24] acts as an operative "Best point of Service" for rare and undiagnosed diseases by providing information not only to the affected individuals and families, but also to the general practitioners, clinicians, and coordinating medical professionals with adequate expertise.

The CeRUD was established in 2014 to pool resources and competencies and to provide affected individuals with the best possible interdisciplinary diagnostic analysis and care. This includes clinical care involving many disciplines represented on the campus of the General Hospital Vienna and the Medical University Vienna. At the same time, CeRUD is involved in various internationally competitive research activities to promote the development of new strategies for diagnosis and treatment of these diseases. The main goals of CeRUD are to: (a) provide interdisciplinary translational research for development of innovative diagnostic tools and improve therapy options while optimizing cost efficiency; (b) develop interdisciplinary diagnostics by connecting required expertise tailored to the specific case; (c) increase the number of healthy years of life and reduce secondary damage to patients; (d) perform research into novel diagnostic tools and therapies.

On February 2016, the 1st Symposium of the Vienna Center for Rare and Undiagnosed Diseases was held in a joint session together with the 3rd International Rare and Undiagnosed Diseases Meeting. Several aspects of rare diseases were covered, from diagnostic options, molecular disease characterization, data analysis and

safe sharing, advancement of patient tailored therapeutic approaches and the challenge to modern society.

2.2.2 Bulgaria

BAPES (the Bulgarian Association for Promotion of Education and Science) is a non-government non-profit organization, established in 2003, working to raise the awareness of rare diseases among the medical community and the society of Bulgaria as whole. BAPES helps to stimulate fundamental, clinical and public health research on rare diseases in Bulgaria, as well as the development and provision of care and services for people with rare diseases and their families [2].

BAPES has consecutively launched the Information Centre for Rare Diseases and Orphan Drugs, ICRDOD (2004) and the "RareDis" Medical Centre (2009), as activities explicitly designed to meet the needs of rare disease patients for reliable information and accurate diagnoses, treatments, follow-up and rehabilitation. BAPES is an active participant in all major European public health projects in the field of rare diseases (e.g., Orphanet, EUROPLAN, EPIRARE, BURQOL-RD, RARE-BESTPRACTICES, STORE). In this respect, BAPES has developed a high level of expertise on the national and regional levels, fostering rare diseases activities in each area. BAPES works closely with other Balkan and Eastern European patient organisations and medical societies from Russia, Turkey, Ukraine, Romania, Serbia, Georgia, Armenia and Macedonia.

BAPES launched a third new project in 2013 – the Centre for Health Technology Assessment and Analysis, CAHTA. This would assume responsibility for the dynamic area of health technology assessment, particularly in the field of rare diseases and orphan drugs. Beginning in September 2013, the three units, ICRDOD, "RareDis" and CAHTA were territorially and functionally united into a single institution – the Institute for Rare Diseases, the very first and only interdisciplinary and multifunctioning rare disease organisation in Eastern Europe. The Institute gives a comprehensive and coherent framework for rare diseases and orphan drugs in the country, helping to achieve the most important objective of BAPES – modern, accessible and quality care for people with rare diseases [15].

2.2.3 Hungary

The National Rare Disease Centre (NRDC) was established in 2008. The NRDC network participates in preparing recommendations for Governmental health authorities and is supported by an advisory group. The member experts are appointed by the Chief Medical Officer. Its members are from the four Hungarian medical universities (nominated by the deans), governmental institutions, and patient

organisations. This group has a key advisory function of strategic planning, but does not influence or control implementation.

NRDC initiated a collaboration with the National Health Insurance Fund for the listing and transparent accreditation of centres of expertise, hospitals, and laboratories working in the field of rare diseases. They considered existing resources and their concentration, as well as eliminating parallelism and formalising existing informal relationships and determining patients' pathways. The NRDC also works with the National Rare Disease Research Coordination Centre established in 2009 under the umbrella of OSZMK, National Public Health Institute, and the University of Pecs. The goal of this centre is to coordinate the development of existing and future networking of all centers dealing with diagnosis and treatment of rare inherited diseases.

In addition, the National Register of Congenital Anomalies (VRONY) operates countrywide according to the EUROCAT protocol. The former case definition of VRONY (congenital anomalies diagnosed from conception to the end of the first year of the newborn) has been extended by eliminating the age limit. Consequently, all diagnosed congenital anomalies are to be reported from 2013 in an obligatory manner. The NRDC has initiated the establishment of an overall registry for rare diseases. Currently, the clinical centres of rare diseases maintain registries of cared patients: these registries do not report their cases to a national data collecting system, and their registration methodology is developed according to the local need of care management and to the research requirements. All of these registries are in line with the Hungarian laws on genetic data handling and on the personal data protection. Hungary contributes to European Registries such as TREAT-NMD, EUROCAT, SCNIR and EUROCARE CF [8, 10].

2.2.4 Sweden

Sweden established the first centre of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999.

In the context of Orphan Drugs, the Swedish Medical Products Agency (MPA) adheres to the European Orphan Drug Regulation definition of a prevalence below 1 in 2000 individuals. However, the information database of the Swedish National Board of Health and Welfare defines rare diseases as "Disorders or injuries resulting in extensive handicaps and affecting no more than 100 individuals in one million inhabitants". The Department of Women's and Children's Health (KBH) has participated in several EU projects on rare diseases, such as Orphanet, EUROPLAN and Rare Best Practices. Orphanet and the Secretariat of ICORD (International Conference on Rare Diseases and Orphan Drugs), which were previously at KBH, have now been transferred to the Centre for Rare Diseases (KCRD) at the Karolinska University Hospital. The aim of KCRD is to improve the situation for children, adolescents and adults with rare diseases. This will be achieved through improved coordination, increased cooperation (regional, national and international) as well as

through increased information, education and research. Centres for rare diseases are now being established at other university hospitals across Sweden.

In 2005, KBH and the Karolinska Institute (KI) organised the first international conference on rare diseases and orphan drugs (ICORD). Conferences have since then taken place annually in many different countries in different continents, including Europe, USA, South America and Asia.

KI is a partner in the EU project on treatment guidelines (RARE Best Practices) project through KBH. Areas of focus are: (i) The collection, evaluation and dissemination of existing treatment guidelines; (ii) Common methodology for developing and updating treatment guidelines; (iii)Training of relevant stakeholders for the dissemination of expertise and knowledge; (iv) A forum for exchange of information and experiences and the development of partnerships.

Furthermore, the Swedish Information Centre for Rare Diseases aims to raise awareness and increase knowledge about rare diseases. The Swedish Information Centre for Rare Diseases produces and updates The Swedish Rare Disease Database. Leading experts on each disease provide informational material, which is reviewed by a scientific advisory board before publication. Patient associations and organizations for the disabled are also important partners. The centre is funded by The Swedish Board of Health and Welfare. The Centre also assists in the retrieval of information on rare diseases and mediates contacts with medical experts and patient associations [9, 16].

With respect to undiagnosed rare diseases, the Wilhelm Foundation is devoted to supporting research aimed at better understanding children who suffer from undiagnosed brain diseases, regardless of whether they are degenerative or non-degenerative [25]. The Wilhelm Foundation organizes congresses with researchers from all over the world, and actively collaborates in an international network for undiagnosed diseases, the Undiagnosed Diseases Network International [22], which was formed at the first World congress for undiagnosed diseases (Rome 2014). Three more congresses were held within this network: in Budapest (2015), in Vienna (2016), and in Tokyo (2016).

2.2.5 Spain

The Spanish Undiagnosed Rare Diseases Program (SpainUDP) has been implemented by the Institute of Rare Disease Research, IIER, ISCIII. The Institute of Health Carlos III is the governmental organization for health research, acting also as a Funding Agency for Health Research at the National Health System; it is a full member of IRDiRC.

In 2015 Spain UDP became fully established after a pilot phase and an agreement was signed between IIER-ISCIII and the Foundation for Biomedical Research of the University Hospital Puerta de Hierro, Madrid (HUPH) for supporting detailed clinical examinations and to perform complementary studies in very complex undiagnosed cases. At the same time, after many years of collaboration in different top-

ics (included undiagnosed cases), a closer collaboration with the Spanish Federation of Rare Diseases patients (FEDER) was established through their help line, namely the Information and Orientation System (SIO), which provides help to rare diseases patients (14 and Manuel Posada, personal communication).

Spain UDP aims to offer a multidisciplinary approach to those patients who have long sought a diagnosis without any success. It is linked to other IIER's national programs, such as: the National Biobank of Rare Diseases (BioNER), which is a founder of EuroBioBank; the Spanish National Rare Diseases Registry – Spain RDR; and the Spanish National Mutations Database (Spain MDB). IIER is also a full member of RD-CONNECT since its inception, contributing their undiagnosed cases to the platform of this project, and fulfilling all the international standards for these purposes. In a first phase of the study, which consists of cases sent to the program by FEDER, all clinical information available must be provided by clinicians and/or by patients and their families. Spain UDP also invites patients entering the Spanish National Rare Diseases Registry without a definite diagnosis. All documents for each patient are carefully reviewed by IIER's professionals, and missing documentation is requested. In addition, a close collaboration with local healthcare services is established.

If actions carried out during the first phase do not achieve a diagnosis, the most appropriate genetic analyses are performed. When necessary, a full week of inpatient clinical testing is organized. Specific meetings between IIER's experts and hospital experts are organized to discuss how to understand the clinical phenotype of complex cases and to plan complementary tests, with administration of sedation if necessary.

IIER centralizes data management by means of a new, secure information system based on SharePoint 2013, which has been specifically implemented to share, store and manage clinical data collected, as well as laboratory tests, images, etc. In addition, the "Phenotips" software is used to store an accurate and standardized description of patients' phenotype (through HPO—Human Phenotype Ontology), and "Phenome Central" allows communicating specific case details within a larger shared international network. Finally, the genotype-phenotype correlation is managed by using the RD-CONNECT platform.

Spain UDP aims to make appropriate diagnoses in rare diseases patients who still have not had a confirmed diagnosis, usually for a long time. At the same time, this multidisciplinary program, linked to a research institute, aims to foster the discovery of new diseases through a translational approach (14 and Manuel Posada, personal communication).

An Undiagnosed Rare Diseases Programme-ENoDis carried-out by CIBERER that is a centre of collaboration and cooperation between biomedical and clinical research groups focusing on aspects of genetic, molecular, biochemical and cell research of rare, genetic or acquired diseases.

The program aims to discover the genetic causes of rare diseases. With a structure based on transversal committees and endowed with its own resources, it manages undiagnosed cases referred by research groups for the following purposes: (a) diagnostic orientation and expert advice; (b) reinterpretation of complex data; (c) generation of new evidence [6].

2.2.6 Italy

The unmet needs of patients with undiagnosed RD are a global issue: joint actions are crucial to help patients and professionals to share expertise and information across borders.

Recently, the National Center for Rare Diseases of Istituto Superiore di Sanità contributed actively to International conferences on undiagnosed diseases sponsored by the United States NIH, and continues to lead the activities of the Undiagnosed Diseases Network International [22], which aims to meet the needs of undiagnosed patients worldwide.

Furthermore, a two-year, bilateral project Italy-USA, focused on Undiagnosed Rare Diseases, has been funded in 2016 by the Italian Ministry of Foreign Affairs and International Cooperation. The main aims of this project are: (a) to collect data from Italian patients with URD through the Italian Network of RD promoting the use of common standards and terminologies for classification; (b) to develop a national database and bioinformatics tools to facilitate data sharing at the international level; (c) to strengthen collaborations between Italy and USA by sharing best practices, genomic and phenotypic data and expertise.

Italian clinical centres involved in the project are: IRCCS, Istituto di Ricerche Farmacologiche Mario Negri, Centro di Ricerche Cliniche per le Malattie Rare, Bergamo; Centro Regionale di Coordinamento per le Malattie Rare, AOU "Santa Maria della Misericordia" di Udine; Genetica Medica, Università degli Studi de L'Aquila, l'Aquila; Centro Multidisciplinare e documentazione su malattie rare, Torino; U.O. Logistica Genetica Medica, Dip. Scienze mediche, Università Ferrara, Ferrara; UOC Genetica Medica, Policlinico Tor Vergata, Rome [5].

Moreover, since 2016 the Telethon Foundation, a non-profit organization recognised by the "Ministry of the University and Scientific and Technological Research"(Ministero dell'Università e della Ricerca Scientifica and Tecnologica)", is conducting a three-year project, "Undiagnosed Disease Program", with the goal of providing a diagnosis to pediatric patients with a genetic disease but without a name. This project involves three Italian medical genetics clinical centres (Ospedale Pediatrico Bambino Gesù in Rome, Ospedale San Gerardo in Monza and Azienda Ospedaliera Università Federico II in Naples) plus a research centre, the Istituto Telethon di Genetica e Medicina, with a considerable experience in the field of Next Generation Sequencing [11].

2.3 Other Worldwide Initiatives: Japan, Australia, Korea, Canada

2.3.1 Japan

The Japan Agency for Medical Research and Development launched a project to refer patients with undiagnosed diseases to a centralised network of specialists for genome analysis. The Initiative on Rare and Undiagnosed Diseases (IRUD) is designed to help people suffering from medically unidentified conditions to find a diagnosis and receive expert consultation, taking advantage of advances in genetic testing techniques [20]. The project is patient-centric and patients are referred to one of 17 hospitals around the nation with doctors expert in rare diseases. If a diagnosis is not obtained at that level, the patients will be referred to one of four designated institutions-the National Center for Child Health and Development and Kelo University, both in Tokyo; Tohoku University in Sendai and Yokohama City University.

These institutions carry-out genome testing using state-of-the-art genomic analyses in order to identify genetic abnormalities that cause rare diseases, including ones involving developmental delays and accompanying physical signs and symptoms in internal organs and limbs.

The IRUD project is funded by the AMED (Agency for Medical Research and Development), a government medical research and development body launched in April, follows the model of the Undiagnosed Diseases Program by the US NIH and the Deciphering Developmental Disorders project in the United Kingdom. Japan's project will allow the nation's doctors to strengthen their network and to share information at an international level. The project includes the establishment of a genome database of people with rare diseases.

2.3.2 Australia

The Department of Health Western Australia (WA) is promoting, within the WA Rare Diseases Strategic Framework 2015–2018, actions for undiagnosed diseases. The Rare and Undiagnosed Diseases Diagnostic Service (RUDDS) refers to a genomic diagnostic platform operating within the Western Australian Government clinical services delivered through Genetic Services of Western Australia (GSWA).

GSWA has provided a state-wide service for clinical genetic care for 28 years, and it serves an integrated genomic diagnostic platform in partnership with other public health system managers and service providers, including but not limited to the Office of Population Health Genomics, Diagnostic Genomics (Path West Laboratories), with executive level support from the Department of Health. The platform: (i) offers multiple options including non-genetic testing; monogenic and genomic (targeted in silico filtered and whole exome) analysis and matchmaking;

(ii) is delivered in a patient-centric manner that resonates with the patient journey; (iii) has multiple points for entry, exit and re-entry to allow people access to information they can use, when they want to receive it; (iv) is synchronous with precision phenotyping methods; (v) captures new knowledge, including multiple expert review; (vi) is integrated with current translational genomic research activities and best practices; and (vii) is designed for flexibility for interactive generation of, and integration with, clinical research for diagnostics, community engagement, policy and models of care. The RUDDS has been established as part of routine clinical genetic services and is thus sustainable, equitably managed and seeks to translate new knowledge into efficient diagnostics and improved health for the entire community [1].

A complementary initiative that dovetails with the RUDDS is the Undiagnosed Diseases Program of Western Australia (UDP-WA). This program has been modeled after other Undiagnosed Diseases Programs, such as the US program. Its purpose is to find answers for children with long-standing, very complex, usually multi-system disorders that are undiagnosed despite intensive efforts. Other key partners include the Western Australian Register of Developmental Anomalies; the Telethon Kids Institute, including through its Centre for Precision Medicine in Children; and the Garvan Institute of Medical Research, including Genome. One, in New South Wales. The critical input and support for initiatives to address undiagnosed diseases of Syndromes Without A Name, Australia; the Genetic and Rare Diseases Network, WA; Tea Lake and the Rare Disease Foundation; Rare Voices Australia and others is highly valued. An Australia-New Zealand UDP Executive has been established to further promulgate the UDP in Australia and New Zealand (Baynam G., personal communication).

2.3.3 Korea

The Genetic and Rare Disease Center tries to establish clinical networks for rare diseases to collect clinical data for patients, increase knowledge of pathophysiology and natural history of rare diseases and, finally, diagnose the rare disease. The Korean Mutation Database is a country-specific database of human gene mutations that was established in September, 2009 [23].

Rare Genomics Korea was initiated to help rare disease patients in South Korea, with a model similar to that of RG USA. It is currently developing an open-source software and analysis pipeline in order to establish and stabilize Next Generation Sequencing (NGS)-based diagnostic services for undiagnosed rare disease patients [21].

2.3.4 Canada

CARE for RARE is a nation-wide research program focusing on the improvement of both the diagnosis and treatment of rare diseases; it is led out of the Children's Hospital of Eastern Ontario (CHEO) Research Institute in Ottawa and includes 21 academic sites across the country. The program is recognized internationally as a pioneer in the field of genomics and personalized medicine. DNA sequencing technology is used to identify new rare disease genes for patients across Canada and around the world, and to develop novel therapeutic approaches. Overall, there are 80 physicians and 50 scientists working to advance rare disease research as part of the program; to date, eighty-five novel genes have been discovered [4].

2.3.5 Phenome Central Database

The Phenome Central portal includes records of patients with a phenotypic description and relevant genetic information (exome sequence or candidate genes). Phenome Central identifies similar patients in the database based on semantic similarity between clinical features, automatically prioritized genes from whole-exome data, and candidate genes entered by the users, enabling both hypothesis-free and hypothesis-driven matchmaking. Users can then contact other submitters to follow up on promising matches. Phenome Central incorporates data contributed by several major rare disease research programs including the FORGE and Care4Rare Canada projects, the US NIH Undiagnosed Diseases Program, the EU Neuromics, the RD-Connect Project and ANDDI rare projects, as well as numerous independent clinicians and scientists. Though the majority of these records have associated exome data, most lack a molecular diagnosis. Phenome Central has already been used to identify causative mutations for several patients, and its ability to find matching patients and diagnose these diseases will grow with each additional patient that is entered [3].

2.4 UDNI: The Undiagnosed Diseases Network International

The unmet needs of undiagnosed patients remain a global issue. To begin to address this, the Common Fund, within the Office of the NIH Director, along with the Wilhelm Foundation, Sweden, has sponsored four International Conferences (Rome, September 29–30, 2014; Budapest, June 26–27 2015; Vienna, February 18–19 2016; Tokyo, November 16–17, 2016). In attendance were representative of up to 22 countries and 4 continents. Based upon these meetings, an international network was formed, the Undiagnosed Diseases Network International-UDNI [22]. The UDNI is modeled in part after the NIH UDP, and has built a consensus framework of principles, best practices and governance. The Board of Directors reflects

its international character, since it includes experts from Australia, Canada, Hungary, Italy, Japan and the USA; other countries are now joining the network. UDNI involves centers with internationally recognized expertise, and its scientific resources and know-how aim to fill the knowledge gaps that impede diagnosis. Consequently, the UDNI fosters the translation of research into medical practice. Active patient involvement is critical; the Patient Advisory Group is expected to play an increasing role in UDNI activities. All information for physicians and patients is available at the UDNI website.

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Chapter 3
Intellectual Disability & Rare Disorders: A Diagnostic Challenge

Malin Kvarnung and Ann Nordgren

Abstract Rare disorders constitute a large and heterogeneous group of diagnoses of which many cause chronic disabilities with significant impact on the lives of affected individuals and their families as well as on the health-care system. Each individual disorder is rare, but when considered as a group, rare disorders are common with a total prevalence of approximately 6–8%. The clinical presentation of these disorders includes a broad diversity of symptoms and signs, often involving the nervous system and resulting in symptoms such as intellectual disability, neuropsychiatric disorders, epilepsy and motor dysfunction. The methods for establishing an etiological diagnosis in patients with rare disorders have improved dramatically during recent years. With the introduction of genomic screening methods, it has been shown that the cause is genetic in the majority of the patients and many will receive an etiological diagnosis in a clinical setting. However, there are a lot of challenges in diagnosing these disorders and despite recent years' advances, a large number of patients with rare disorders still go without an etiological diagnosis. In this chapter we will review the etiology of rare disorders with focus on intellectual disability and what has been learned from massive parallel sequencing studies in deciphering the genetic basis. Furthermore, we will discuss challenges in the etiological diagnostics of these disorders including issues that regard interpretation of the numerous genetic variants detected by genomic screening methods and challenges in the translation of massive parallel sequencing technologies into clinical practice.

Keywords Rare disorders • Intellectual disability • Neurodevelopmental disorders • Whole exome sequencing • Whole genome sequencing • Massive parallel sequencing • Clinical diagnostics

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3.1 Introduction

Rare disorders constitute a large and heterogeneous group of diagnoses. Each individual disorder is rare, but when considered as a group, rare disorders are common with a total prevalence of approximately 6–8% [56, 10].

The clinical presentation of these disorders includes a broad diversity of symptoms and signs, ranging from mild features affecting only part of the body to severe manifestations involving multiple organ systems. The nervous system is commonly affected, resulting in symptoms such as intellectual disability (ID), neuropsychiatric disorders, epilepsy and motor dysfunction. Age of onset ranges from the prenatal period into late adulthood and it is estimated that half of the affected individuals are children [56, 10]. Many of the rare disorders cause chronic disabilities with significant impact on the lives of affected individuals and their families as well as on the health-care system. In order to optimize treatment and care as well as counseling regarding prognosis and recurrence risks, it is crucial to determine the specific etiology of these disorders. The diagnostic methods for establishing an etiological diagnosis in patients with rare disorders have improved dramatically during recent years. With the introduction of genomic screening methods, it has been shown that the cause is genetic in the majority of the patients and many will receive an etiological diagnosis in a clinical setting. However, there are a lot of challenges in diagnosing these disorders and despite recent years' advances, a large number of patients with rare disorders still go without an etiological diagnosis.

3.2 Rare Disorders

The term "rare disorders" is widely used for disorders or diseases that affect few people and there are currently two definitions or cut-off levels regarding what should be considered as rare in this context;

- In Europe, a disease or disorder is defined as rare when it affects fewer than 1 in 2000 [40].
- In the USA, a disease or disorder is defined as rare when it affects fewer than 200,000 Americans at any given time [42]. Considering a population of 319 million people in the USA, this definition can be translated into a disease or disorder that affects fewer than approximately 1 in 1600.

Despite the rarity of these disorders, many people are affected. The high total prevalence of 6–8% is explained by the large number of rare disorders, which today equals nearly 8000 [1, 36]. The prevalence distribution within the group of rare disorders is skewed. A few of these disorders are relatively common with a prevalence above 1/20,000, while the vast majority of the disorders are very rare [35]. It has been estimated that 80% of all rare disease patients are affected by approximately 350 rare diseases [46], while the rest of the patients are affected by a plethora of very rare disorders. At the extreme end, there are disorders that have been described only in one or a few patients or families.

3.3 Intellectual Disability

Intellectual disability (ID) is a feature in many rare disorders as well as in more common disorders such as Down syndrome. The world-wide prevalence has been estimated at approximately 1% [30].

According to "Diagnostic and Statistical Manual of Mental Disorders, 5th Edition" (DSM-5), ID is defined as a neurodevelopmental disorder that **begins in childhood** and is characterized by significant limitations in both **intellectual functioning** and in **adaptive behavior** (Fig. 3.1) [12].

Intellectual functioning refers to general mental capacity, such as learning, reasoning and problem solving. A way of measuring intellectual function or intelligence is via a standardized test with a resulting IQ score. Generally, an IQ test score below 70 indicates deficits in intellectual functioning. However, DSM-5 does not use specific IQ scores as a diagnostic criterion, but instead there is a general notion of functioning two or more standard deviations below the general population.

Adaptive behavior is the collection of conceptual, social, and practical skills that involve the ability to carry out age-appropriate daily life activities. According to DSM-5, this criteria is met when at least one domain of adaptive functioning (conceptual, social or practical) is impaired to such a degree that support is needed.

Depending on the severity, ID can be classified as mild, moderate, severe or profound. In DSM-5, the severity is defined upon the level of support required. This basis for determining severity emphasizes the adaptive functioning rather than IQ scores, as support-needs are directly linked to adaptive functioning. A general guide to assessment of severity is given in Table 3.1.

ID can occur in isolation (non-syndromic) or in combination with associated features (syndromic), such as congenital malformations, facial dysmorphology, disproportionate stature, visual/hearing impairment or additional neurological and

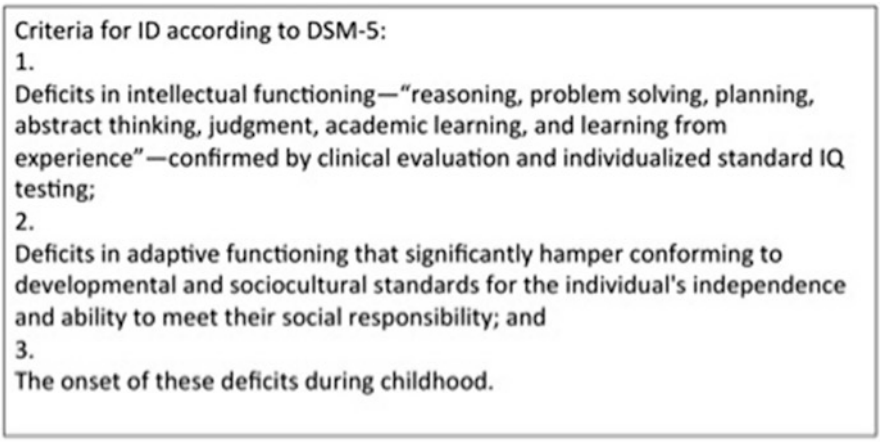

Fig. 3.1 Criteria for intellectual disability. The figure shows a schematic overview of the criteria for intellectual disability as defined according to DSM-5

Table 3.1 Severity of intellectual disability

Severity of ID	Level of support
Mild	Can live independently with minimum levels of support
Moderate	Independent living may be achieved with moderate levels of support, such as those available in group homes
Severe	Requires daily assistance with self-care activities and safety supervision
Profound	Requires 24-hour care

The table serves as a guide for assessment of severity of intellectual disability

neuropsychiatric diagnoses. Frequently co-occurring diagnoses are autism spectrum disorders (ASD), attention deficit and hyperactivity disorders (ADHD) and epilepsy. The co-morbidity spectrum indicates that there may be underlying etiological factors that are common to ID and other neurological/neuropsychiatric disorders.

3.4 Etiology of Rare Disorders and ID

During the course over the last 25 years there has been enormous advances in deciphering the etiology of rare disorders and ID. It has been shown that the majority of these disorders have a genetic basis, while others have non-genetic causes such as infections, auto-immunity and environmental factors. For a proportion of the disorders, the etiology is still unknown [56].

3.4.1 Non-genetic Causes

A number of non-genetic factors may harm human development, either during the pre-, peri-or postnatal period. Maternal infections during pregnancy (e.g. toxoplasmosis, rubella, cytomegalovirus), toxic substances (e.g. prenatal alcohol exposure, prenatal or postnatal lead exposure, prenatal exposure to harmful pharmaceuticals such as valproate), nutritional deficiencies (e.g. prenatal iodine deficiency), perinatal asphyxia, complications of prematurity (e.g. hypoxemia and periventricular hemorrhage), brain radiation, encephalitis and traumatic brain injuries are all factors that may cause damage to the development in general and neurodevelopment in particular. In some patients, the association between one or several of these factors and a diagnosis of ID is evident, while in others causation is difficult to assess. For the latter cases, a genetic etiology should also be considered.

3.4.2 Genetic Causes

3.4.2.1 Different Types of Genetic Causes

Traditionally, disease-causing genetic variants have been divided into chromosomal abnormalities, deletions/duplications (also known as copy number variants (CNVs)) and monogenic variants. Division into these groups is still useful, but with advanced understanding of the mechanisms behind genetic disorders, the boundaries between the groups have become blurred. Genetic variants could be regarded more as a continuum ranging from small changes in the DNA sequence (single nucleotide variants (SNVs) or insertions/deletions of a few nucleotides) and repeat expansions to structural variants of varying sizes. Structural variants can be either balanced or unbalanced with the latter also referred to as CNVs [48]. The size cut-off for what should be defined as a CNV was originally set at deletions or duplications >1 kb, but a more recent size definition is >50 bp [29]. Most of the rare genetic disorders are caused by variants that reside either within a protein-coding gene or include one or several such genes, but in some cases the underlying defect may be localized to a non-coding region [41, 51]. In addition, there are other types of rare variants such as uniparental disomy that may cause disease.

3.4.2.2 Genetic Causes of Rare Disorders

Recent years' advances in the field of genetics are reflected in the increasing number of known disease genes and disease-causing chromosomal aberrations as well as in the number of diseases or disorders with a known molecular cause [3, 31, 39]. These data are recorded in the catalogue "Mendelian Inheritance in Man" (MIM), available online as "Online Mendelian Inheritance in Man" (OMIM), which lists more than 8000 phenotypes or diseases with a presumed genetic cause. Since 1990, the molecular etiology of more than 4500 of these disorders has been identified and the number of known disease genes is 3075 as of February 1, 2016 (Fig. 3.2a) [36, 2]. Despite the enormous progress in recent years, the basis is still unknown for nearly half of the diseases.

For disorders that have a known molecular cause, the inheritance pattern is autosomal recessive in about half of the cases, autosomal dominant in 43% and X-linked in 6% (Fig. 3.2b) [36].

3.4.2.3 Genetic Causes of ID

Similar to what is known about genetic etiology in the rare disease group as a whole, the etiology of ID is characterized by an extreme heterogeneity. However, there are a few frequently occurring causes of ID – the most common ones being Down syndrome (trisomy 21), occurring in approximately one out of 700 live births [38],

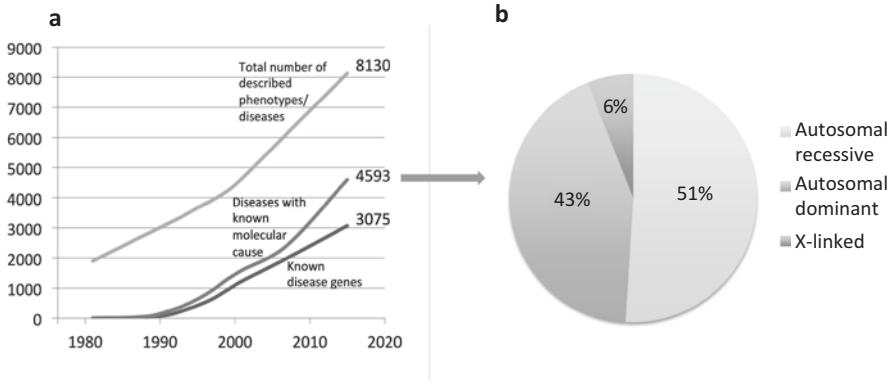

Fig. 3.2 Number of entries in MIM/OMIM over time and inheritance of genetic diseases. (**a**) Diagram showing the cumulative number of entries into MIM/OMIM regarding known disease genes, genetic diseases with a known molecular cause and total number of described diseases (with a presumed genetic etiology), over the last 30 years. (**b**) Pie chart showing the inheritance patterns for diseases with a known molecular cause

Fragile X syndrome (trinucleotide expansion in the *FMR1* gene) with an estimated frequency of 1 in 5000 males [6] and a few ID syndromes caused by recurrent CNVs (e.g. 22q11 deletion).

Etiological studies on cohorts of patients with ID indicate that up to 40% of the patients are affected by monogenic disorders. Most patients with a monogenic form of ID are affected by an autosomal dominant disorder, while some are affected by X-linked (5–10% of all patients) or autosomal recessive (2–4% of all patients) disorders [8, 11, 16, 43, 53]. The number of genes with an established association to ID is steadily increasing and now exceeds 700 genes [53]. Some of the more frequently affected genes are *SETD5, ADNP, ARID1B, GRIN2B, SCN2A, CHD7, KAT6B, TCF4* (autosomal dominant) and *ATRX*, *CUL4B*, *IL1RAPL1, PQBP1* (X-linked) [18]. Still, none of these genes individually explains more than 0,1–0,5% of the ID cases. Many of the genes implicated encode proteins for synaptic, transcriptional, and chromatin remodeling pathways. These pathways are commonly affected also in other neurodevelopmental disorders, such as autism and epilepsy and there is a genetic overlap where many of the genes can cause multiple phenotypes [9, 49, 53].

Another 20% of all ID patients are affected by disorders caused by deletions or duplications that span >500 bp of the genome, so called copy number variants (CNVs) [16, 53]. On a population basis, CNVs can be either recurrent or non-recurrent. Recurrent CNVs generally arise by nonallelic homologous recombination (NAHR) during meiosis with essentially identical breakpoints even in unrelated individuals [26]. Frequently recurring CNVs associated to known disorders include 15q11–q13 deletion associated with Prader–Willi and Angelman syndromes, 7q11 deletion associated with Williams–Beuren syndrome, 22q11 deletion associated with velocardiofacial syndrome and 17p11 deletion or duplication associated with Smith–Magenis and Potocki–Lupski syndromes, respectively [55]. In contrast,

non-recurrent CNVs do not result from a predisposing genomic architecture and can thus occur anywhere in the genome. The individual breakpoints in non-recurrent CNVs are often unique. However, overlap between similar CNVs in different individuals may occur, which make clinical comparisons and delineations of specific syndromes possible also for a few of the non-recurrent deletions or duplications.

In addition, 11% of the patients have larger chromosomal aberrations, including aneuploidies and the remainder of all patients, approximately 30%, suffer from disorders that are still of unknown etiology or due to non-genetic factors. These figures contrast to what was known on the etiology of ID ten to fifteen years ago when 80% of the patients were considered to be affected by a disorder of unknown origin or due to non-genetic factors [50]. The etiology of ID is summarized in Fig. 3.3.

Taken together, the data from 2003 and 2015 illustrate the tremendous progress within this field, which has been enabled by the rapid advances in methodology; the introduction of microarrays and more recently massive parallel sequencing, during the same time period.

Through etiological studies it has also become clear that for the vast majority of all ID patients with an identified genetic cause, the genetic variant is not inherited, but instead *de novo* in origin. This is true not only for ID patients with aneuploidies and microdeletions/microduplications but also for those who are affected by monogenic disorders. In fact, for cases with sporadic, severe ID, *de novo* variants are believed to account for approximately 60% of the etiology in an unselected population [53]. Notably, these figures are different in specific populations such as those where consanguinity is prevalent. In these populations, autosomal recessive disorders account for a much larger proportion of the ID cases [34].

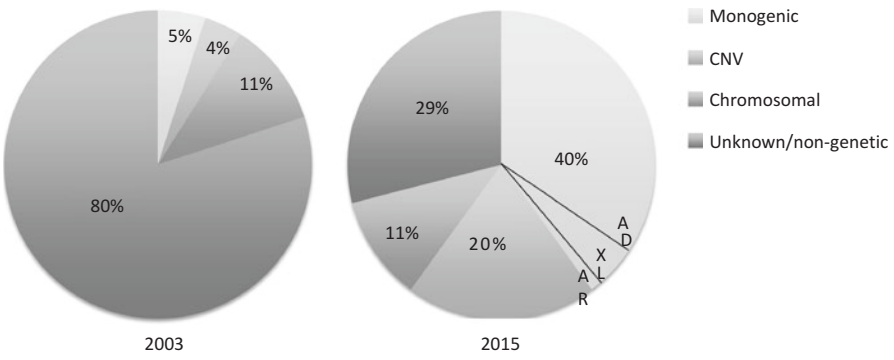

Fig. 3.3 Established causes of intellectual disability in 2003 and 2015

3.5 Genetic Diagnostics in Rare Disorders and ID

The diagnostic routine for most patients with rare disorders and/or ID includes a medical history (prenatal – present), physical examination, metabolic screening, neuroimaging and genetic investigations.

A first tier genetic analysis is often a chromosome microarray (array comparative genomic hybridization (aCGH) or single-nucleotide polymorphism (SNP) genotyping array) which detects copy-number changes, including aneuploidies. The resolution of this method is approximately 50 kb, while smaller aberrations may go undetected by this method. However, microarrays can detect CNVs that are several orders of magnitude smaller than those visible by standard karyotype analysis and have now replaced the G-banded karyotype as the first tier analysis in rare disorders and ID. In a clinical setting, the diagnostic yield is approximately 15% [32].

In addition, many patients undergo targeted analysis of the *FMR1* gene (Fragile X syndrome).

Based on clinical findings, targeted analyses of other monogenic disorders are considered for those with a distinct phenotype. However, the symptoms and signs of many rare disorders and ID are unspecific and linking the phenotype to a certain gene solely based on clinical findings is often difficult or even impossible.

With the introduction of massive parallel sequencing (MPS) methods into clinical diagnostics, it is now possible to sequence the whole genome or selected parts, such as the exome, which makes it possible to achieve an etiological diagnosis even for disorders with an extreme heterogeneity and/or unspecific phenotypes. Sequencing all genes (the exome) in an individual will detect approximately 30,000 genetic variants [25]. In order to reduce the number of potentially disease-causing variants that need manual assessment, the data is filtered by using databases with known normal variants, tools that predict the functional effect of the variants and, importantly, genetic data from the parents and other family members for segregation analysis and correlation to inheritance. Since the majority of patients with ID are affected by disorders that are due to *de novo* variants and thus not present in parental samples, filtering against genetic data from the parents facilitates the analysis. By the approach of whole exome sequencing with DNA-samples from the patient and both parents (trio), the diagnostic yield in a clinical setting is approximately 30% [33, 52].

Development of bioinformatics methods for the detection of structural variants, including CNVs, from data generated by whole genome sequencing is underway.

In the near future, as costs continue to decline and analytical methods evolve, MPS technologies are likely to replace chromosome microarrays as the first tier genetic analysis in rare disorders and ID. Not only would this approach increase the resolution for CNV detection, it would also enable a concurrent analysis of small sequence variants and different types of structural variants. There is reason to believe that a proportion of the patients that go without an etiological diagnosis today are affected by disorders that are caused by a combination of different genetic variants, which require a simultaneous analysis of the total burden of disease-causing variants in order to establish the etiology.

3.6 Challenges in Genetic Diagnostics

Despite the advances in technology over the last years and the increase in diagnostic yield for patients with rare disorders and ID, there is still a large proportion of patients in whom the etiologic diagnosis remains unknown. Improving diagnostic yield, while minimizing false positive results and doing this in a time- and cost-efficient manner, is challenging. In a clinical diagnostic setting, there are a number of issues regarding the translation of modern technologies into clinical practice. Major challenges are interpretation of the numerous genetic variants detected and further development of methods to improve detection rates and diagnostic yield. Furthermore, there is a need to develop standards for best practices in analysis, interpretation and reporting clinical genome sequencing results.

3.6.1 Improving Detection Rates for CNVs and Sequence Variants

By applying WGS instead of WES, the diagnostic yield increases significantly. For a population of patients in whom no etiology was established by a combination of microarray and WES, the molecular etiology could be identified in 42% by WGS. The etiologies detected by WGS were small CNVs (38% of the diagnosed cases) and sequence variants in coding regions (62% of the diagnosed cases) [16]. In other words, some of the sequence variants in coding regions are missed by WES and small CNVs are difficult to detect on microarray or WES. WGS would therefore be the method of choice in a clinical setting, if cost was not an issue. In the future, costs are likely to drop, enabling a more widespread use of WGS.

3.6.2 Interpretation of Genetic Variants

A major challenge, in addition to detecting genetic variants, is interpreting these variants and establishing a causal relation to a specific disease phenotype. Genetic screening methods such as chromosomal microarrays and MPS have the potential of detecting millions of genetic variants in a single individual. For most patients with a rare disorder or ID, only one or a few of these variants are pathogenic (i.e. causative of the disease-phenotype), while the remainder is part of normal genetic variation. Identification of the disease-causing variant(s) in a particular patient requires a process that includes measures for filtering and interpretation of detected variants.

3.6.2.1 Normal Variation in the Human Genome

The different types of genetic variants that may cause rare disorders and ID are outlined above, with the most common ones being small changes in the DNA sequence (SNVs or insertions/deletions of a few nucleotides) or structural variants of varying sizes. During the past ten to fifteen years, it has become increasingly clear that the same types of genetic variants are present all over the genome in any human and account for normal inter-individual genetic variation [14, 24, 57]. The genomes from two individuals are 98–99% similar, while the remainder differs between the two. A large study on human genetic variation estimates that the difference between the genome of one individual and a reference genome is 0.1% due to SNVs and 1.2% due to CNV/indels.[37] These figures correlate to findings that individuals carry on average 3 million SNVs and more than 1000 CNVs (>500 bp) when compared to a reference genome [7, 25].

Furthermore, recent studies have shown that the genome from a healthy individual may contain as many as 100 seemingly deleterious variants, mostly in a heterozygous state, but also some (0–20) bi-allelic variants [21, 27]. There are several possible explanations for the absence of a disease phenotype despite these variants. It has been shown that many human genes are haplosufficient [19], so for heterozygous variants, there may be sufficient expression from the wild type allele. Regarding bi-allelic variants, there may be residual protein function, compensation by similar genes/proteins, variants that only affect non-essential transcripts or variants in genes that are dispensable [21].

Some of the variants that are seen in an individual have arisen *de novo*. All humans carry a number of SNVs that are not present in samples from the parents. The number is estimated at approximately 70 SNVs per individual genome [4] or approximately one non-synonymous SNV per individual exome [43]. These figures correlate to the age of the father with an increase of 2 SNVs per year [23]. *De novo* CNVs or indels are not as prevalent as *de novo* SNVs. Large *de novo* CNVs (>50 kb) occur in approximately one out of 50 individuals [20] while smaller *de novo* variants (indels <50 bp) occur in all individuals at a rate of approximately 9 per individual genome [4].

3.6.2.2 Disease-Causing Genetic Variants Versus Normal Genetic Variants

As stated above, each human genome contains millions of variants that are not present in a reference genome and some of these are seemingly deleterious and/or *de novo* variants without pathological effects on the phenotype. For this reason, predicting the functional effect of a genetic variant and identifying the causative genetic variant in a patient is sometimes very challenging.

In order to achieve this, measures for filtering, prioritization and evaluation of the detected variants are required (Fig. 3.4) [28].

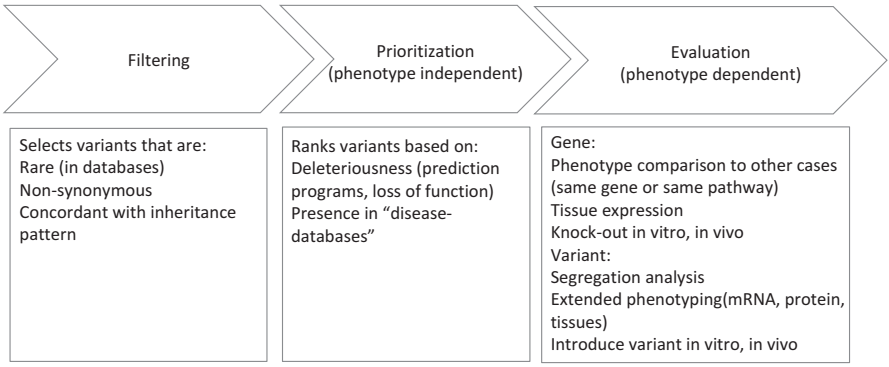

Fig. 3.4 Overview of the process for interpreting genetic variants detected by genomic screening

Filtering and prioritization are facilitated by comparison of patient data to data from additional family members (most often the parents), the use of databases for normal variants and disease-causing variants as well as tools for predicting the functional effect of genetic variants. Great efforts have been made in creating useful databases with collections of normal variants and/or disease-causing variants to aid in the interpretation of variants identified in patients. Databases that collect disease-causing variants are for example DECIPHER [15], which traditionally have focused on CNVs and the Human Gene Mutation Database (HGMD) [47], whose main focus has been on SNVs. However, both databases now include different types of variants. Regarding normal variants, these are recorded in, for example, Database of Genomic Variants (DGV) [29] with main focus on CNVs, and dbSNP [45] or ExAc [13], who both focus on SNVs.

A fraction of the variants in disease databases may be incorrectly annotated as pathogenic [54] and normal variant databases may contain pathogenic variants, making false positive and false negative results a reality. Further development and use of databases may facilitate the process and improve the outcome in clinical diagnostics.

For predicting pathogenicity of genetic variants there are numerous programs using different algorithms and hence, the outcome may differ between different programs. These programs should be regarded only as an aid in prioritization and should not be used to determine pathogenicity of a variant.

After narrowing down the number of potential pathogenic variants by filtering and prioritization, manual evaluation of the variants is possible. Evaluating the potential pathogenicity of a variant largely depend on the phenotype observed in the individual as well as in other members of the family. Additional targeted clinical investigations based on the genetic findings may be warranted.

Comparison of the observed phenotype to other cases with variants affecting the same gene or genes in the same pathway is informative. Recording of phenotype data in databases has become increasingly important for assisting in the interpretation of

variants and assigning pathogenicity to variants. The comparison of phenotypes in different patients who have variants affecting the same gene or genes is highly informative in the process of assessing genetic variants. Many databases, such as DECIPHER, have included phenotype data in a standardized format based on the Human Phenotype Ontology (HPO) [22]. Other databases such as OMIM, include phenotype data in a less strict manner.

3.6.3 Detection and Interpretation of "Alternative" Genetic Variants

A proportion of the patients in whom routine genetic diagnostics fail to identify the etiology may be affected by disorders caused by alternative types of genetic variants and mechanisms.

Genome wide screening for alternative variants or mechanisms include search for somatic mosaicism, variants in non-coding regions of the genome, balanced structural variants, repeat expansions, epigenetic aberrations such as imprinting defects and uniparental disomy (UPD). For some of these, there are numbers on their frequency in cohorts of patients with rare disorders, e.g. mosaicism for CNVs can be detected in 0.5–2% of the patients [5, 11] and UPD in <1% of the patients [11]. One concern is the interpretation of variants in non-coding regions of the genome including variants that affect genomic structure and transcription. Development of methods, including bioinformatic methods, to detect all of these variants and to interpret them is likely to increase diagnostic yield in a clinical setting.

3.6.4 Challenges in Translation of MPS Technologies into Clinical Practice

3.6.4.1 From the Point of the Genetic Lab

In addition to the more technical challenges outlined above, there are many issues regarding the translation of novel genetic diagnostic methods into the health care system. These issues regard infrastructure, regulatory standards, training and best practice guidelines for reporting. Numerous computational analytical approaches are currently in various stages of development and clinical use. A standardization of these programs as well as protocols focusing on the bioinformatic analyses and data storage are required. Guidelines for reporting genetic results, including incidental findings, should be used to facilitate the dialogue between the genetic laboratories and the clinicians. Furthermore, the need for personnel who is trained and qualified regarding MPS technology and data analysis has to be met and multidisciplinary

teams that include molecular biologists, bioinformaticians, physicians, IT engineers and software developers need to be established in order to optimize the results.

3.6.4.2 From the Point of the Clinician

With the introduction of MPS methods for the diagnostics of rare disorders and ID, there has been a shift in the diagnostic approach, which in a way warrants a novel way of looking at clinical genetic diagnostics. Much of this change concerns the way phenotypic data is used for establishing a diagnosis in patients. Historically, time and money were spent on gathering clinical information that could be used to group patients together, sometimes followed by targeted genetic analyses, in order to establish a diagnosis. As of today and in the future, clinical data may instead be used to facilitate the interpretation of variants generated by genomic screening methods, in order to achieve a diagnosis. Targeted genetic analyses based on an extensive phenotype would thereby be replaced by targeted clinical investigations based on an extensive genetic analysis. However, cost is a limiting factor when applying these analyses in a clinical setting. In order to reduce cost, alternatives such as analyzing only selected genes in an individual may be an option, rather than analyzing all genes in a trio setting (patient and parents). By doing this, diagnostic yield will go down, but studies show that the yield still remains at a level that warrants clinical utility of gene panels. Analyzing panels of up to 565 genes implicated in neurodevelopmental disorders in a patient-only setting leads to a diagnosis in approximately 11–25% of the cases [18, 44]. The difference in yield between different studies reflects differences in inclusion criteria for patients rather than a correlation to the number of genes in the panel.

3.6.4.3 Ethical Considerations

It is difficult to anticipate the full range of uses, consequences and impact of implementing MPS in routine clinical diagnostics. Ethical issues, both in research and in clinical practice are diverse, complex and may change over time as methods develop and implementation progresses. Today, ethical considerations regarding WES and WGS mainly concern different aspects of informed consent, data handling and the return of results. The latter includes issues related to incidental findings, *i e* findings that are not related to the phenotype/diagnosis that prompted the genetic analysis. If and how to report these findings is still under debate. Often it is suggested to only return incidental findings that regard diseases that can be prevented or cured. An active search for specific incidental findings is recommended by the American College of Medical Genetics, who states that clinical labs should be required to analyze 56 genes that increase the likelihood of diseases for which there is an intervention [17]. The debate on how to handle incidental findings will probably continue in the future and local guidelines may be developed to ensure patient autonomy and protection.

3.7 Concluding Remarks

Despite the numerous challenges in clinical diagnostics of rare disorders in general and intellectual disability in particular, there has been enormous progress in the field in recent years and this will most likely continue in the near future with wide spread clinical applications of massive parallell sequencing technologies. The benefit to the patient of recieving an etiological diagnosis is tremendous, which justify huge efforts to overcome the challenges that are faced when introducing MPS into clinical practice. Altogether, the use of MPS leads to significantly improved diagnostics in rare disorders and ID, which is crucial for optimizing treatment and care as well as for counseling regarding prognosis and recurrence risks.

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Chapter 4
Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework

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Abstract Public health relies on technologies to produce and analyse data, as well as effectively develop and implement policies and practices. An example is the public health practice of epidemiology, which relies on computational technology to monitor the health status of populations, identify disadvantaged or at risk population groups and thereby inform health policy and priority setting. Critical to achieving health improvements for the underserved population of people living with rare diseases is early diagnosis and best care. In the rare diseases field, the vast majority of diseases are caused by destructive but previously difficult to identify protein-

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coding gene mutations. The reduction in cost of genetic testing and advances in the clinical use of genome sequencing, data science and imaging are converging to provide more precise understandings of the 'person-time-place' triad. That is: who is affected (people); when the disease is occurring (time); and where the disease is occurring (place). Consequently we are witnessing a paradigm shift in public health policy and practice towards 'precision public health'.

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Patient and stakeholder engagement has informed the need for a national public health policy framework for rare diseases. The engagement approach in different countries has produced highly comparable outcomes and objectives. Knowledge and experience sharing across the international rare diseases networks and partnerships has informed the development of the *Western Australian Rare Diseases Strategic Framework 2015–2018* (RD Framework) and Australian government health briefings on the need for a National plan.

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The RD Framework is guiding the translation of genomic and other technologies into the Western Australian health system, leading to greater precision in diagnostic pathways and care, and is an example of how a precision public health framework can improve health outcomes for the rare diseases population.

Five vignettes are used to illustrate how policy decisions provide the scaffolding for translation of new genomics knowledge, and catalyze transformative change in delivery of clinical services. The vignettes presented here are from an

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Australian perspective and are not intended to be comprehensive, but rather to provide insights into how a new and emerging ‘precision public health’ paradigm can improve the experiences of patients living with rare diseases, their caregivers and families.

The conclusion is that genomic public health is informed by the individual and family needs, and the population health imperatives of an early and accurate diagnosis; which is the portal to best practice care. Knowledge sharing is critical for public health policy development and improving the lives of people living with rare diseases.

Keywords Public health • Policy • Translation • Information sharing • Translation • New knowledge • Community engagement

4.1 Background

Rare diseases (RD) are a public health priority [35, 45, 106]. There are an estimated 5000–8000 rare diseases, which when combined, affect up to 6–8% of the population. Globally, this amounts to over 400 million people living with a rare disease, making rare diseases a major global public health issue [35, 45, 106]. While more than 80% of rare diseases are genetic, most of which are due to pathogenic protein-coding mutations, others are caused by infections, auto-immune disorders and exposure to harmful substances.[1] Nevertheless, there are common features across the range of rare diseases and common health needs experienced by those living with a rare disease. These features include the fact that many RD: first manifest in childhood and then continue across the life-span; cannot be prevented or cured (although early diagnosis can result in early intervention); are complex, multi-systemic conditions resulting in considerable dysfunction and disabilities; and have no effective treatment [45, 61, 62].

The collective impact of rare diseases on the community is the impetus driving governments to develop coordinated policy and operational health service approaches to address the significant health needs of the individuals, and families living with a rare disease. These approaches must acknowledge the idiosyncratic nature and varied aetiology of rare diseases, and aim to improve management and reduce the associated human, community and system cost. An effective mechanism

[1] Nearly all genetic diseases are rare diseases, not all rare diseases are genetic diseases. There are also very rare forms of infectious diseases, auto-immune diseases and rare cancers. To date, the cause remains unknown for many rare diseases. http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN

for addressing these challenges is through the development of policy frameworks by governments, which integrate a range of initiatives across the health care system into a single policy approach. Through their clear direction, policy frameworks help ensure that health systems translate and optimize the application of new knowledge and rapidly advancing technologies in a coordinated and strategic fashion, to improve the patient journey and outcomes for all people living with a rare disease [35, 45, 105]. The common element catalyzing the transformation of global rare diseases is the people engaged in this enterprise and their commitment to leaving a better future for all people living with rare diseases. The authors contributing to this chapter have, with their teams and colleagues, committed hard won knowledge, expertise and individual perspective to making a difference to people world-wide living with a rare disease. They are witnesses to the impact of the government policy on improving the health system experience for a group of people at most need in our communities (Table 4.1).

The international landscape for rare diseases has changed significantly since Posada del la Paz and Groft first published Rare Diseases Epidemiology in 2010 [53, 85] including increasing government recognition globally. This is particularly evident in the European Commission actions, US legislation and more recently

Table 4.1 The power of a diagnosis

Benefits	Comments
Certainty	The power of knowing the cause of the condition at the end of the diagnostic odyssey, including improved prognostication.
Reduced isolation	Offering the possibility of connection for shared experience.
Reduce unnecessary investigations	No further need for investigations which may be invasive, time-consuming and/or costly.
Access to improved or best practice medical care, including reducing inappropriate management	Targeted follow-up and surveillance by what is known from the diagnosed condition and biologically related disorders; and possibility of drug repurposing.[a]
Clarify recurrence risk	To increase certainty and restore reproductive confidence.
Provide additional reproductive options	A molecularly confirmed genetic diagnosis provides options for prenatal or pre-implantation genetic diagnosis.
Access to social and educational services	Available for selected other rare disorders.

[a]Drug repurposing: using a given drug for a new indication (disease)

Japan's identification of rare and undiagnosed diseases as a major focus under a structural realignment in their health research [2].[2] This progress has led to the ascertainment of global priorities, the development of a number of international plans for rare diseases [41, 46, 95], and the formation of global networks and international partnerships [60]. These global partnerships are a key to driving high level policy, and establishing guidelines and position statements that provide the international context for the development of national and local rare disease policy frameworks and plans.

WA Health provides care to more than 2.5 million Western Australians across the vast 2.5 million km^2 geographical area of the State; a land mass approximately one third of the Australian continent; and making it the largest single jurisdictional health system in the world. The geographical isolation, including the distance to other Australian State and Territory borders, limits cross-border movement in the population and means that health service needs are generally accessed within the state health system. These characteristics promote population based studies and approaches to public health issues.

In 2001, in response to a report on the potential impact of genomics health services, the Department of Health, Government of Western Australia (WA Health) established the Office of Population Health Genomics (OPHG) as a policy unit to translate new genomics knowledge into the public health system. In 2010, WA Health made a decision, informed in-part by contemporaneous policies and recommendations in the European Union [42, 43, 45, 47, 95], USA [5, 8, 44], and the UK [31, 103, 104], to identify the issues and begin to map the key unmet needs of people in Australia living with a rare disease [33, 80]. OPHG worked successfully to influence the WA Health Executive to support the *WA Rare Diseases Strategic Framework 2015–2018* (RD Framework) and adopt the attending implementation plan [36, 37]. The RD Framework was built on input from stakeholders including consumers, medical specialists, allied health professionals, health planners, health administrators, researchers and policy-makers through multiple engagement opportunities and approaches [77, 78, 80]. The outcomes were communicated to stakeholders and the broader public through multiple media and government channels [32, 33, 36, 37, 80]. The RD Framework provides a mechanism for the coordination of WA Health initiatives for rare diseases and is structured around four priorities, which are to:

- advance rare diseases planning in Western Australia and Australia;
- promote a person-centric approach throughout WA Health for people living with a rare disease;

[2] The expanding role of genetics in medicine and health necessitates international collaborative efforts to create sound and just frameworks from which to build and further the research and applications of genomic technologies. Policy makers have a significant role to play in the redirection of local and global resources into genetic research and development to target the specific health needs of their communities. Their advocacy can advance genomics research and technologies, enhance the transfer and exchange of genomic information, encourage global collaborations, and improve health services worldwide. http://www.who.int/genomics/policy/Genomicsandpolicy/en/

- contribute to a high-quality health system for people living with rare diseases; and
- foster world-class research on rare diseases [37].

A key component of the RD Framework is the need to ensure that genomics knowledge and technologies are effectively translated from research and development into the WA health system, to achieve health benefits for people living with rare diseases. Such translation is expected to lead to health system improvements such as more precise diagnosis, early intervention, treatments and secondary prevention strategies that slow or prevent the progress of disease and disability. In this way, the RD Framework is an example of a 'precision public health' framework. Precision public health is an emerging field that relates to the use of new and existing technologies to more precisely identify and describe individuals and their environment, so that clinical services and public health practices can be more precisely tailored, for example to at-risk groups, and improve the overall health of the population[3] [29, 65, 66]. This is achieved by extending the focus of precision medicine on individuals to acknowledge that technological advances may also contribute to improvements in health status at the population level [6, 7, 88]. The data and information produced by the use of new and existing technologies may result in more precise: epidemiology; knowledge of the determinants of health; targeting of health disparities; population-based screening; population-wide diagnostic and secondary prevention services; and surveillance of, and responses to, communicable diseases [29, 63]. In addition to genomics technologies, other technologies contributing to precision public health include applications in: other 'omics' fields such as phenomics and exposomics [64]; bioinformatics; health informatics; information communications technology; spatial technology; data linkage capability; and predictive analytics [6, 7, 63, 66, 88].

In this chapter we present five vignettes, reflecting whole-of-health system examples, to illustrate policy initiatives within the RD Framework that are being implemented. This demonstrates the role precision public health frameworks can play to support the translation of technology and new knowledge into a public health setting. We describe how policy initiatives, while implemented locally, have been informed by international partnerships and global consortia. We demonstrate some of the unmet needs for people living with RD, the continuing need for evidence to inform healthcare decision making, and translational clinical and research outcomes arising from the implementation of the RD Framework. It also highlights the dependence of transformation on the international interplay of people sharing knowledge and experiences. These vignettes are:

1. Population-wide evidence-building approaches to inform public health policy
   (a) Experiences and health system needs of people living with RD **[Vignette 1]**
   (b) Epidemiology of RD to quantify the impact on the health system **[Vignette 2]**

[3] http://journal.frontiersin.org/researchtopic/4526/precision-public-health

2. Population-wide clinical genetic diagnostic services
   (a) Towards achieving a diagnosis for most rare diseases **[Vignette 3]**
   (b) Solving the unsolved, the Undiagnosed Diseases Program (UDP) **[Vignette 4]**
3. Research translation for population-wide improvements in care and public health
   (a) International partnerships fostering world-class translational RD research **[Vignette 5]**
4. What next…. development, and sharing of population wide infrastructure and resources
   (a) Objective phenotyping
   (b) Disease classification, coding and RD Ontologies
   (c) Knowledge Management Platforms
   (d) Population-based reference and representative data, including from healthy and affected indigenous people

Through these vignettes we demonstrate the application of various technologies, in areas such as data linkage, genomics (e.g. MPS), bioinformatics and information technology. These are enabling the production of data that is being used to transform health systems in terms of diagnosis and care. While the vignettes shared are local, they were enabled by the generous and open sharing across the globe that is a mark of the success and achievements made in rare diseases over the years.

4.2 Population-Wide Evidence-Building Approaches to Informing Public Health Policy

To date, there is a relative paucity in the literature of studies to demonstrate the collective impact of rare diseases on individuals, the health system and society. As such, the RD Framework includes the objective of building epidemiology and health system evidence for RD. A solid foundation of evidence is required so that policies, programs and services effectively respond to the needs of those living with rare diseases. Evidence provides contextual information within which decisions can be made about the responsible translation of knowledge and technologies, including that arising from genomics, into the health system, to achieve improved health outcomes for those living with RD. WA Health has recently conducted two studies that explore the experiences and needs of people living with RD, and the collectively impact of RD on the WA Health system. These studies are included as vignettes in this Chapter as they illustrate how such evidence is needed to inform the appropriate implementation of technological advances into health systems.

4.2.1 *VIGNETTE 1: Australian Rare Disease Patient Experiences*

The Australian public health system strives to provide excellent care to all Australians including those living with a rare disease. Consequently ahead of any plans to improve services for people and families living with RD, it was important to understand their healthcare priorities and identify gaps in an otherwise high standard Australian health system [37, 80]. There are still very few studies that use whole population approaches to examine whether the healthcare needs of people living with rare diseases are being met. Furthermore, the Australian literature has been almost silent on the experiences of Australian adults living with rare diseases in relation to diagnosis, information provision at the time of diagnosis, use of health and support services and involvement in research on their condition [79].

In an online survey of Australian adults (aged 18 years and over) there were 810 eligible responses from people with a confirmed rare disease diagnosis [79]. Of the respondents, 92% had a confirmed molecular diagnosis. To receive a diagnosis, 30% waited five or more years, and 66% had seen three or more doctors. Of those achieving a diagnosis, 46% had received at least one incorrect diagnosis. These data mirrored European findings, in which 25% of individuals waited 5–30 years for a diagnosis and 40% had an initial diagnosis that was wrong [46].

This illustrates the shared experiences of people living with rare diseases and the magnitude of the global RD public health issue. In the Australian study, almost three quarters (72%) reported that they received insufficient or no information at the time of diagnosis [79]. In the 12 months prior to the survey, over 80% of respondents had used the services of a general practitioner and a medical specialist while around a third had been inpatients at a hospital or had visited an emergency department. While in the adult survey only 15% of respondents had ever used paediatric services, of those over half (53%) experienced problems in the transition from paediatric to adult services [79].

These data strongly suggested to WA Health policy makers that structural changes to Australian healthcare systems may be required to improve the integration and coordination of diagnosis and care for people living with a rare disease. Such changes are likely to improve the patient journey and create opportunities for increased efficiencies within the health system. The data further highlighted that health professionals may need greater awareness of rare diseases to improve the diagnostic process and support to provide information to meet the needs of people newly diagnosed with rare diseases (Fig. 4.1).

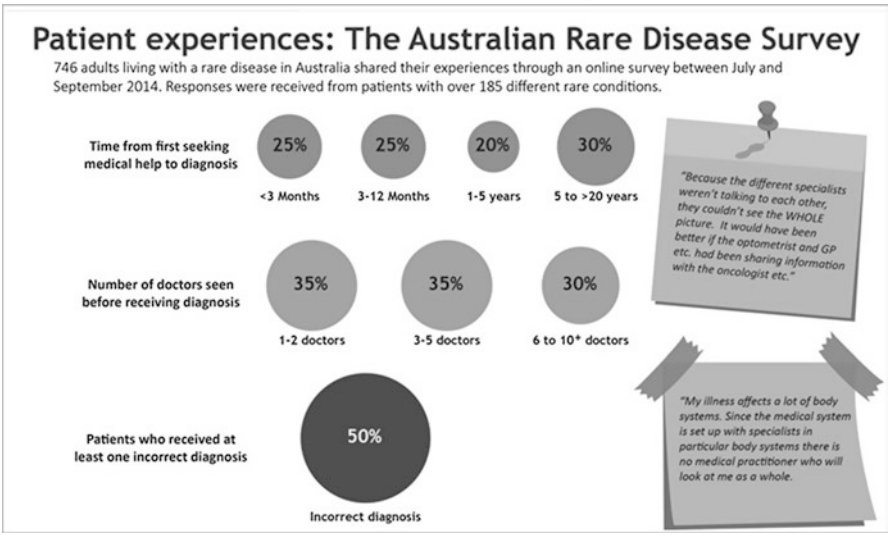

Fig. 4.1 Infographic showing findings in Australia that reported approximately 30% of patients waited for more than 5 years to receive a diagnosis, a similar number saw more than six doctors before receiving a diagnosis and half had at least one incorrect diagnosis [79]

4.2.2 VIGNETTE 2: Health System Impact

Despite the single health system for all Western Australians and the exceptional health data collections and other whole-of-population record systems, RD in Western Australia remain largely invisible. This is, at least in part, due to the inadequate RD codes in the International Classification of Diseases Australian Modifications (ICD-10AM) used in our public health record systems.

The situation in WA resembles that of other health jurisdictions across Australia and internationally. The issues faced by all governments in relation to RD are to delineate and understand the impact on their community and the health system. The barrier is the lack of reliable and robust data and evidence, epidemiologic and health economic data, describing the true burden of RD. Intuitively, it is recognized that RD have a disproportionately larger impact on the health system in Western Australia than patient numbers would predict. The outcomes of the experiences of adults living with a RD [79], outlined in Vignette 1, supported this presumption, since it appeared that health service use would likely be higher for people living with rare diseases than for the general population. This outcome identified the need for whole–of-population epidemiological and data-linkage studies on the impact of rare diseases on the healthcare system. In order to provide evidence of the burden of rare diseases on the WA Health system and to help guide the implementation plans of the RD Framework, WA Health led a study using data linkage methodologies to identify a cohort of RD in our extensive health data collections [59].

Data linkage is a technique for connecting pieces of information that are thought to relate to the same person, family, place or event. Information is created when a person comes into contact with certain services, for example, when they visit an emergency department, are admitted to a hospital or register the birth of their child. If these different bits of information can be connected to a person, then privacy-preserving data linkage approaches it can be used to produce evidence for improvements in the health of the WA community. The Data Linkage Branch (DLB) situated within WA Health links many data collections from WA Health system and other agencies enabling precise chains of data relating to an individual in Western Australia to be aggregated and analyzed. Studies using linked data methods have demonstrated population based trends and identified causal links to disease, such as the importance of ensuring adequate folic acid levels in women of childbearing age to reducing the incidence of neural tube defects in babies [11, 26, 27]. Western Australia has been recognized internationally for data linkage[4] innovation over many decades, and for population health research [59]. Projects and research using linked data have contributed to a range of policy, legislative and investment measures that have improved the health and well-being of Western Australians.

A privacy-preserving data-linkage study was devised to investigate hospital service use to better understand the collective health and economic impacts of RD on the WA health system [109]. To achieve this, a novel methodology was developed, which entailed constructing a set of diagnostic codes to select a rare disease cohort from hospital administrative data alongside advanced data linkage methodologies. Outcomes included health service use and hospitalization costs for the rare disease cohort.

The results showed that in 2010, the cohort members alive represented approximately 2.0% of the Western Australian population. The cohort accounted for 4.6% of people admitted to hospital, 9.9% of inpatient admissions and a greater average length of stay than the general population. The total cost of hospitalizations for the cohort represented 10.5% of 2010 state hospital admission costs; a five-fold greater per capita hospitalization cost, at a price tag of AU$395 million for that year alone [109] (Fig. 4.2).

A further approach to generate data on rare diseases to assess the impact of rare diseases to inform public health system planning is to take advantage of genomic sequencing's ability to uncover the carrier status of disease alleles. Since this carrier status is typically unrelated to the phenotype for which the assay was performed, tested patients can serve to inform the calculation of the burden of autosomal recessive diseases by exploiting the Hardy-Weinberg equilibrium. Even in populations where Hardy-Weinberg equilibrium is skewed due to inbreeding, statistical methods can be used, to accommodate this when making such calculations [53].

[4] http://www.datalinkage-wa.org.au/data-collections. Accessed 31 August 2016

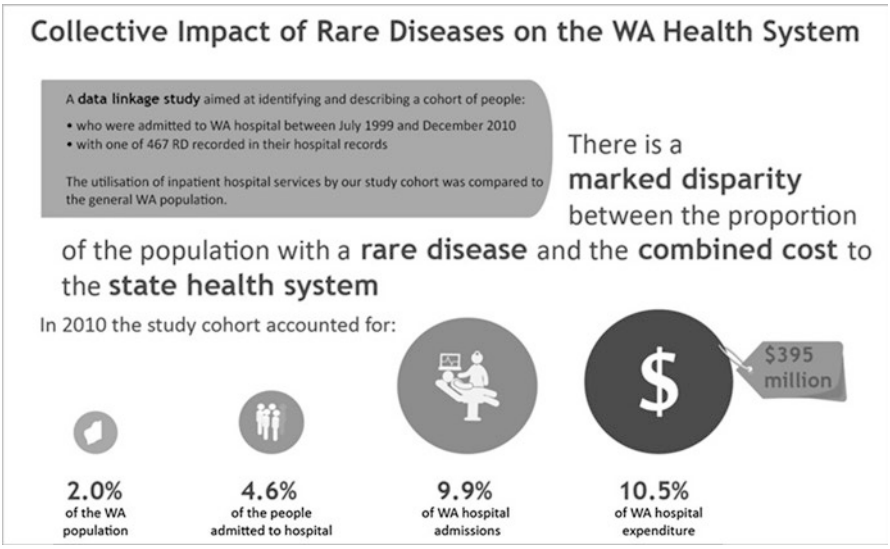

Fig. 4.2 Infographic representing the marked disparity between the proportion of the population with a rare disease and their combined health system costs [109]

4.2.3 Summary

Implementation of the RD Framework is being informed by data on the patient journey and the impact of RD on health services. In concert with the RD Framework, these data are identifying key unmet needs and helping to inform system changes in WA Health for improving the patient journey. This includes the need to increase diagnostic capability to better manage health service use.

4.3 Clinical Genetics Diagnostic Service Improvements

The Australian data on the patient journey [79] and the impact on WA Health [39, 40, 109], identified the importance to people living with a rare disease of obtaining an early, accurate confirmed diagnosis.[5] This highlights the position statement by Sorenson [97] that accurate diagnosis—and the appropriate use of diagnostic tools—is a key driver toward the successful transformation of our healthcare system. Recognising this, the RD Framework includes the objective of building on

[5] "In just 4 years, more than 1000 families with different undiagnosed rare diseases have had their causal genes identified, often with direct and immediate clinical impact. Advancement in this area has led to substantial changes to patient management, including tailoring of medications and halting invasive procedures." Dr. Kym Boycott http://www.cihr-irsc.gc.ca/e/49244.html. Accessed 31 August 2016.

existing WA Health services for the screening and diagnosis of RD. The RD Framework acknowledges that systemic changes will contribute to this including improved integration of health care services across the public health system.

Improved RD health systems' integration requires, among other things, two public health pillars to be addressed [24]:

(i) **Monitoring health status, including genetic factors, to identify health problems within the community:** Incorporating knowledge and awareness of the genetic contribution to health problems to enable refined decision -making about resource allocation and provide a basis for prioritizing and targeting public health program objectives; and
(ii) **Ensuring the availability and accessibility of diagnostic tests and services and associated interventions to improve health and prevent disease;** including assuring access to high-quality genetic testing programs and management services.

Genetic Services of Western Australia (GSWA) has provided a state wide, comprehensive, genetic service for the population of Western Australia for nearly 30 years and was established around the service flow model of clinical assessment, and genetic counselling, followed by investigations that may include sequential monogenic testing where deemed clinically appropriate. Similar to other whole population-based clinical genetic referral services, not enriched by highly selected disease cohorts, a definitive diagnosis with a high level of certainty with or without a molecular confirmation has been reported at around 9–10% [18, 19].

The advent of chromosomal microarray, followed by the clinical application of massively parallel sequencing (MPS) has resulted in a markedly increased genetically confirmed yield for rare diseases [3, 18, 19, 28, 69]. This is modifying the diagnostic paradigm, creating the opportunity for clinicians to more precisely make diagnostic recommendations. The impact of this will be outlined in Vignettes 3 and 4 which focus on improving the genetic diagnostic service through the implementation of the *Rare and Undiagnosed Diseases Diagnostic Service* (RUDDS); and the introduction of an *Undiagnosed Diseases Program* in Western Australia (UDP-WA).

4.3.1 VIGNETTE 3: Rare and Undiagnosed Diseases Diagnostic Service (RUDDS)

GSWA in collaboration with OPHG and PathWest the laboratory arm of the WA Health, embarked on a translational program to implement MPS into clinical service. The approach was built on accumulated successes and agile capacity building by the PathWest MPS laboratory team from early 2011. Based on deep technical experience, which was further informed and guided by the RD Framework [37] and patient experiences, the GSWA and PathWest began the implementation of

the *Rare and Undiagnosed Diseases Diagnostic Service* (RUDDS) in 2013 [39, 40, 79, 109].

The target group for the RUDDS is complex undiagnosed cases using the services of GSWA. This is particularly the case when *in silico* filtered or whole exome/genome analysis is being considered as an approach to diagnosis. Cases are presented weekly at multi-clinician meetings of GSWA geneticists and genetic counsellors to achieve consensus for further investigations. Fig. 4.4 shows the service flow. Briefly, if available, a single diagnostic test is undertaken. If no diagnosis is obtained at this stage, *in silico* targeted exome analysis is considered and offered to the patient if the phenotype of the disease is consistent with this type of analysis. If no diagnosis is achieved here, whole exome analysis is considered, and offered to the patient if the phenotype of the disease is consistent with this type of analysis. Furthermore, to help obtain a diagnosis, data may be shared with international matchmaking platforms such as Patient Archive and Phenome Central (see [84] and Sect. 4.5 of this chapter). Whether or not a genetically confirmed diagnosis is obtained, at any stage through the service, patients are ultimately referred to appropriate clinical pathways or management and/or available clinical trials.

The RUDDS is established as an integral part of routine clinical genetic services and is sustainable and equitably managed. Provision of the RUDDS pipeline within a public health setting and with multi-expert review was an approach tailored to local circumstances, including optimal use of limited health resources targeted to the unmet need of a population most likely to have immediate clinical utility and deliver patient benefits. The RUDDS pipeline is consistent with fundamental public health genomics tenants within a clinical state-wide public health service [24]. Specifically, the RUDDS is implemented under best practice standards of clinical genetic service delivery, aligned to the patient journey and patient needs, provides equitable access and achieves aspirational aims to deliver an optimized health outcome for each family. Furthermore, the RUDDS service is extended through outreach clinics to meet the needs of the Aboriginal and non-Aboriginal Australians living in rural and remote regions within WA Health's 2.5 million km^2 spread.

The major achievement following the introduction of the RUDDS was the creation of an agile and iteratively improving, diagnostic platform within the WA public health system. This platform aligned to the diagnostic needs of the rare diseases community. The RUDDS ensures that new genomics knowledge and technology are able to be translated in a timely and cost effective manner into the broader genomic diagnostic settings. The RUDDS supports equitable state-wide diagnostic health care provision through the integration of genomic diagnostics. By iterating within the clinical service, known or unanticipated real-world bottlenecks were identified and were pragmatically addressed.

In the first 12 months (2014–2015) after implementation, the RUDDS improved the causative monogenic detection rate from a historical service baseline of 9% to 30%, for this heterogeneous and diagnostically challenging clinical cohort [18, 19]. This is comparable to international experience with the clinical implementation of genomic sequencing across the diversity of presentations typical of clinical genetic

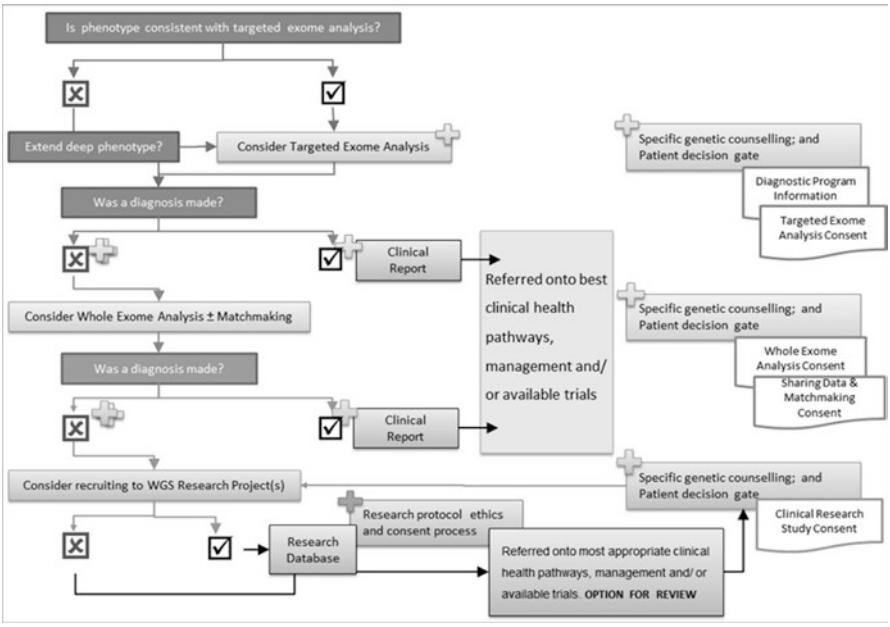

Fig. 4.3 A diagrammatic representation of the 3-fold increase in molecular confirmation of disease in this heterogeneous and diagnostically challenging patient population entering the RUDDS [18, 19]

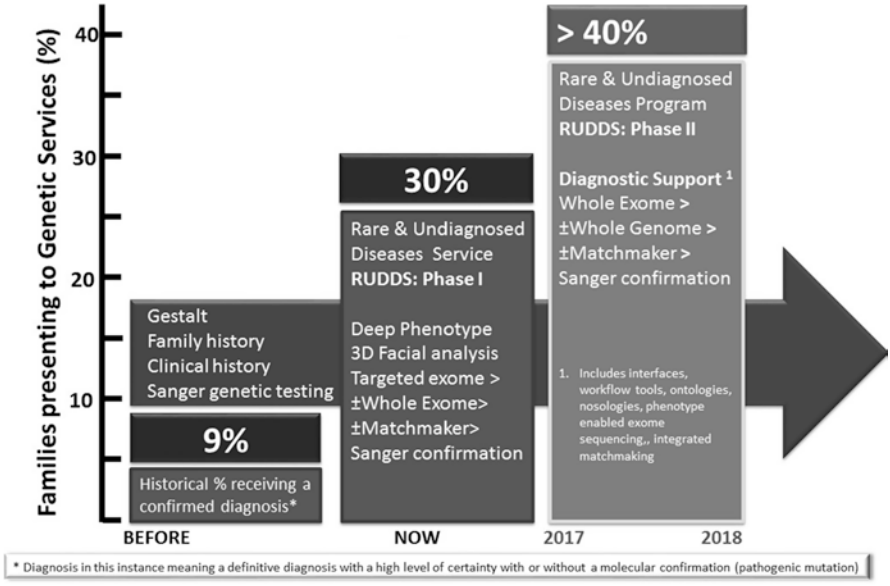

Fig. 4.4 Schematic of the Rare and Undiagnosed Diseases Diagnostic Service (RUDDS) service flow

practice, which reported diagnostic yields around 25–30% [23, 69, 87, 111]. Therefore the service efficiency gains as experienced through RUDDS are at the upper end of this range in diagnostic yield. This transformative change was achieved within existing service as a result of the intergovernmental collaboration across PathWest Diagnostic Genomics Laboratory, GSWA and the policy development and translational work undertaken by the OPHG within the Public Health Division, WA Health (Figs. 4.3 and 4.4).

Case study 4.1: An illustrative case summary from a family whose child received a molecularly confirmed diagnosis as a result of being referred into the RUDDS:

4.1 Case Study 1
A child was initially referred with craniosynostosis and the query of possible Saethre-Chotzen syndrome based on craniofacial phenotype. Following genetic consultation, and building on accurate phenotyping through the identification and specifics of his multisystem presentation, the possibility of a diagnosis of Noonan syndrome was raised. Sequential monogenic testing of individual RASopathy genes (*PTPN-11, SOS-1, RAF-1, HRAS, KRAS*), as well as analysis sequencing and MLPA of the gene most commonly associated with Saethre-Chotzen syndrome (*TWIST*), did not identify a mutation. Massively parallel sequencing with in-silico filtering to the phenotype identified a novel NRAS mutation confirming Noonan Syndrome. The relevant paternal investigations such as cardiac echocardiogram and renal ultrasound were organised. This case highlights the increased capacity to achieve a confirmed molecular diagnosis and the potential relevance to family medical care.

4.3.2 Summary

The RUDDS pipeline presented in Vignette 3 demonstrated a 3 fold improvement in molecular confirmation, from 9 to 30%, for a diagnostically challenging group of patients entering the RUDDS. This is consistent with recent publications from other clinics [3, 19, 93] and cohort studies. It is anticipated this will increase to 40% or higher in the intermediate term through experience and addition of new tools to assist clinical decision-making. Key to improving the diagnostic yield is the need for studies to benchmark the 'diagnostic yield' of genomic sequencing tools. Recent studies addressing the critical gaps in our knowledge of the yield of diagnostic genomic tools by revisiting the analysis of autosomal recessive diseases facilitated by the unbiased approach of positional mapping demonstrate very significant improvements that can achieved for diagnostic rates through improved analysis of existing data [94]. It is hoped this promising study, and others in progress, will lead to improved variant calling, critical for improved diagnostic yield in clinical set-

tings, and it further highlights the need for a range of analytic refinements that will inform improved representation and use of phenotypic and familial information.

Given the heterogeneity of presentations and inheritance patterns represented in clinical genetic practice, currently and likely in the intermediate term, the majority of RD patients will be remain undiagnosed and so, complementary approaches are required. Accordingly, an approach targeted to those who have especially complex presentations and that are particularly extensive users of health services was established, the Undiagnosed Diseases Program in Western Australian (UDP-WA).

4.3.3 VIGNETTE 4: The Undiagnosed Diseases Program WA (UDP-WA)

In 2008, the USA National Institutes of Health (NIH) established the first Undiagnosed Diseases Program (UDP). The UDP was established through the concerted efforts of the National Human Genome Research Institute, the NIH Clinical Center, the Office of Rare Diseases Research, and other NIH research institutes and centers. The UDP was conceptualized and developed specifically to provide a diagnosis for individuals who had long sought one without success. A second critical goal was to obtain insights into novel disease mechanisms and pathways [48, 49].

The success of the initial NIH UDP prompted a significant expansion under the NIH Common Fund to establish an Undiagnosed Diseases Network (UDN) through an extramural initiative comprising seven premier clinical research institutes across the USA. More recently the UDP model has expanded as a global network. The Undiagnosed Diseases Network International (UDN-I) [99] is supported by a position statement from clinicians, researchers and patient organizations, across four continents, with the expressed mandate to support global improvements in RD diagnosis through core principles and implementation approaches [45].

GSWA piloted WA Health's Undiagnosed Diseases Program in 2015, before formally launching the program as the UDP-WA in April 2016.

The UDP-WA has an initial focus on children who remain undiagnosed despite numerous hospital admissions and specialist assessments across multiple disciplines. Eligible patients: are generally at least 6 months old; have chronic, complex and typically multisystem diseases; and have clinical factors supporting the possibility of obtaining a diagnosis with current approaches.

Initially cases are referred to the Program Director by specialists at either GSWA or the local children's hospital and then triaged to be involved in the program. A interdisciplinary Expert Panel of specialists, drawn from GSWA and the children's hospital, review the existing medical history of program patients and make recommendations for further clinical assessment. If recommended by the Expert Panel, the patient attends a day facility at the children's hospital for up to 5 days where

they undertake the range of tests and examinations set out by the Expert Panel. This may or may not include MPS. With patient consent, data is shared with national and international partners to maximise the opportunity for finding a diagnosis. Based on the findings of all tests and examinations the UDP-WA team determines whether a definitive diagnosis can be made. The parent/caregiver then attends a meeting with the Program Director to discuss the findings, including recommended treatment and management options. A written report is prepared and a copy given to the parent/caregiver.

The UDP-WA is the first program to be implemented entirely within a public health clinical service stream budget. To date other UDPs rely to a greater or lesser extent on research funds and/or benefactors. The UDP-WA is driven by the combined and focused power of clinical experts from multiple disciplines operating contemporaneously in real-time; as compared to being based around a single organ system or clinical specialty, or being chronologically disparate. The resultant clinical phenotype is the key to helping inform investigations. This includes MPS sequencing provided through the Diagnostic Genomics arm of WA Health's PathWest Laboratories which uses the clinical phenotypic data provided to prioritize relevant candidate pathogenic genetic changes. It also includes whole genome sequencing conducted by the program partner Garvan Institute for Medical Research's Kinghorn Center for Clinical Genomics and Genome One.[6]

The UDP-WA has so far involved a small numbers of patients and is therefore unlikely to make an immediate significant impact on the overall definitive diagnostic rates. However, it is anticipated that the benefits to families, and to the health system, of an accurate diagnosis are likely to be significant. To understand the patient needs in managing the information and outcomes from the program OPHG has established interview protocols to capture the experiences of parents of children with an undiagnosed condition as they enter and progress through the UDP-WA. To understand the benefits from the public health policy framework perspective OPHG is evaluating the impact of cases on the health system where a diagnosis is achieved. The findings of the qualitative and quantitative studies will help inform continuous improvement identifying and refining the patient-centred outcomes measures for the UDP-WA for future monitoring of the program. By integrating policy development with the clinical flow of the UDP-WA, WA Health is ensuring it can respond to the needs of the families entering into the program, and also analyze the program and build further evidence based on 3–5 years' of experience. To serve the needs of RD families, these data are crucial to ensuring a sustainable ongoing clinical service. WA Health proposes to use this process to identify indicators and implement ongoing monitoring and linkages with the appropriate models of best practice (Figs. 4.5 and 4.6).

[6] https://www.genome.one/; also see http://www.garvan.org.au/news/news/new-era-in-genetic-disease-diagnosis-with-australia2019s-first-whole-genome-testing-service-to-be-launched-today

Fig. 4.5 Case files of the first two children seen through UDP-WA (both stacks of patient folders were missing three volumes at the time of the meeting)

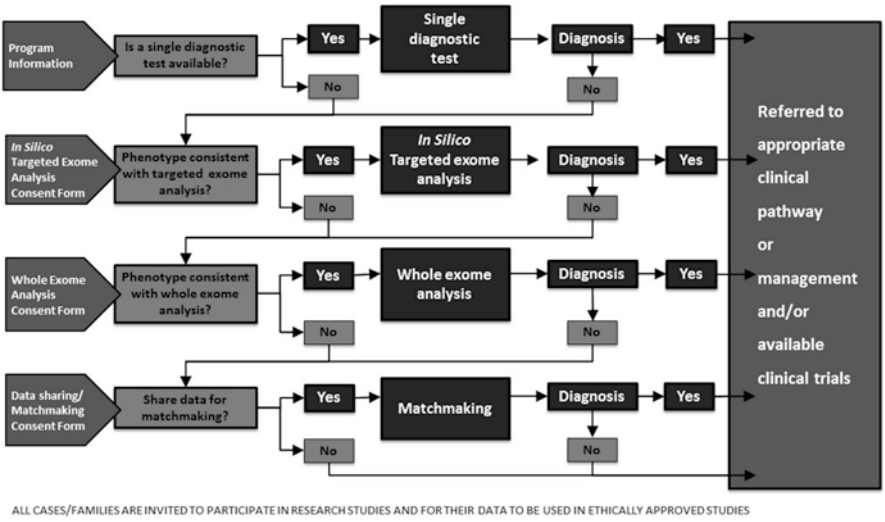

Fig. 4.6 Schematic of the UDP-WA pathway

4.2 Case Study 2
The first child seen through UDP-WA child was a 7 year old girl, who prior to the UDP had experienced a 7 year diagnostic odyssey with nearly 50 hospital admissions, multiple different specialist clinic appointments and referrals to international experts and a virtual international expert network. The UDP-WA cross-disciplinary approach led to a definitive diagnosis of a condition, tricho-hepatoenteric syndrome, with a prevalence of about one in 1 million people. Because of the diagnosis the family has been referred into the appropriate management pathways, which reduces unnecessary and expensive service, and provides the family and medical system with increased certainty. It also allowed the family to connect with other families for support and to reduce isolation.

4.3.4 Summary

The UDP-WA is one of a complementary suite of approaches that is being iterated as a cohesive part of the clinical diagnostic services in WA to address the need of those with undiagnosed diseases. To date the UDP-WA has provided diagnoses for those in metropolitan and regional areas to deliver improved clinical care; is creating a dynamic platform for in-service genomic and phenomic education that traverses a diverse range of specialties; is retaining and recapturing clinical expertise, including from retired clinicians; and is supporting the education of junior medical staff.

4.4 Research Translation for Population-Wide Improvements in Care and Public Health

Western Australia has a world-class academic and research sector, which has resulted in innovations in technology that have improved the efficiency and effectiveness of the health system. As outlined in the RD Framework, it is important that local expertise is complemented with multi-disciplinary international collaborations and partnerships as this will enable progress for RD research. A key facet of this collaborative approach is to support and develop capacity for clinical and translational research that will ultimately improve healthcare for people living with RD. The focus of translational research is to progress the transfer of knowledge beyond “bench-side” research into validated and appropriate technologies that are incorporated within the health system and public policy practice, to improve care and population health.

In recent years, several international collaborations and partnerships have emerged to build capacity in translation research and thereby facilitate the translation of knowledge into health benefits for populations. Several of these are discussed in the next vignette.

4.4.1 VIGNETTE 5: International Partnerships Fostering World-Class Translational RD Research

In Europe, beginning in 2006, a group of funding agencies established a transnational program E-Rare,[7] fostering rare diseases research funding. The E-Rare consortium grew from 6 to 26 funding bodies and expanded beyond European countries by integrating Canada, Israel and Japan. Together, E-Rare partners invested more than €80 million across almost 100 transnational research consortia, significantly advancing rare diseases research through partnerships and collaborations and laying the foundations for establishing a sustainable funding model to support targeted international rare diseases funding program.

In 2009, the European Commission's Directorate-General for Research and Innovation (DG RTD) and the USA National Institutes of Health (NIH) met to discuss the need for expanded and further integrated efforts to address the global imperative for governments to collect public health data on rare diseases. This meeting led to conceptualization of the International Rare Diseases Research Consortium (IRDiRC)[8] [11]. Formally launched in 2011 to foster international research collaboration and investment in the field, IRDiRC had two aspirational objectives: (i) to contribute to the development of 200 new therapies, and (ii) to develop the means to diagnose most rare diseases by the year 2020 [34]. IRDiRC was founded with 25 members and three international patient organizations. It has since expanded globally to include over 40 members and through this global reach, has the potential to drive the policy changes that enable the collection of data on patients living with rare diseases across Europe, North America, Asia, Australia, and the Middle East.[9] IRDiRC members and the groups funded by IRDiRC members emphasize the need for collaboration in rare diseases research, the involvement of patients and their representatives in all relevant aspects of research, and the importance of sharing of data and resources. The work of this group is critical for the development of new rare disease knowledge, which is in turn vital for governments to develop informed, collaborative and evidence-based policy and for industry to be guided in the development of new therapies for rare diseases [9, 10, 66, 67].

[7] The management of E-Rare programme is financed by the European Commission. In addition, in 2015 under the E-Rare3, the EC contributed for the first time in co-financing of research projects. E-Rare consortium is a founding IRDiRC member.

[8] www.irdirc.org

[9] http://www.irdirc.org/about-us/members/. Accessed 31 August 2016.

More broadly from a genomics policy perspective, the IRDiRC partnered with the Global Alliance for Genomics and Health (GA4GH)[10] to develop policy and guidelines around consent, data sharing and frameworks for ethical and secure data sharing, as well as promoting standards for nomenclature. Similarly, IRDiRC work is linked with the Global Genomic Medicine Collaborative (G2MC),[11] a USA National Academies of Sciences, Engineering, and Medicine initiative to capture and disseminate best practices for genomic medicine (in bioinformatics, education, evidence, pharmacogenomics and policy) across the global genomic medicine community.

Other partnerships and global initiatives specifically targeting rare diseases that are linked with the IRDiRC include, but are not limited to, RD-Connect[12]; TREAT-NMD Alliance[13]; RARE Bestpractices[14]; RD-Action[15]; European Reference Networks (ERN)[16]; the USA Office of Rare Diseases Research with its Rare

[10] **GA4GH** was formed to help accelerate the potential of genomic medicine to advance human health. It brings together over 400 leading institutions working in healthcare, research, disease advocacy, life science, and information technology. The partners in the Global Alliance are working together to create a common framework of harmonized approaches to enable the responsible, voluntary, and secure sharing of genomic and clinical data. http://genomicsandhealth.org/. Accessed 31 August 2016.

[11] **G2MC** is an action collaborative among global leaders in the implementation of genomic medicine in clinical care. The primary purpose is to identify opportunities and foster global collaborations for enabling the demonstration of value and the effective use of genomics in medicine. Engaging multiple stakeholders across the globe, under the auspices of the Roundtable on Genomics and Precision Health, to improve global health by catalyzing the implementation of genomic tools and knowledge into health care delivery globally. http://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch/Innovation-Collaboratives/Global_Genomic_Medicine_Collaborative.aspx Accessed 31 August 2016.

[12] **RD-Connect** is a unique global infrastructure project funded by the EU that links up databases, registries, biobanks and clinical bioinformatics data used in rare disease research into a central resource for researchers worldwide. http://rd-connect.eu/. Accessed 31 August 2016.

[13] **TREAT-NMD** is a EU-funded network for the neuromuscular field that provides an infrastructure to ensure that the most promising new therapies reach patients as quickly as possible. Since its launch in January 2007 the network's focus has been on the development of tools that industry, clinicians and scientists need to bring novel therapeutic approaches through preclinical development and into the clinic, and on establishing best-practice care for neuromuscular patients worldwide. http://www.treat-nmd.eu/. Accessed 31 August 2016.

[14] **RARE-Bestpractices** is a global platform, funded by the EU, to improve the management of rare disease patients with the primary aim to promote communication on the management of rare diseases by disseminating peer validated guidelines and tools globally. http://www.rarebestpractices.eu/. Accessed 31 August 2016.

[15] **RD-Action** is a European Commission Joint Action to improve knowledge on rare diseases, disease classification and orphan drugs and to support the development of national and European policies in the field, RD-ACTION will ensure that there is an integrated, European approach to the challenges faced by the rare diseases community. http://www.rd-action.eu/. Accessed 31 August 2016.

[16] **ERN's** for rare diseases are being developed to serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States, and with international partners, to ensure the availability of information and pathways to inform best care and therapies. http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#fragment0. Accessed 31 August 2016.

Diseases Clinical Research Network (RDCRN)[17] and the Undiagnosed Diseases Network-International (UDN-I)[18] [99].

Through the efforts of IRDiRC members, and other concerted efforts, there have been marked improvements in disease classification and coding [12, 14, 82, 83, 86] with a growing acceptance of standard nomenclature and development of policies for ethical and secure privacy- preserving data sharing for rare and genetic diseases [51, 74, 75, 76]. This is being complemented by significant developments in genomics knowledge and technologies, which are driving faster and more accurate diagnoses [18, 19, 23, 48, 99] and the development of personalized treatments, labelled as 'precision medicine' [52, 72, 110]. While the benefits to individuals of such targeted approaches are clear, the same knowledge and technologies are also providing opportunities to better understand and assess the impact of disease at a population level. In line with this, the emerging precision public health paradigm is leading to the development of policies and programs targeted to at-risk groups, in order to improve the overall health of the population[19] [66]. The use of genomics in such public health approaches is a key to driving improvements in healthcare delivery for people living with rare diseases.

The integral component of international partnerships for research is patients and families living with rare diseases. They are the single most transformative aspect of the RD sector, in areas that include but are not limited to: research and clinical networks; the new approaches to therapies and clinical trials; the gene and disease pathway discoveries unlocking new knowledge; the sharing of data and creation of matchmaking platforms; and through to the translation of this new knowledge for the benefit of all by translation into the public health setting.

In partnerships around the globe, patients and patient organizations have joined with governments, industry, clinical academia and philanthropic organizations to speak with one voice. People living with a RD, and their families, seek a diagnosis which will enable the doctors and other professionals to provide the best care in their setting which in turn will improve their journey. To achieve these outcomes, and the equitable care all citizens expect of their health system, RD patients under-

[17] **RDCRN** is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrolment and data sharing. Through the RDCRN consortia, physician scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the USA. http://www.ncats.nih.gov/rdcrn. Accessed 31 August 2016.

[18] In 2008, the National Institutes of Health's (NIH) Undiagnosed Disease Program (UDP) was initiated to provide diagnoses for individuals who had long sought one without success. Following three international meetings (Rome, Budapest and Austria), the Undiagnosed Diseases Network International (UDNI) was established, modelled in part after the NIH UDP. Undiagnosed diseases are a global health issue, calling for an international scientific and healthcare effort. To meet this demand, the UDNI has built a consensus framework of principles, best practices and governance. The UDNI involves centers with internationally recognized expertise, and its scientific resources and know-how to fill the knowledge gaps that impede diagnosis. Consequently, the UDNI fosters the translation of research into medical practice. Active patient involvement is critical.

[19] https://cvp.ucsf.edu/PPHS-Summit-Report-For-Posting.pdf; and http://journal.frontiersin.org/researchtopic/4526/precision-public-health

take to willingly lay open their lives and the lives of their loved ones. This, in and of itself, might seem to be a higher price to pay than others in the community with a smaller health burden are expected to pay. However, the reality is that the RD community has increasingly become self-organized through patient organizations, many of which are international and a number of newer organizations are truly global and provide voice to more than 300 million people living with RD.[20]

In this Chapter, the authors are not able to do justice to the phenomenal drive and patient empowerment derived from the national and international patient organizations and networks. However, the two recent global developments below serve as a testament to the escalation in the international networks of patient organizations and also to the many decades of accumulated and expanding influence of RD patients and their families in driving change.

(i) Rare Diseases International (RDI)[21] is a EURORDIS-led initiative, in partnership with the National Organization for Rare Disorders (US), the Canadian Organization for Rare Disorders, the Japanese Patient Association, the Chinese Organization for Rare Disorders, the Indian Organization for Rare Diseases, the Ibero-American Alliance for Rare Diseases (ALIBER), the French Alliance for Rare Diseases (Alliance Maladies Rares), the International Patient Organization for Primary Immunodeficiencies (IPOPI), Rare Voices Australia, Dystrophic Epidermolysis Bullosa Research Association International (DEBRA International), among other groups. RDI brings together national and regional rare disease patient organizations from around the world as well as international rare disease-specific federations to create the global alliance of rare disease patients and families. RDI's mission statement is to be a strong common voice on behalf of the people living with a rare disease around the world, to advocate for rare diseases as an international public health priority, and to represent/enhance the capacities of its members.

(ii) Rare Diseases International[22] will represent the global rare disease patient community through a Board presentation to the newly formed NGO Committee for Rare Diseases,[23] established under the umbrella of the Conference of NGOs with Consultative Status to the United Nations Economic and Social Council (CoNGO).

The purpose of the NGO Committee for Rare Diseases will be to serve as an advocacy platform that unites a diversity of constituents around the issue of rare

[20] http://icord.se/wp-content/uploads/2016/10/Helen-Clark-UNDP-Administrator-to-ICORD-Cape-Town-Oct-2016.pdf?bcsi_scan_c221d61a0ea4ff4c=4DVH79WrWv1IYuVp5dgOBmGuzAQmAAAAuiRi8A==&bcsi_scan_filename=Helen-Clark-UNDP-Administrator-to-ICORD-Cape-Town-Oct-2016.pdf

[21] http://www.eurordis.org/sites/default/files/press-release-ICORD-RDI-Collaboration-Final.pdf

[22] http://www.rarediseasesinternational.org/actions/ngo-committee-for-rare-diseases/

[23] The creation of the NGO Committee for Rare Diseases was approved by a vote of CoNGO member organisations in April 2014. Its inception meeting as a Substantive NGO Committee within CoNGO took place in October 2015 in New York. The formal inauguration of the Committee is currently scheduled for early November 2016 at the United Nations headquarters in New York. Accessed October 2016 http://www.ngocommitteerarediseases.org/about-us/

diseases. This further enables the RD community to be more closely connected and encourages collaboration 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 for Rare Diseases shall endeavour to improve the visibility and understanding of rare diseases within the United Nations system and at the global level, but also to help extend the current body of knowledge about the spread and impact of rare diseases across the world. It will also help to open up new avenues for cooperation with international NGOs in other fields with which connections with rare diseases can be identified – e.g. disability, children's rights, to name but a few.

In a separate recent statements, Helen Clark, Administrator of the United Nations Development Programme and Chair of the United Nations Development Group[24] has highlighted the importance of empowered lives in building resilient nations[25] and further reinforcing this message in relation to RD stating that "*No country can claim to have achieved universal healthcare if has not adequately and equitably met the needs of those with rare diseases*".[26]

Within her powerful statement were the observations that: rare diseases are an important part of the development agenda and the sustainable development goals; greater investments are required from governments to address the absence of adequate market incentives for unmet health needs such as rare diseases; and sustainable development requires whole of government and society responses[24].

These statements recognised and specifically identified that the RD sector was a multi-stakeholder community that offers a model of the collaboration that is needed to achieve important health-related targets in the UN Sustainable Development Goals.

4.5 What Next…… Development, and Sharing of Population Wide Infrastructure and Resources

Despite the growing incorporation of genomics into public health and clinical practice, for most of those people living with a rare disease, too much remains unchanged today. There is still a great deal that needs to occur to further improve our understating of the impact of rare diseases and to develop cohesive national

[24] United Nations Development Group, a committee consisting of the heads of all UN funds, programmes and departments working on development issues United Nations Development Programme.

[25] http://www.undp.org/content/undp/en/home/presscenter/speeches/2013/01/31/helen-clark-empowered-lives-resilient-nations-why-health-matters-to-human-development-.html

[26] http://icord.se/wp-content/uploads/2016/10/Helen-Clark-UNDP-Administrator-to-ICORD-Cape-Town-Oct-2016.pdf?bcsi_scan_c221d61a0ea4ff4c=4DVH79WrWv1IYuVp5dgOBmGuzAQmAAAAuiRi8A==&bcsi_scan_filename=Helen-Clark-UNDP-Administrator-to-ICORD-Cape-Town-Oct-2016.pdf

policies to support translation of the new knowledge into public health strategies. More explicitly, there are still too many families for whom a diagnosis has yet to be provided [3, 19, 93], so they can access evidence-driven best care, a core pillar of our health systems. There remains a data deficiency, and consequently a knowledge gap, in terms of disease classification; disease coding; international adoption and integration of phenotyping standards and standard ontologies. As a consequence, there is also a paucity of evidence and public health data on the impact of rare diseases on the health system, and the true impact on the families living with the conditions and the wider community. Moreover, while the efforts of the IRDiRC are a first step [9, 10], there is still not a shared global agenda, from government and funding agencies, designed to maximize the impact and benefits that may be derived from the limited funds available for rare disease research. A number of emerging technologies and approaches are providing opportunities to address some of these deficits.

4.5.1 Data Acquisition, Storage and Linking Tools

The availability of low-cost MPS has revolutionized the discovery pipeline for determining the aetiology of genetic disorders leading to new avenues for diagnostics and treatments [38]. The next translation horizon for the clinician, and for informing RD public health policy, is for secure clinical (phenotypic) and genomic data storage and tools that enable the smoother linking of diagnostic genomic pathology services to families and clinicians [70, 71]. These developments will further democratize the public health benefits arising from the new genomics knowledge and are becoming increasingly enabled by advances across data science fields.

Capturing structured phenotype-disorder knowledge is critical for maximizing the understanding of RD. Achieving this in the context of the real-time clinical data acquisition is essential to enable clinical and research breakthroughs in disease identification.

One of the main challenges and first steps towards a confirmed molecular diagnosis is for the medical scientists to interpret and prioritize candidates from the millions of variants in the patient genome. In particular, amongst the 55,000 variants in protein coding regions, and approximately 250,000 variants affecting the estimated 5% of the genome that represent promoters and enhancers [89].

There are varied paths to achieving a diagnosis and sometimes this occurs with little phenotypic information being conveyed to the laboratory, even if sometimes extensive phenotyping has been performed prior to selection of a patient for molecular analysis. However, phenotype has been the clinical mainstay to determine the underlying genetic aetiology of RD in patients, and now in the genomics era to substantially reduce the search-space for genomic variation [55, 58]. Paradoxically, phenotype acquisition and phenotype driven analyses also represent the major

limitation to accurate and rapid diagnosis. More specifically, the incomplete linking of detailed phenotypic terms to genomic variants presents a limitation in providing clinical confidence around variant calls. The subtext to these limitations is the need to adopt standardized phenotypic nomenclature, and disease classification terms and coding, to facilitate genotype–phenotype reference data bases and privacy-preserving data sharing.

4.5.2 Objective Phenotyping

Phenotyping is a key component of precision medicine initiatives for improved rare diseases diagnosis and care. 3D facial analysis (3DFA) is one domain enabler [17]. The RD community has collectively nominated key issues to be addressed to improve the lives of people with rare diseases [80]. These include timely and accurate diagnosis and improved therapeutic options. The latter requires objective means to monitor existing and novel therapies Amongst promising approaches to this is 3DFA. Following proof of principle studies, deeply precise 3DFA is being increasingly implemented in the RD domain, currently through expert clinical feedback cycles [18, 19, 20, 22, 56].

3DFA is non-invasive, non-irradiating and provides a precise objective tool for clinical evaluation across a broad range of, typically rare, conditions with well-established facial dysmorphic patterns [21]. Additionally, it provides insights into undetected or under-appreciated facial diagnostic signatures [56]. Hundreds of disorders that are collectively and variably described as ‘dysmorphic syndromes’ or ‘developmental disorders’ have characteristic facial features.[27] Furthermore, a significant proportion of congenital anomalies, also referred to as birth defects, and which collectively affect 5–6% of the population, are associated with facial dysmorphology. Many congenital anomalies are associated with rare diseases [100]. This occurs either through the presence of congenital anomalies in known syndromes with well documented facial dysmorphology (e.g., cardiac anomalies in Noonan syndrome), or as is evident in the recurrent co-coding of individual congenital anomalies and facial dysmorphism in individuals [108].

The RD Framework has enabled 3DFA to be implemented within the RUDDS [19] and the UDP-WA. 3DFA is also is aligned to state-wide rare diseases policy [33, 36, 81] and is being used as part of engagement programs aimed at improving models of genetic health care provision for Aboriginal Australians.[28]

[27] Possum [Internet]. 2016 [cited 5th August 2016]. Available from: www.possumcore.com

[28] https://www.royhill.com.au/wp-content/uploads/2016/08/World-First-New-WA-Initiative-to-Improve-Health-Outcomes-for-Aboriginal-Children-1.pdf

4.5.3 Disease Classification, Coding and RD Ontologies

The analysis of phenotypic abnormalities provides a translational bridge from genome-scale biology to a patient-centered view on human disease pathogenesis. Computer standardized descriptions of the human phenotype, such as Human Phenotype Ontology (HPO) [25, 55, 68, 90, 91, 92], have become a key element in a number of algorithms being used to support genomic diagnostics. Further development and integration of the HPO into clinical data sets is critical to advancing diagnostics.

Human Phenotype Ontology
HPO is a structured, comprehensive and well-defined set of 116,000 phenotypic annotations for over 7000 rare diseases that describe the abnormalities seen in human disease. In addition, the HPO project provides a collection of disease-phenotype annotations, i.e., computational assertions that a disease is associated with a given phenotypic abnormality. For instance, the disease Marfan syndrome [MIM:154700] is annotated to the HPO terms Arachnodactyly [HP:0001166], Ectopia lentis [HP:0001083], and 46 other HPO terms. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4572507/

Genetic and rare diseases are significantly under-represented in healthcare coding systems [15] contributing to a lack of ascertainment and recognition of their importance for healthcare planning and resource allocation. System inadequacies in coding of RD results in a poor understanding of RD epidemiology and natural history; which in turn prevents clinical research and knowledge translation from occurring in the public health setting.

The uncertainty around the number of rare diseases, with estimates from 5000 to more than 8000 partly reflects that underlying lack of broad adoption of granular classification and coding for rare diseases.

Systematic efforts to establish an inventory of rare disorders began in 1966 with the Mendelian Inheritance in Man (OMIM) which documents genetic defects based on knowledge of genetic phenotypes as a proxy for genes, and then on human genes when identified [4]. Orphanet, an initiative of the French National Institute of Health and Medical Research (INSERM) and the French Ministry of Health [86], was established in 1997 to create a systematic rare disease database and knowledge base for all rare diseases. Furthermore, The Orphanet Rare Disease Ontology (ORDO), developed by Orphanet and the European Bioinformatics Institute, integrates different information technology resources to provide a common framework for computational analysis of rare diseases; it thereby presents a structured vocabulary for rare diseases, capturing relationships among diseases, genes and other relevant features

[107]. In 2015 Orphanet was elevated, under a European Commission Joint Action,[29] as a knowledge base for rare diseases across the European Union [83]. The value of the Orphanet knowledge platform was further realized by the World Health Organization decision to use of the Orphanet classification and coding to update ICD-10 and design ICD-11 [12]. These classifications and disease codes need to be embedded in knowledge management platforms that support curation and that enable combination with other data types, e.g., genomic data, to unlock knowledge for discovery and clinical utility.

4.5.4 Knowledge Management Platforms

The curation of disease-phenotype annotations has been, to date, performed manually [86]. There is a critical unmet need to develop automated methods of curating and managing the increasingly complex and expanding RD databases, and linking the literature and Electronic Health Records (EHRs) to conceptual systems like HPO. Automated systems would help to coalesce the vast amount of information contained in scientific publications on the association of mutations to phenotypes, and from millions of existing patient records to enable health system and service planners to observe and record the temporal manifestations of clinical disorders. Moreover, it would advance the ability to classify and code most rare diseases, and better inform precision public health policy development. More recent, and ongoing, developments include the introduction of a new knowledge management platform to support data curation.[30] These developments are also in concert with the International Consortium of Human Phenotype Terminologies establishing standard terms to enable interoperability between phenotype and genotype databases, critical for interpretation of genomic variants in rare diseases [13].

Patient Archive[31] and PhenoTips[32] [50] are two examples of phenotype-centric genomic knowledge platforms developed to support rare disease diagnosis and care. Developed independently, but with a mutual commitment to ensure interoperability and knowledge sharing, both Patient Archive and PhenoTips have developed unique features and data visualization that share the common underlying phenotypic standards.

One feature of Patient Archive that is proving useful in the clinical setting is its natural language enabled concept recognition tool. The concept recognition tool uses intelligent natural language text processing techniques that translate phenotypic nomenclature from unstructured patient case notes, reports and other text into ontological entities and represents it in standardized HPO terms [54]. Furthermore,

[29] www.rd-action.eu

[30] http://rd-connect.eu/platform/registries/orphanet-knowledge-base/

[31] http://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/clinical-genomics/about-kccg/teams/phenomics-team#Patient_Archive

[32] https://phenotips.org/

Patient Archive uses the HPO captured phenotypes to provide the connection points for integrating cross-species phenotype knowledge bases such as those being assembled under the Monarch Initiative [67].

Patient Archive tools are being further underpinned by rare disorders knowledge sources, such as Orphanet and the Orphanet Rare Diseases Ontology (ORDO), which has utility in helping to guide the clinical interpretation of whole genome sequencing.

Both Patient Archive and PhenoTips are being embedded for clinical implementation in research and clinical settings internationally. In Australia, Patient Archive is being installed in the WA Health system as well as a number of premier rare disease research sites across Australia. It is our goal to embed this system into systematic data collections and clinical environments to further support rare disease diagnosis and care.

In the Asian Pacific region, the Japanese Agency for Medical Research and Development (AMED), a newly launched funding agency for medical R&D[33] has established the Initiative on Rare and Undiagnosed Diseases (IRUD) [2]. Since IRUD launched in 2015, the program has successfully grown to a nation-wide registry of over 1500 undiagnosed patients with 7 families of "N-of-2" case matching and greater than 500 families of "N-of-1" in a collaborative network of more than 170 hospitals across Japan (AMED personal communication, 28 October 2016). The IRUD Registry, IRUD Exchange, is a bespoke modification for AMED of the Patient Archive platform.

Relatedly, these platforms are being implemented in diverse nodes of the Undiagnosed Diseases Network International (UDNI), which currently includes premier research and clinical institutions across four continents with funding from multiple jurisdictional institutes of health. More recently, Patient Archive has enabled the informatics platform in the clinical accreditation process of the Genome One,[34] and the Garvan Institute for Medical Research a premier clinical diagnostic centre in Australia. Patient Archive is supporting electronic capture of phenotypic data that is interfaced with existing clinical processes and with evolving electronic health records. AMED are currently using the phenotype enabled IRUD Exchange platform, with the suite of enabling tools for sharing data and the MatchMaker Exchange API, to improve their genetic diagnosis of rare diseases. Furthermore they aim to collect and integrate over 40 years of retrospective clinical data on rare diseases that have been accumulated by Ministry of Health Labor and Welfare of Japan.

[33] On January 11, 2016 JST (January 11 EST), the Japan Agency for Medical Research and Development (AMED) signed a Memorandum of Cooperation with the National Institutes of Health (NIH) in Washington D.C. The agreement covers cooperative research projects, joint seminars, symposia and other scientific meetings, and the exchange of personnel and researchers. AMED expects the agreement to lead to collaboration in areas such as research into rare and undiagnosed diseases. AMED established three overseas offices in FY 2016 in the United States (Washington D.C.), United Kingdom (London), and Singapore.

[34] https://www.genome.one/; also see http://www.garvan.org.au/news/news/new-era-in-genetic-disease-diagnosis-with-australia2019s-first-whole-genome-testing-service-to-be-launched-today

The inbuilt interoperability of the IRUD Exchange platform with the Patient Archive, MatchMaker Exchange, PhenomeCentral via PhenoTips and the UDNI will enable increased analytical power to help solve intractable diseases.

Integrating phenotypic data using HPO terms with genomics data on an individual patient level and exchanging such data in a safe, ethical and efficient privacy-preserving way is increasingly important [57, 74, 75], and the European Commission has established the RD-Connect platform within the 7th framework programme aligned to the IRDiRC framework and including strong international contributions, spearheaded by Western Australia [51, 101]. RD-Connect allows privacy-preserving data linkage according to the FAIR principles (Findable, Accessible, Interoperable, Reusable) extending to Rare Disease biomaterials (via biobanks) and patient data (via registries), with the potential to integrate other –omics (transcriptomics, proteomics, metabolomics) [101]. While genomics data in combination with deep phenotypes are usually sufficient for diagnosis or gene identification, the other –omics will be required to understand the full spectrum of severity (modifier genes), explain variability and progression (biomarker) and support the development of treatments.

The majority of patients with rare disease lack a molecularly confirmed diagnosis after exome and genome sequencing. Finding one or more additional case(s) with a deleterious variant in the same gene and overlapping phenotype may provide sufficient evidence to identify the causative gene, however this data is frequently siloed. The 'Matchmaker Exchange' project is addressing this challenge and it involves an expanding collaboration towards a federated platform (Exchange) to facilitate the matching of cases with similar phenotypic and genotypic profiles (matchmaking) through standardized application programming interfaces (APIs) and procedural conventions [84]. Both PhenoTips, via PhenomeCentral [30], and Patient Archive, directly, enable this through their ability to support the integration of phenotypic and genomic data that is federated with Matchmaker Exchange [84].

4.5.5 The Population Basis for Reference and Representative Data to Achieve a Diagnosis

Genomic and phenomic innovation when aligned to patient need, and enabled by policy frameworks, are improving the lives of people with rare diseases. The global community must implement these advances equitably to reduce existing and potential health disparities, including between non-Indigenous and Indigenous peoples, such as Aboriginal Australians [16, 73, 96, 98]. Since clinical genomics is still in the early stages of translating the new knowledge generated across genetic and rare diseases through precision medicine initiatives [102] and precision public health frameworks [6, 7] we have a unique opportunity, and indeed an imperative, to embark on this journey in partnership with Indigenous people. This journey requires the generation of appropriate genomic reference ranges, and improved models of

culturally safe and appropriate genomic health care delivered through community engagement. Examples of the beginning of this journey and its implementation in clinical service are described in Chapter XX. The establishment of large variome databases that have sufficient representation of diverse ethnicities is critical to the proper interpretation of variant significance. Recent examples include that numerous mutations that had been reported among Arabs could be challenged, and generally revised down from 'pathogenic', using an Arab-specific variome database rather than commonly used databases, which currently have poor representation of people of Middle Eastern ancestry [1].

4.6 Conclusion

Herein we have described how initiatives and government decisions in other countries informed the Western Australian Department of Health in developing the *WA Rare Diseases Strategic Framework 2015–2018.* We outline how this policy initiative is an example of a precision public health framework, aligned with the need to translate new and emerging technologies into more precise diagnostic and treatment approaches to achieve improved health outcomes for the population of people living with RD.

Five vignettes written in a narrative style have demonstrated how application of the precision public health paradigm, and the resulting policies, are providing an overarching framework for sustainable translation (transformation) within the public health system and ensuring equitable access to clinical best practice. Importantly this Chapter relays that such transformation is already upon us, and precision public health frameworks need to reflect this. New knowledge and technologies are already being translated into public health systems, enabling improved diagnostic and treatment approaches. This has been, and continues to be, driven by the experiences and unmet needs of people living with RD, in particular regarding the need for early, accurate diagnosis, which is the bedrock of good clinical practice. It is important to remember that the needs of people living with RD and their families should underpin the implementation of technologies into public health systems, not the technology *per se*.

While the RD Framework policy initiatives are implemented locally, they are informed by collaborations nationally, internationally and globally. In particular, multi-disciplinary international collaborations and partnerships have enabled and been catalysis for significant progress in RD clinical and translational research. A key facet of the success of collaborative networks is the patient organisations and their networks working with medical researchers, clinicians, government policy makers and industry to identify needs and seek solutions in understanding, managing and treating rare diseases. This approach has been fundamental in providing the support and in developing capacity for clinical and translational research that will ultimately improve healthcare for people living with RD.

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Part III
Registries, Natural History of Rare Diseases and Biobanks

Chapter 5
Natural History, Trial Readiness and Gene Discovery: Advances in Patient Registries for Neuromuscular Disease

Rachel Thompson, Agata Robertson, and Hanns Lochmüller

Abstract Inherited neuromuscular diseases (NMDs) are genetic disorders that affect the skeletal muscles or the nerves controlling muscle function. With a new generation of diagnostic options and recent advances in translational research improving the opportunities for therapy development for these rare conditions, capturing patient information in databases collecting a range of clinical and genetic data together with contact details has assumed an increasingly important role in trial planning and recruitment as well as natural history data collection. Here we provide an overview of a decade of patient registration activities in the NMD field, with a particular focus on patient registries set up with trial readiness in mind. A summary is provided of databases collecting precise genetic information focused on confirming the causative mutation and their evolution into registries that combine genetic data with additional clinical information useful for trial feasibility and recruitment. Use of these systems for a range of purposes beyond trial recruitment, including natural history assessment, care standards monitoring, genotype-phenotype correlation and disease burden evaluation is also described within the context of research networks (TREAT-NMD) and European Reference Networks (ERN-EURO-NMD). New initiatives including registries using controlled vocabularies for computational accessibility that focus on phenotypic data capture for gene discovery are analysed, and examples of the lessons learned at every stage are provided in order to allow new patient registration initiatives to benefit from the extensive experience gained.

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Keywords Neuromuscular disease • NMD • Trial readiness • Trial recruitment • Natural history • Data sharing • Interoperability • Phenotype ontologies • Next-generation sequencing • Genetic databases • Patient registries

5.1 Introduction

The neuromuscular field provides a comprehensive case study for exploration of the evolving concept of the rare disease patient registry. Neuromuscular diseases are a broad group of rare genetic disorders that are characterised by impaired function of the skeletal muscles as a result of defects either in the muscles themselves or the nerves that control them. Although individually rare, there are now almost 800 NMDs associated with over 400 genes [28], and the disorders collectively affect 37 in 10,000 of the population [42]. While most NMDs share the common feature of muscle weakness, there is such a wide variation in other phenotypic features, age of onset, rate of progression and severity that a detailed clinical workup has long been the mainstay of diagnosis and management. Much of this clinical and phenotypic data has typically remained within the treating clinician's centre, but formal capture of disease-related features in national or international systems has been essential to understand these conditions in detail and has expanded over the years and evolved through several stages.

Since the elucidation of the genetic cause of the first NMDs, gene-specific mutation databases have been established to record the range of variation in many of the more common genes associated with the neuromuscular phenotype [3, 21]. With the advent of potential therapies for some NMDs, recognition that the natural history or course of progression of the disease is crucial as a baseline measurement against which treatments could be assessed led to the establishment of standardised outcome measures for a range of functional characteristics and their capture in natural history databases [39, 46]. The development of highly mutation-specific therapies such as antisense-mediated exon skipping resulted in an understanding of the need to capture the causative mutation alongside the clinical data and to retain the link back to the patient to allow trial recruitment [4]. Most recently, the rapid expansion of new sequencing approaches allowing the entire genome or the entirety of the protein-coding region of the genome (the exome) to be analysed has revealed the true extent of inter-individual genetic variation and resulted in a new breed of patient registry focused on gene discovery through standardised and computer-accessible phenotypic data collection that facilitates contextualisation of the genomic data [56]. Valuable lessons have been learned at each stage of evolution of neuromuscular registries and future developments will need to take advantage of the best practice developed for each purpose while continuing to evolve to reflect the advances in the field.

5.2 Locus-Specific Databases: Foundations for Reliable Diagnosis

After the completion of the human genome project in 2001, the need for systems that enabled carefully curated reporting of genetic data to assess the range of sequence variation within specific genes and its connection with disease became more pressing. Locus-specific databases (LSDBs) such as the Leiden Open Variation Database (LOVD) [21] and Universal Mutation Database (UMD) [3] systems were developed to meet this need, and neuromuscular disease gene databases such as the Leiden Muscular Dystrophy Databases were pioneering examples of disease-focused locus-specific systems that continue to be used by diagnostic labs to this day to establish whether a particular variant has previously been reported as causative of the disease phenotype. On the arrival of mutation-specific therapies for some NMDs such as antisense-mediated exon skipping for Duchenne muscular dystrophy [63], LSDBs also proved valuable for predicting the proportion of patients amenable to skipping of each exon in the *DMD* gene, enabling pharmaceutical companies to focus development on the compounds that would treat the largest number of individuals [2]. However, since the overall number of patients in whom a particular variant is seen is dependent on reporting by diagnostic labs back into such systems, which is not universal, establishing reliable prevalence estimates is challenging with this approach. In addition, phenotypic data collection in LSDBs is typically minimal, so opportunities for genotype-phenotype correlation are limited, and there is no link back to the patient for recruitment into clinical trials. Translational research projects such as TREAT-NMD therefore advocated a combination of the locus-specific approach to collecting precise genetic details with the collection of additional data useful for trial recruitment.

5.3 Registries for Trial Readiness: The TREAT-NMD Experience

TREAT-NMD [62] is a global neuromuscular network that aims to facilitate translational research in NMDs [27]. Initially funded in 2007 as a ‘network of excellence’ under the European Union’s Sixth Framework Programme, TREAT-NMD was launched at a time where genetic therapies for neuromuscular diseases were just starting to move into human trials. The network thus recognised the need for [51] and importance of [11] patient registries as a means to recruit potentially eligible participants for clinical trials. The gene-specific registries developed under the auspices of TREAT-NMD have become a key mechanism for the collection of genetic and clinical information securely linked back to the individual in a manner that not only facilitates clinical trial recruitment and trial feasibility planning but also provides a valuable resource for epidemiology studies, genotype–phenotype correlation, and natural history and care standards evaluation. Within its broader remit of

readying the NMD field for clinical trials, TREAT-NMD also further developed a range of other resources, including standards for animal model assessment [68], international sharing of biosamples through the EuroBioBank network [40], and a network of clinical sites with specialist expertise in NMD care and research [47].

Owing to the state of therapy development at the time, the TREAT-NMD patient registry initiative initially focused on Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA); however, from the outset it was intended that the model could be replicated and applied to other inherited muscle disorders. Prior to the establishment of TREAT-NMD, independent registries for DMD containing a total of around 2500 registered patients already existed in the Czech Republic, France, UK and USA [4]. However, an analysis of the data elements collected revealed that not all registries collected data suitable for trial planning, and a comparison of the differences in data elements between registries revealed that that cross-registry comparisons would be virtually impossible. Bringing together the registry owners to harmonise and agree datasets enabled consensus to be reached on the priorities for the field and the data items most useful to be captured internationally and proved a strong catalyst for global patient registration – from the four pre-existing databases in 2007, there are now 65 national DMD registries at various stages of maturity and development. A conservative estimate of the total number of individuals registered in these databases based on an internal TREAT-NMD survey in 2015 is that there are substantially more than 15,000 patients with DMD across all affiliated registries (personal communication).

5.3.1 Flexible Models and Data Federation

Working with pre-existing registries meant that the TREAT-NMD model needed to be designed for flexibility. The federated system in which national registries exist independently and contribute to a central hub allows registries to retain ownership of their own data, while still enabling aggregation of data on an as-needed basis to answer cross-resource questions. This also allows flexibility in the data collection method to take account of national and cultural differences. In some countries, patient organisations have taken the initiative to establish registries for NMDs [25, 49, 65], while in others they are set up within the healthcare system or academia [7, 31]. Data may be reported by the patients themselves, by healthcare professionals, or by a combination of the two. Depending on the prevalence of the condition, a national or international setup may be most appropriate. For the more common neuromuscular conditions such as DMD, SMA, myotonic dystrophy type 1 (DM1) and facioscapulohumeral muscular dystrophy (FSHD), national registries have been established [20], and these have the advantage of in-country support and local contacts, which helps to increase uptake. For the rarer conditions such as congenital muscular dystrophies [54] and limb-girdle muscular dystrophies [58], individual national registries may not be justifiable because the number of patients in each country is so low, perhaps numbering in the single figures for each genetically

Table 5.1 Disease-specific registries by type

Disease name	Abbreviated name	Type of registry	More info
Congenital muscular dystrophies	CMD	International	www.treat-nmd.eu/resources/patient-registries/list/cmd/
Congenital myasthenic syndromes	CMS	International (under construction)	www.treat-nmd.eu/resources/patient-registries/list/cms/
Charcot Marie Tooth Disease	CMT	International	www.treat-nmd.eu/resources/patient-registries/list/cmt/
Duchenne/Becker muscular dystrophy	DMD/BMD	National	www.treat-nmd.eu/resources/patient-registries/list/dmd-bmd/
Facioscapulohumeral muscular dystrophy	FSHD	National	www.treat-nmd.eu/resources/patient-registries/list/fshd/
GNE myopathy (hereditary inclusion body myopathy)	HIBM/GNE Myopathy	International	www.treat-nmd.eu/resources/patient-registries/list/gne-hibm/
Limb girdle muscular dystrophy type 2A, 2B, 2I	LGMD	International	www.treat-nmd.eu/resources/patient-registries/list/lgmd/
Myotonic dystrophy	DM	National	www.treat-nmd.eu/resources/patient-registries/list/dm/
Myotubular and centronuclear myopathy	MTM and CNM	International	www.treat-nmd.eu/resources/patient-registries/list/mtm-cnm/
Spinal muscular atrophy	SMA	National	www.treat-nmd.eu/resources/patient-registries/list/sma/

distinct disease entity. In such cases a single global registry may be established. International registries face additional challenges that national registries do not, such as the need to cater for different languages and legal jurisdictions, and the potential lack of local contact points to engage patients, answer queries and promote registration. Successful models for such international systems do exist, and have dealt with these challenges by making the registry interface accessible in multiple languages and by working closely with clinicians and patient organisations in each country in order to ensure awareness of the registry and provide support for uptake. Table 5.1 provides an overview of the various national and international registries working with TREAT-NMD.

5.3.2 Common Datasets Focused on Trial Planning, Feasibility and Recruitment

At the time the TREAT-NMD registry initiative began, it was evident that lack of knowledge of where patient populations eligible for trials were located was a major bottleneck in the clinical trials process, resulting in individual trials taking several years to meet recruitment goals [29]. The DMD registries brought together through

the TREAT-NMD initiative therefore agreed that their primary focus would be the facilitation of planning, feasibility studies and recruitment for clinical trials, and the data items they collect were harmonised to reflect this goal. The common dataset was agreed internationally and comprises a list of mandatory and highly encouraged items that all registries affiliated with TREAT-NMD agree to collect [4]. Both mandatory and highly encouraged datasets are stored nationally and subsequently aggregated globally in anonymised form through the global DMD registry, while each national registry remains free to collect any additional data desired for its own purposes. The genetic and clinical data collected by the registries through the mandatory and highly encouraged items act as a first-pass filter of inclusion criteria for clinical trials, providing companies running trials with an accurate source of patient numbers by region and thus enabling them to assess trial feasibility and calculate the number of sites they might need to open to meet recruitment targets. Capturing contact details and consenting patients for recontact then allows potentially eligible patients to be informed about trials for which they may be eligible through the registry as a trusted intermediary, facilitating recruitment while ensuring that companies never receive patient contact details directly. The model has proved highly successful: since 2008 the global DMD registry has facilitated 20 feasibility enquiries and four recruitment enquiries from pharmaceutical companies and academic groups running clinical trials (see Table 5.2) and the model has been reused for several other neuromuscular conditions (see Case Study 5.1). The enquiries operate on a fee-for-service or partial cost-recovery basis, with academic enquiries being free of charge and commercial enquiries incurring a small fee which is used for running costs and funding training and meetings for registry curators.

5.3.3 Data Quality and Fitness for Purpose

The TREAT-NMD system allows data entry through a wide range of mechanisms, including patient self-report. At the time the initiative was launched, there was some concern among academics over whether patient-entered data would be as reliable as clinician-entered data. The TREAT-NMD experience has shown that where questions relate to patient ability, symptoms or daily experience, for example age when certain motor milestones were gained or lost, patient-reported data is at least as reliable as data entered by clinicians. In the clinical trial and regulatory fields more broadly there has also been substantial recent focus on the value of patient-reported outcomes as indicators of the utility of a drug or intervention [13]. However, two key factors to consider when selecting data items are who is the person most likely to have the information, and who is able to review or curate the entry. The patient and the treating clinician may not always have access to the genetic report or have the expertise to enter it using standard HGVS nomenclature; the geneticist may not have details of the patient's natural history; the patient may not know the outcomes of lab or clinical tests that have been performed. To address these issues, the TREAT-NMD registries have taken several steps. Depending on the data elements required,

Table 5.2 Enquiries from third parties to the TREAT-NMD global registries and CTSR

Year	Type of enquiry			Diseases	Registry used			Geographic coverage
	Feasibility enquiry	Trial recruitment	Other		Patient Registry	CTSR	Patient Registry & CTSR	
2009	4			DMD (3); FSHD (1)	2	1	1	Europe, USA, Canada (1); Europe, USA (1); Worldwide (2)
2010	5			DMD (4); SMA (1)	2		3	Europe (1); Europe, USA, Canada (1); Europe, USA, Canada, Japan (1); Worldwide (2)
2011	1	2	1 (refinement and update of the feasibility study)	DMD (3); SMA (1)	3	1		Worldwide (3) Europe (1)
2012	1	1		DMD (1); GNE (1)	1	1		Europe, USA (1); Worldwide (1)
2013	2			DMD (2)			2	Worldwide (2)
2014	3	1		SMA(1); DMD (2); DMD/FSHD/LGMD (1)	1	2	1	Worldwide (4)
2015	2		1 (research project)	DMD (1); SMA (2)			3	Worldwide (3)
2016 (mid-year)	1			DMD (1)			1	Worldwide (1)

Case Study 5.1: Developing a Common Core Dataset for Myotonic Dystrophy Type 1 (DM1)

As the number of clinical trials in DM1 began to increase, it was recognised that systems capturing standardised patient data would be of value for trial planning and recruitment. In 2009 the DM1 community came together in a dedicated workshop devoted to natural history and trial readiness [57]. Based on the successful experience with DMD and SMA, an internationally harmonised core dataset was agreed, and all pre-existing registries agreed to make their datasets compatible with this approved dataset. The DM1 field had several pre-existing registries with rich natural history and clinical data including longitudinal data capture, and proponents of these systems stressed the added value of these comprehensive datasets. The final decision for the core dataset to be a more streamlined one was taken for pragmatic reasons, understanding that comprehensive data collection usually requires dedicated staff and dedicated funding, and that for successful trial recruitment a smaller dataset with greater participation is more feasible and more valuable. In 2016 a follow-up ENMC workshop entitled *Developing a European Consortium for Care and Therapy* was able to reassess the success of the DM1 registry initiative and core dataset 7 years later. In the intervening period several new registries were established and existing registries showed increased participation, revealing that patient registration in DM1 continues to be of significant importance. These registries have successfully been used for patient recruitment into research including clinical trials, and the comprehensive registries (DM-Scope) run by the French and French Canadian groups [14] continue to provide valuable additional data beyond the core dataset. Overall compliance with the core dataset is relatively high, with exceptions for certain items. The overall conclusion is that the core dataset was a valuable first effort at harmonisation and that future efforts should work towards a better integrated international system with attention paid to computational interoperability (manuscript in preparation).

some registries may allow combined data entry by clinicians, geneticists and patients, each answering the questions they are best equipped to answer [20]. In all cases, registries have a dedicated curator responsible for verifying the data entered. Where registries use the patient self-report mechanism but require the causative genetic mutation as a mandatory item, the curator will usually receive the genetic report from the patient or the genetics lab and enter it directly. This curation stage is a key quality assurance step and an additional factor that adds to the reliability of the TREAT-NMD registries and makes them a dependable resource for trial planning, feasibility and recruitment.

When making use of data from any registry it is important to take into account how the data were collected and any biases and restrictions this may give rise to. As an example, the streamlined core dataset collected by the TREAT-NMD DMD

registries was not designed with detailed natural history studies in mind and therefore cannot replace the detailed longitudinal data collection of a registry like the North Star database [53]. However, capturing the North Star dataset on an ongoing basis requires funding for trained physiotherapists to administer standardised tests and for data entry technicians to enter the longitudinal data, which requires significant resources and is available only to those patients seen in specific clinics. The North Star dataset is therefore currently only collected in a limited number of countries for a subset of patients seen in a small number of expert centres, with extensive funding from patient organisations and the national health system. The DMD registries, in contrast, collect a restricted number of data items of relevance for natural history, but these data items are collected on 15,000 patients worldwide and can in most cases be reported by patients themselves. While limited in scope, the size of the cohort and standardisation of data items nevertheless allows valuable and statistically significant conclusions to be drawn from a combination of the data items, and this has been used to good effect in a number of studies to make correlations between e.g. steroid use and age of loss of ambulation [66]. In summary, registry data may not only be valuable for its original purpose but may have substantial value for reuse, but when making use of data from any patient registry, it is important to understand the original rationale for its collection and assess its reliability and fitness for purpose in the new context.

5.3.4 Funding and Sustainability

Whatever the precise setup of the registry, capturing patient data on an ongoing basis inevitably comes with setup and running costs. These include costs for the software solution and the secure server to host it, and personnel costs for the curator and any other staff responsible for communicating with patients and entering data. A survey by the EPIRARE project in 2013 [55] found that registry funding in Europe comes from a wide range of regional, national, academic and charitable sources and that almost 50% of registries have no long-term sustainability solution. A similar situation is found in the neuromuscular registries: a survey of the national SMA registries affiliated with TREAT-NMD in 2013 found that only 25% were set up with funds from national authorities, while the majority obtained funding from patient organisations, other foundations or multiple sources [6]. In general, therefore, the funding situation for most registries is somewhat insecure. While it could be argued that a single global system would minimise duplication of effort and reduce the need for multiple national systems to find their own funding, the federated system does have benefits from the sustainability perspective because lack of funding for one individual registry does not threaten the viability of the others, and national initiatives often have recourse to regional and national research and healthcare-related funding sources that international initiatives cannot access. As described above, the TREAT-NMD-affiliated registries operate a fees-based model for enquiries and recruitment for commercial studies, and this is a valuable source of revenue for facilitating the

international networking and training for registry staff, but by no means covers full operating costs for the individual registries.

5.3.5 *Registries as Conduits for Information and Best-Practice Sharing*

Patient registries that collect contact details for participants can also be used as communication tools to keep participants informed about research activities and other news about the disease of interest. This concept was explicitly set out in the TREAT-NMD registry charter and internal surveys suggest that receiving relevant updates and being informed about clinical trials ongoing in their condition is welcomed even by those individuals who may not themselves be eligible for the trial, since it provides a sense of community and allows patients to feel they are being kept up to date about advances in the field.

The TREAT-NMD patient registries also take the concept of training and information-sharing for registry managers and curators very seriously, providing regular electronic updates designed for further dissemination to registry participants and hosting annual meetings and training sessions for the curators themselves to receive research news and share best practice. Support in setting up a new registry is provided in the form of a toolkit on the TREAT-NMD website [61] which provides advice on registry design, data items, ethics submissions, consent documentation, promotion, and governance. Although some items are NMD-focused, this resource is available for the RD community as a whole. The TREAT-NMD registries have also received recognition from the International Rare Diseases Research Consortium (IRDiRC) as 'IRDIRC Recognized' resources [35], a label that acts as a quality indicator showing that the resource has been evaluated against a specific set of criteria and marks them as resources of importance for the international rare disease research community.

5.4 Use of the Neuromuscular Patient Registries: A Decade of Experience

At the time of writing there are over 100 registries affiliated to or working with TREAT-NMD, covering 10 diseases or disease groupings (see Table 5.1). These registries have been used for a wide variety of purposes, from trial planning and recruitment to further studies on burden of illness, natural history and care standards implementation. Here we discuss a selection of uses to which the registries have been put since 2007.

5.4.1 *Patient Identification and Recruitment and Selection of Clinical Trial Sites*

All inherited NMDs are classed as rare diseases – defined in the EU as conditions with a prevalence of less than 1 in 2000 [50] and in the USA as those affecting fewer than 200,000 US citizens. Trials in rare diseases can be challenging for a number of reasons, including the limited number of patients available for recruitment and the resulting need for trials to be run in multiple countries simultaneously to meet recruitment targets, as well as the lack of trial experience in the clinical community and lack of validated outcome measures to assess treatment response. For many NMDs, the natural course of progression is not well characterised, which makes establishing clear clinical endpoints difficult. Patient registries not only help with finding patients fulfilling the eligibility criteria but also speed up the process of getting in touch with them to inform them about the trial.

Identification of suitable clinical centres with the required specialist expertise and personnel can be another challenging aspect of clinical trials in rare NMDs. TREAT-NMD established a Care and Trial Site Registry (CTSR) to facilitate selection of clinical trial sites. The CTSR is an online self-registration database for neuromuscular clinical centres hosted by the University Medical Center Freiburg, Germany [47]. The information collected by the CTSR is based on details that the pharmaceutical companies would typically request from sites at the feasibility stage of clinical trial planning, as well as the European Union Committee of Experts for Rare Disease (EUCERD) quality criteria for centres of expertise for rare diseases in member states [17]. The information collected encompasses details on patient cohorts, care settings, research and education, and clinical trial infrastructure. By combining information on clinical centres from the CTSR with details on the number of potentially eligible patients within travelling distance of a particular site from the patient registries, a company planning a trial can more accurately establish which sites will meet its recruitment targets and how many sites are likely to be needed in total to power the trial. The registries and CTSR are regularly used by pharmaceutical companies for such enquiries (see Table 5.2). The model has also been extended through the EU-funded NeurOmics project to cover a range of neurodegenerative diseases, which has resulted in the integration of a number of new centres responsible for cohorts of patients with neurodegenerative conditions [24].

5.4.2 *Working with the Pharmaceutical Industry – The Need for Transparent Governance and Oversight*

International translational research and associated infrastructural development performed within academia has to take into account the needs and expectations of pharmaceutical and biotech companies engaged in therapy development. The majority of the TREAT-NMD affiliated registries have been set up with trial facilitation as

their primary goal, so working closely with industry is essential. The regular use of the TREAT-NMD registries by third parties (industry and academia) seen in Table 5.2 demonstrates that they have gained recognition as a valuable resource for clinical trials. These collaborations with industry have been made possible thanks to careful consideration of governance and oversight from the early planning stages. The process of third party access to the data within the registries has been developed with the best interest of patients in mind – protecting confidentiality while facilitating the trials that for many participants are the primary reason for registering. The mechanism for oversight developed within TREAT-NMD is designed to be responsive and effective and compliant with industry timelines. All participating registries sign up to the TREAT-NMD Registries Charter [59] and nominate a representative to the TREAT-NMD Global Registry Oversight Committee (TGDOC) [60]. When a company makes a request for data or wishes to use the registries for recruitment, the TGDOC as a whole reviews the request and decides whether it is in line with the registries charter and in the patients' best interests. The aim is to be as light-touch as possible and not to replace the work of an ethics committee, but simply to ensure due procedure is followed. The TGDOC also monitors and reviews the cost-recovery payments that are requested from commercial entities who contract the registries for data and recruitment enquiries.

Case Study 2: Recruitment for an International SMA Trial

In 2010 a feasibility enquiry from a pharmaceutical company was received to identify patients and trial sites for a phase II/III clinical trial in non-ambulant patients with SMA type II and type III (age 3–25). Thanks to the CTSR, 38 appropriate sites with SMA expertise were identified in 19 countries in Europe and through the patient registries 641 genetically confirmed patients were identified as potentially eligible for the trial. This was followed in 2011 by the opening of trial sites in six countries and recruitment of patients supported by the patient registries in those countries. To assist with recruitment, the registries sent targeted information on the trial and the contact information for the local trial site to patients in the registry who appeared to meet the basic inclusion criteria for the trial. For information and transparency purposes, all enrolled patients were also informed that the trial was taking place, which helped ensure that even those patients unlikely to be eligible had confidence that they were still being kept up to date and that all patients were aware that this research was going on. The target of recruiting 150 patients was reached within less than 9 months, and the company concerned acknowledged that support from the registries and CTSR was a major contribution to this result at both the feasibility (planning) and recruitment stages of the clinical trial.

5.4.3 Reuse of Registry Data for Additional Studies

The secondary aim of the TREAT-NMD patient registries beyond facilitation of clinical trial feasibility studies and recruitment is to facilitate research into epidemiology and natural history, establish genotype-phenotype correlations, enable mutation analysis and assess standards of care. At both a national and international level the registries have been used for a range of additional purposes and some examples are presented here.

5.4.4 Natural History and Genotype-Phenotype Correlations

A detailed understanding of the natural history of the disease is essential to facilitate drug development in rare diseases. With the increasing number of clinical trials, it is critical to consolidate the data available to the scientific community to understand the natural history of NMDs and also to use the available data from registries and natural history studies to evaluate outcome measures for planned efficacy studies [8]. As already described, the data collected through recruitment-focused registries can provide valuable information about certain natural history milestones despite the restricted core dataset. However, some registries do also collect additional information of interest such as quality of life, outcomes related to pain and fatigue and other aspects that increase understanding of the condition and its progression, particularly if this data is collected longitudinally.

The particular strength of genetic registries such as those affiliated with TREAT-NMD is that they collect information about the causative mutation, something that is often lacking in natural history studies, and therefore enable better understanding of genotype-phenotype correlations. Having an understanding of the type as well as the frequency of causative mutations and their correlation with the associated phenotypes is invaluable for research and diagnosis as well as clinical care. Particularly since a number of therapies currently under development (e.g. antisense-mediated exon skipping or stop-codon suppression in DMD) are mutation-specific, meaning that only a certain sub-population of diagnosed patients will benefit, the need to capture the precise mutation that causes the condition alongside the clinical data is becoming increasingly crucial for the development of new treatments. Thanks to the harmonised dataset and the fact that HGVS (Human Genome Variation Society) nomenclature is used by the TREAT-NMD affiliated DMD registries, it was possible to carry out a mutational analysis of the data from the global system. The analysis demonstrated the allelic heterogeneity of the *DMD* gene in a cohort of over 7000 patients [5], providing valuable data on the range and prevalence of mutations that can potentially benefit from novel therapies.

Case Study 3: Global FKRP Patient Registry
The Global FKRP Registry is an international registry that collects genetic and clinical data about people affected by conditions caused by mutations in the FKRP (Fukutin-Related Protein) gene, namely limb girdle muscular dystrophy type 2I (LGMD2I) and the rarer conditions congenital muscular dystrophy MDC1C, Muscle Eye Brain Disease (MEB) and Walker-Warburg Syndrome (WWS). The registry includes a combination of patient-self-reported and clinician-reported data and includes elements chosen with clinical trial readiness in mind such as demographics, genetic mutation, motor, respiratory and cardiac function alongside other measures such as pain and quality of life questionnaires [58]. Data collection is repeated annually, which provides a longitudinal source of information contributing to the understanding of the natural disease course of each condition. Collecting genetic details together with this detailed clinical information provides a valuable mechanism for ascertaining genotype-phenotype correlations in those affected by FKRP-related conditions.

5.4.5 Disease Prevalence and Epidemiology

The small numbers of people affected by individual NMDs can discourage pharmaceutical companies from investing in drug development programmes for these conditions. Having an accurate understanding of prevalence and incidence of the condition and an understanding of the patterns, causes, and effects of health and disease conditions in defined populations assists companies in planning their drug development and marketing programmes as well as providing information useful for research. There are limitations to utilising the registries for prevalence estimates due to their incomplete coverage of the population and bias towards research-active patients. Nevertheless, the registries have been utilised as one source of information to estimate disease prevalence, and a recent public-private partnership between a pharmaceutical company and TREAT-NMD performed a study of SMA prevalence taking information gathered through the SMA registries and cross-referencing it with information gathered through other sources such as genetic laboratories and hospital records to provide an overview of patients who might benefit from future therapies for SMA currently in development [69].

5.4.6 Development, Assessment and Dissemination of Standards of Care

For neuromuscular conditions such as DMD where no curative therapies yet exist, it has been known for some time that receiving multidisciplinary care in line with best practice guidelines results in greater life expectancy and quality of life [16, 44],

but the way in which clinical care is implemented in practice particularly across various range ages and in different countries was until recently not widely explored. With the increase in international clinical trial activities for rare NMDs, there was a recognition not only that best-practice care benefited patients even in the absence of curative therapies, but also that multinational trials required a standard baseline of care in order for patients recruited at different sites to be comparable as a trial population. Registries have been a valuable mechanism for disseminating information about care standards, helping to inform patients about the care they should expect to receive from their doctors, as well as for recruiting patients for studies assessing the extent to which such standards are applied in practice [34].

Case Study 4: Using Registries to Assess Care Standards Implementation: The CARE-NMD Project

CARE-NMD was a three-year EU-funded project launched in 2010 that studied implementation of best-practice care guidelines for DMD across Europe [48]. Comprehensive international clinical care guidelines for DMD were published in 2010 [9, 10] and their subsequent widespread dissemination included a family guide translated into over 30 languages and dissemination through patient organisations and through national DMD registries. As part of CARE-NMD, a multinational study exploring the extent to which the care guidelines were adhered to in seven European countries – Bulgaria, the Czech Republic, Denmark, Germany, Hungary, Poland and the United Kingdom – was carried out. The use of the patient registries in the distribution of the questionnaires provided a valuable mechanism for reaching the patients and families directly, allowing the anonymity of the respondents to be maintained, but ensuring that the age-appropriate and language specific questionnaires were distributed to the respondents. This study showed substantial inter-country variation in adherence to the guidelines, with adherence generally lower in Eastern European countries, but with substantial gaps in care provision across all countries studied and greater disparities in the adult than the paediatric population, showing the need for further work to integrate the guidelines within national healthcare systems [64].

5.4.7 Socioeconomic Studies on Burden of Illness

Cost-of-illness studies are a means of quantification of the economic burden of a disease on the individual, their family and society as a whole. Such studies help to gain a better understanding of the full scope of the financial burden associated with the disease because they can demonstrate indirect costs associated with patient or carer productivity losses and not simply the direct healthcare costs [32]. This is valuable information for pharmaceutical companies bringing a product to market, since an intervention that modifies the disease course can also affect the financial

burden, for example enabling a parent to keep working rather than having to give up work to look after their affected child. While the TREAT-NMD registries do not capture sufficient data to perform such studies directly, they have been used to recruit families for the in-depth studies, and at a subsequent stage, milestones at which burden of illness increases, for example at loss of ambulation, can be correlated with the relevant data elements captured in the registry in order to provide statistical information about the cost:benefit ratio of a treatment intervention.

Case Study 5: DMD Burden of Illness
In 2012, a multinational health economics study for DMD was conducted with the support of the DMD patient registries [33]. The aim of the study was to understand the real costs of DMD from the perspective of person with the condition, caregivers and society. Patients with DMD were identified through the national DMD registries from Germany, Italy, UK, and the USA. A total of 770 patients and their primary caregivers in Germany (173), Italy (122), the UK (191) and the USA (284) completed a questionnaire on their experience of living with DMD and its impact on medical care, employment, leisure time and quality of life.

Use of the registries to contact families enabled the researchers to reach the required study population in a very streamlined way and guaranteed that that only people with the condition and their carers were approached. In this way the registries and the registered patients contributed to the first international study of its kind, enabling researchers to quantify the many different costs accompanying a rare condition such as DMD and showing that there is a considerable financial burden carried by affected families. This is important data when assessing cost versus benefit when a drug receives marketing approval and showed that registries that are able to recontact patients for additional followup can be a highly effective mechanism for gaining such detail even when it is not part of the original registry dataset.

5.4.8 Postmarketing Surveillance

The need to perform a Phase IV clinical verification study (postmarketing surveillance) is a condition that may be set by the regulatory authority (EMA or FDA) at the time it grants a pharmaceutical company a license to market a drug/therapy. Postmarketing surveillance may include collection of data on the safety of the therapy, including unexpected side effects, and efficacy of the therapy, for a period of time after the drug is available on the market. Pharmaceutical companies typically set up drug-specific postmarketing registries to fulfil this regulatory requirement. For rare diseases, there has been a steer from the regulators towards disease-specific

instead of drug-specific surveillance registries, i.e. registries for individual diseases that would receive data from multiple studies/companies. As well as being more cost-effective than setting up a new registry for each new therapy, this would have the advantage of enabling non-proprietary data such as natural history from control cohorts to be reused by the community. However, setting up a disease-specific system is a complex issue with many stakeholders to be considered, including patients, patient organisations, patient registries, clinicians, regulators and the relevant pharmaceutical companies. The need to firewall certain proprietary data items while enabling others to be shared has made commercial partners wary of this approach, but the concept is being piloted in a number of neuromuscular conditions, and the aim is to link the data with cohorts from the patient registries in order to provide control data from individuals not receiving the therapy.

Case Study 6: GNE Registry Platform

To address the challenges of studying the natural course and heterogeneity of GNE myopathy, a rare adult-onset muscle disease, a public-private partnership was established between Newcastle University, TREAT-NMD and Ultragenyx Pharmaceutical to run a longitudinal disease monitoring program (NCT01784679) [23]. This project combines an international online registry, a linked natural history study (selected clinics) and potentially in future postmarketing data collection under one umbrella. Over 3 years over 80 patients have taken part in the natural history study and 230 in the online registry. The registry has enhanced understanding of the epidemiology of GNE myopathy and genotype distribution and has enabled the estimation of a progression timeline of reaching milestones in the natural course of the disease. Within the associated natural history study, a comprehensive longitudinal physiotherapy assessment was conducted in ambulant and non-ambulant patients. The findings have resulted in better understanding of yearly decline in upper and lower extremity power.

Several clinical trials are currently ongoing in GNE myopathy and therefore a solution for postmarketing data collection is anticipated to be needed in the future. This platform may become part of the overarching registry as an additional postmarketing platform to collect medication-specific information, allowing parallel data collection and comparison with natural course of the disease, safety and efficacy and comparison with other methods of treatment if and when available. Where patients are enrolled in the registry and natural history study and then enrolled in a therapeutic trial, the speed of disease progression before and after the treatment could be compared in the same individual, meaning that the patient can become their own control. This approach has the potential to avoid data fragmentation and allow efficient analysis of the data and knowledge obtained over the years.

Lessons 1: Trial Readiness Lessons

- Reach clear consensus on the primary purpose of data collection and select data items accordingly.
- Do not make the dataset comprehensive at the expense of usability, especially where data entry is voluntary. If the registry aims for maximal uptake, minimising the number of items collected should be considered, particularly for clinician-reported systems.
- Capturing clinical data items that frequently form the basic inclusion criteria for clinical trials enables registries to be used to calculate numbers of eligible patients in a particular region, thus helping with trial planning and trial site selection.
- Where registries are used by pharmaceutical companies for feasibility studies and recruitment, cost recovery models can help recoup some of the registry running costs.
- For registries focused on trial recruitment, collecting personal data is essential in order to recontact the patient, but such data must be stored securely in line with national data protection legislation, and the patient must provide informed consent for recontact.
- Best practice developed within TREAT-NMD mandates that potentially eligible patients are always contacted for recruitment by registry staff as a trusted intermediary, avoiding providing sensitive patient data to third parties such as pharmaceutical companies.

5.5 Registries for Genomic Research

The rapid advances in next-generation sequencing (NGS) in recent years have resulted in new requirements for patient-level phenotypic data capture. In neuromuscular disease, the gene-based registries described above – predicated on the association of clinical data with the precise disease-causing variant – remain the most useful entry point for patient recruitment for therapeutic trials, but gene-specific registries naturally cannot capture data on patients in whom the primary pathogenic variant is not known. Across neuromuscular disease, around 30% of all patients presenting at a specialist clinic may remain without a confirmed genetic diagnosis after gene-by-gene testing for the most plausible genetic defects linked to the phenotype. Such undiagnosed patients are with increasing frequency either referred for NGS-based diagnostics within the healthcare system or enrolled into genomic research projects for gene discovery. Here they may undergo diagnostic gene panel sequencing, in which a targeted set of genes already associated with the phenotype are analysed; whole-exome sequencing (WES), in which the entirety of

the protein-coding part of the genome is sequenced; or whole-genome sequencing (WGS), in which the entire genome including non-coding and regulatory regions is sequenced. Given that there may be as many as 50,000 points at which one individual's exome sequence differs from another, and a significant number of these variants may be predicted as potentially pathogenic by *in silico* prediction tools, analysis of the genetic information in isolation does not usually provide sufficient evidence to home in on the likely causative variant amid this 'noise'. Using a highly detailed clinical phenotype to inform the genomic analysis therefore remains essential. However, to allow new bioinformatics tools to reach their full potential in this process, clinical data collection must undergo a standardisation procedure even beyond the harmonisation created through the use of common data elements described above. Across the rare disease field, the Human Phenotype Ontology (HPO) [30] has become a leading means to achieve a 'computationally accessible' phenotype for gene discovery, and has been extensively used in neuromuscular gene discovery projects. In the NeurOmics project [41], sets of phenotypic common data elements or case report forms devised by disease experts for ten neuromuscular and neurodegenerative diseases were 'mapped' to HPO terms and the resulting data capture forms were made available in a dedicated instance of the PhenoTips software solution, a user-friendly online system that facilitates clinical data entry using the HPO. These data capture forms have been reused for phenotypic data collection for several additional neuromuscular projects totalling over 2000 patients.

5.5.1 Finding Similar Patients to Solve Unsolved Cases – The Matchmaker Paradigm

The major advantage of computationally accessible phenotypes for gene discovery is that the hierarchical structure of the ontology enables a computer to assess similarity between different cases that may have been annotated with more or less granular phenotypic descriptors, while the standardisation provided by the ontology also enables computer-based queries across multiple databases that make use of the same system. This 'matchmaking' approach [43] is now allowing combined genotype-phenotype queries to be made across different resources holding genomic and phenotypic information about undiagnosed patients – enabling, for example, the undiagnosed patients with a neuromuscular phenotype held within the RD-Connect system to be compared with the cohorts of neuropathy patients held within the Genesis database [24] or the undiagnosed paediatric cases sequenced in the Canadian Care4Rare program [52] and increasing the likelihood of finding a 'match' or confirmatory case that after the necessary validation steps can result in these two patients receiving a genetically confirmed diagnosis.

Lessons 2: Genomics Lessons

- Phenotypic data collection remains essential in the genomic era to contextualise inter-individual genetic variation and establish the causal mutation.
- To enable computers to assist with assessment of phenotypic similarity, an additional data standardisation step such as use of the Human Phenotype Ontology is required.
- Patient registries collecting clinical phenotypic data together with genomic information at an individual patient level in a standardised, interoperable manner provide a wealth of valuable data for research into disease mechanisms and genotype-phenotype correlations.

5.6 Ethical and Consent Issues and Patient Participation

Patient registries contain personal and medical information that is considered 'sensitive data' under many forms of national legislation as well as under the new EU General Data Protection Regulation (GDPR) that was adopted in 2016 and is due to enter into application in 2018 [1]. Ensuring that data are handled in accordance with legal and ethical best practice and taking patient expectations into account has been an important aspect of the NMD experience from the start. Several EU-funded projects including TREAT-NMD have involved the patient voice and active discussion of ethical, legal and social issues (ELSI) through mechanisms such as the Project Ethics Council, a high-level board with diverse expertise that provides a forum for open discussion of issues arising from project activities [38]. Such mechanisms are felt to be valuable ways of ensuring open and transparent dialogue on often complex issues and also of guiding researchers who may not be familiar with the ELSI domain. Importantly, these questions are not purely about restricting data use: it has been shown that patients do have an advanced understanding of the benefits of data sharing and often expect their data to be reused for the benefit of research into their condition. However, they do expect to be informed about the ways their data will be used [37]. In 2007 the TREAT-NMD registries charter set out the need for all participating registries to gain explicit informed consent from all participants on the use of their data for research purposes and also established the key principle of return of benefits to patients [52]. New genomics projects such as RD-Connect have further developed these same ideals in the context of genomic data, and a charter of principles for data sharing has been published to enshrine the values of enabling data sharing for the benefit of patients with rare diseases [36]. Best practice guidelines suggest that the informed consent process for research involving capture of

sensitive patient data should explicitly involve this discussion [22] and place the risks and benefits in context [26].

5.7 The Future for Neuromuscular Disease Registries

5.7.1 Approaches for Data Linkage and Computational Analysis

The recognition of the need for full interoperability of datasets held in different systems and different locations is perhaps one of the most significant lessons learned from the neuromuscular experience. The need for harmonisation of the items captured by different national registries was recognised by the TREAT-NMD registry efforts at an early stage, and the 'mandatory' and 'highly encouraged' items defined by the consortium went some way to addressing this. Nevertheless, bringing together datasets from 65 different countries, as in the case of the DMD registries, exposed numerous differences in the way the harmonised data items had been interpreted by local systems. Each difference, while not insurmountable, adds an extra burden for data integration. Does the system collect age at loss of ambulation as an age in years, or does it collect date of birth and date of loss of ambulation? Is steroid use collected as a Boolean yes/no, as a drug name, or as dates treatment started/finished? Harmonising these kinds of differences requires additional calculation steps that cannot be automated by a computer but need manual intervention. Then, if several people want to reanalyse the same data, each may end up re-doing the same manual intervention. Data experts working with large-scale research data have proposed guiding principles for making data Findable, Accessible, Interoperable and Reusable (FAIR) [67], and these principles are being piloted on several neuromuscular registries as mechanisms for making data linkable 'at the source' so that the harmonisation step only has to be done once and not each time the data are reanalysed. FAIR data resources use best practices for storage and annotation of the data they hold, with the goal that they should be discoverable and reusable for further analysis. Since many patient registries are hosted using bespoke software solutions developed with ease of data capture but not necessarily interoperability in mind, this process requires buy-in from the solution developers themselves as well as commitment from the registry curators and disease experts to accurately annotate and describe their data using appropriate semantic models. A number of NMD registries are now becoming part of this initiative under the auspices of TREAT-NMD and RD-Connect, and this is likely to significantly improve the ability to perform

queries across multiple registries in different countries, as well as adding value to the data held within each resource by providing the opportunity to link data on the same individual across multiple databases, for example associating a genomic dataset in a genomic repository with a phenotypic dataset in a registry and a biosample stored in a biobank.

Lessons 3: Data Management Lessons

- Interoperability of data collected in a registry dramatically increases its value for reuse and is of particular benefit in the rare disease domain, where every dataset has value.
- Interoperability should ideally be considered during registry setup rather than 'retrofitting' onto an existing registry – but even the latter is possible and should be advocated in cases where there is a benefit to bringing together data across resources to answer aggregated queries.
- Development of common data elements or common case report forms/questionnaires for data capture is a valuable first step towards harmonisation, but it is also important to consider interoperability at a deeper computational level through semantic modelling and use of ontologies in a comprehensive assessment of compliance with the FAIR principles.
- To achieve full interoperability of a registry dataset, multidisciplinary collaboration between disease/clinical domain experts and data interoperability experts is essential, since neither side possesses the full understanding alone.

5.7.2 European and Global Policy and Infrastructure Issues and Cross-Border Healthcare

The TREAT-NMD-affiliated registries were largely initiated as research cohorts: collections of individuals interested in participating in clinical trials, or patients seen by clinicians with a research interest in NMDs. Many were instigated because national and local healthcare systems simply did not capture the data items that began to assume new importance in the clinical trial era. However, the value of patient registration is gaining increasing recognition in the rare disease healthcare context, with the realisation that registries are valuable repositories of data that can inform healthcare planning, gather data on levels of implementation of care standards, provide epidemiological and statistical information, assist with patient outreach, and provide a link between healthcare and research [18]. In this area too, data interoperability at a computational level is important, since many medical information or electronic health record (EHR) systems capture valuable patient data that often cannot easily move outside the healthcare 'firewall' to be reused for research

[12]. National initiatives have approached the patient registry challenge from a variety of perspectives, from the comprehensive and labour-intensive manual data integration that has taken place in the UK to develop first a national cancer registry and now a rare disease registry within the public health system, [45], to innovative methods to bring the research to the data in initiatives such as the 'Personal Health Train' run under the auspices of the Dutch Techcenter for the Life Sciences in the Netherlands [15]. These two examples offer differing solutions to the same underlying integration challenge: recognising the heterogeneity of data sources and understanding that data integration simply will not happen if the data submitter has to bear too onerous a burden, the former solution aims to minimise the burden on the submitter to provide data and relies on registry staff to take on the integration burden through centralised processing, while the latter aims to make the underlying data stores FAIR, so that reuse can be far more automated while still allowing the data to remain in their original secure location.

At a disease-specific level, patient registration will be an important part of the new European Reference Networks for rare diseases due to be launched in 2017 [19]. ERN-NMD, the network for the neuromuscular field, has taken on board the lessons of the TREAT-NMD and RD-Connect experience and will use this knowledge as the starting point for patient registration in the context of the network in order to facilitate the network's diagnostic and translational research goals in addition to the cross-border healthcare activities.

5.8 Conclusion

Over the past decade, the neuromuscular field has shown that patient registries capturing key clinical and genetic information are an important resource for translational research. The rare disease field benefits particularly from such infrastructure owing to the scarcity of patients meeting inclusion criteria for trials and the need to gather multinational cohorts to enable research to better define natural history, epidemiology and genotype-phenotype correlation. The TREAT-NMD experience has clearly demonstrated that enrolment into clinical trials is facilitated by registries that have been set up for this purpose and collect contact details together with key inclusion-related clinical data items, and has also shown that such data can not only be used for its original purpose but also mined for valuable additional correlations that are made possible by such large-scale data acquisition. The limitations of the streamlined datasets collected in the TREAT-NMD registries must be acknowledged (dedicated studies will always provide more data points per patient for analysis) and the recruitment bias taken into account (unlike healthcare or population-based registries, trial recruitment registries may not be representative of the population as

a whole and contain a higher proportion of participants explicitly interested in taking part in research). Nevertheless, the data gathered provide enormous value for research in themselves as well as the opportunity to go back to the patient for additional study, and the lessons learned from the neuromuscular community may also be extrapolated to other rare disease areas. These include practical questions about best practice in registry setup as well as conceptual questions about purpose and scope. Clearly defining the purpose of the registry and its recruitment targets at the start of the process and using this to guide setup and definition of the data items collected improves the chances that the registry will be fit for purpose, collecting the optimal dataset from the optimal number of participants. Consideration of resources and funding will help avoid issues with lack of time for data entry and issues of long-term sustainability. Patients and families are able to provide reliable data entry for many data items in recruitment-focused registries and are often highly motivated to do so. Regardless of the original source of the data entry, including curation/verification of the data entered is an important reliability step. The needs of all stakeholders who may make use of the data should be explicitly addressed during the registry setup phase in order to prevent later mismatches: pharmaceutical stakeholders may have requirements for particular mechanisms to secure regulatory compliance, while clinicians, patients and researchers may have differing views on the essential data to collect, and going through a consensus process prior to launch helps iron out these differences. Registries should explicitly benefit the patients whose data they contain and must continue to evolve in order to remain relevant as research advances. In this regard, interoperability and linkage with other data sources (biobanks, omics data, imaging, and clinical trial records) adds value to the data collected in an individual registry, and registries should be encouraged to be aware of the broader international context in which they operate in order the maximise the utility of the data they collect, maintain its currency, and prepare for future advances.

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Chapter 6
Facilitating Clinical Studies in Rare Diseases

Rashmi Gopal-Srivastava and Petra Kaufmann

Abstract In recent years, there have been many scientific advances and new collaborations for rare diseases research and, ultimately, the health of patients living with rare diseases. However, for too many rare diseases, there still is no effective treatment, and our understanding of the incidence, prevalence, and underlying etiology is incomplete. To facilitate the studies needed to answer the many open questions there is a great need for the active involvement of all stakeholders, most importantly of patient groups. Also, the creation of streamlined infrastructure for performing multi-site clinical studies is critical, as is the engagement of multidisciplinary teams with shared focus on a group of diseases. Another essential component of such efforts is to collect standardized data so that downstream meta-analyses and data sharing can be facilitated. To ensure high-quality protocols and datasets, a central data management and coordinating center is important. Since there are more than 6000 rare diseases, instead of focusing on single rare disease, it is more impactful to create platforms and methods that can support a group of rare diseases.

Keywords Rare diseases stakeholders • Rare Diseases Clinical Research Network Program • Patient advocacy groups as research partners • Central Data Management and Coordinating Center • Multi-Site Studies • Standardized data collection • Single IRB for multi-site studies

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In this chapter we describe the Rare Diseases Clinical Research Network (RDCRN) program as an example for performing such multi-site studies. The RDCRN consists of several consortia focusing on a group of related rare diseases with patient advocacy groups (PAGs) as research partners, and a single Data Management Coordinating Center (DMCC) providing clinical research tools, support, and resources.

The RDCRN program is an initiative of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH), USA. The objective of this network is to facilitate clinical research in rare diseases through support for 1) collaborative clinical research, including longitudinal studies of individuals with rare diseases, clinical studies and/or phase trials; (2) training of clinical investigators in rare diseases research; (3) pilot and demonstration projects (4) a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms; and (5) access to information related to rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public. In addition, we describe how the RDCRN DMCC is beginning to collaborate with the Clinical and Translational Science Awards (CTSA) program at NCATS, so that rare disease studies can take advantage for the NCATS SMART IRB Reliance Platform allowing for the review of a multi-site protocol by a single IRB.

6.1 Introduction and Background

It is estimated that there are more than 6000 rare diseases or conditions that lead to significant morbidity and mortality, and that approximately 30 million people in the United States are affected by rare diseases. Through an Amendment to the Orphan Drug Act of 1983 [15] a rare disease is defined as a condition affecting less than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the drug in the United States.

A Special Emphasis Panel was convened in 1999 [2] by the NIH Office of Rare Diseases, now known as the Office of Rare Diseases Research (ORDR) at the NCATS. This panel was comprised of academic scientists, representatives of voluntary patient support groups, pharmaceutical, biotechnology and device industries, and other Federal agencies. The recommendations made by this panel were focused on the special research opportunities and health care issues posed by rare diseases. These recommendations included four major areas: (1) Stimulating Research on Rare Diseases and Conditions with specific emphasis on clinical research and training of clinical research scientists, establishing diagnostic and treatment centers with informatics support, and promoting the collaboration of the voluntary patient support groups, health care systems, and industry; (2) Utilizing other NIH-funded research resources and the development of a centralized information database containing research resources, made available to research investigators, physicians, and patients for their use; (3) Coordination of Rare Diseases Research and Development Activities,

with a primary responsibility of ORDR to coordinate activities and act as a liaison between the rare diseases community and the NIH, including the public, and intramural and extramural investigators at the NIH Institutes/Centers (ICs) and other Federal agencies, manufacturers, and voluntary organizations; and (4) Identifying Emerging Opportunities in Rare Diseases Research, specifically through the establishment of specialized research and diagnostic centers to attract the interests of industry to promote advances and products for the prevention, diagnosis, and treatment of rare diseases.

In November 2002, ORDR at NIH was directed by the Rare Diseases Act of 2002 (Public Law 107–280) [16] to support regional centers of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases. This law provided the legislated mandate for publishing funding opportunity announcement in order to address the needs of and facilitate clinical research for rare diseases. In response, ORDR created a program called Rare Diseases Clinical Research Network (RDCRN Program) which is described below [8]. In addition to the RDCRN program, the ORDR has added since 2002 an information center for rare diseases and a registry program. ORDR was located within the office of NIH Director, and now has been part of the National Center for Advancing Translational Sciences (NCATS) for past 5 years.

Genetic and Rare Diseases Information Center (GARD) This information center [6] was created in 2002 by the ORDR in partnership with National Human Genome Research Institute (NHGRI) to provide the public with access to current, reliable, and easy-to-understand information about rare or genetic diseases.

GARD provides comprehensive information about rare and genetic diseases to patients, their families, health care providers, researchers and the public. The online database for this program, in English and Spanish, provides accurate, up-to-date information about ongoing research, symptoms, treatment options and other details. In addition, GARD information specialists are also available through this program to discuss questions by phone in English and in Spanish. Sources for GARD and other hard-to-find information include the National Library of Medicine, scientific conferences, support groups, and clinical trials and research.

The Global Rare Diseases Registry (GRDR) Program GRDR [7] was also recently developed by ORDR, NCATS. The goal is to build a Web-based resource that integrates de-identified patient information from many different registries for rare diseases. The GRDR program aims to create a number of related tools and resources, including common data elements, data policies, and informed consent templates.

6.2 Challenges for Clinical Research in Rare Diseases

There are several challenges associated with performing clinical studies including natural history studies in rare diseases [17]. There is a need for identification and coordination of experts in the field, and for research resources for small populations of rare diseases patients geographically dispersed around the country and globe.

There remain challenges in getting to a diagnosis for rare diseases, to implementing clinical studies and to designing trials for small samples. Such challenges continue to make it difficult to translate scientific advances into health benefits for rare diseases. Many rare diseases are not well characterized and their pathophysiology is unknown. There are not many therapeutic options and treatment can be challenging. In rare diseases research, it is critical that researchers establish collaborations of scientists at multiple sites sharing tools and protocols. Also needed are rigorous characterization and longitudinal assessment of rare diseases in order to facilitate discovery of biomarkers of disease risk, disease activity, and response to therapy. In addition, high quality longitudinal data are needed for the development of meaningful clinical outcome measures. Because of the geographic dispersion of rare diseases patients, it can be challenging to recruit participants for research studies.

6.3 Goals of RDCRN Program

To address some of these challenges, the RDCRN program was established in 2003 to facilitate research into the identification of biomarkers for disease risk and disease severity/activity, and measures of clinical outcome applicable to clinical trials. It also encourages development of new approaches for preventing, diagnosing, and treating rare diseases. The specific goals of RDCRN program are to facilitate clinical research by

- Creating multi-site consortia comprising of a multi-disciplinary team focused on a group of at least three related diseases.
- Making meaningful large-scale clinical studies possible (longitudinal studies, Natural History Studies are required) by establishing uniform protocols for data collection, by cost sharing infrastructure; utilizing centralized data repository and data sharing for rare diseases.
- Collaborating with patients advocacy groups (as research partners).
- Training new investigators.
- Supporting pilot projects program.
- Providing Website resource for education and research in rare diseases.
- In addition, depending on the state of knowledge of the particular diseases, some RDCRN consortium projects include strategies for assessing current therapeutic interventions, or new clinical trials.

Description of RDCRN Program The Rare Diseases Clinical Research Network (RDCRN) program is comprised of 22 multi-site rare diseases consortia (consortia) and a single Data Management and Coordinating Center (DMCC). The RDCRN program is an initiative of NCATS and it supports collaborative and coordinated network of multi-site consortia comprised of investigators at multiple institutions/sites and patient advocacy groups committed to investigation of rare diseases working in partnership to enhance communication and sharing of resources

in a multidisciplinary approach [21]. The NCATS has partnered up with ten ICs of NIH to provide funding and scientific partnership for the cooperative agreement awards for these consortia and DMCC. The RDCRN program focuses on the collection of clinical information to develop biomarkers and new approaches to diagnosis, prevention, and treatment and promote the training of new clinical investigators in rare diseases research. In addition, this program supports an integrated and comprehensive approach to data collection, storage, and management, and the integration of clinical data with other unique data, including genetic, imaging, pathologic, and laboratory data.

Each consortium is led by a physician-scientist and consists of clinical investigators at multiple institutions and a multi-disciplinary team including biostatisticians at multiple, and relevant organizations, including patient advocacy groups and focuses on at least three related rare diseases, disorders, conditions or syndromes [1, 4, 5] (Table 6.1).

6.3.1 Special Features of RDCRN Program

- The RDCRN is unique in its approach to addressing rare diseases as a group. Each consortium studies a group of minimum three related rare diseases.
- The direct involvement of PAGs as research partners is a major feature of this network.
- Collaboration with ten NIH ICs is also a critical component to facilitate research on multiple rare diseases.

6.3.2 Focus on Observational (Longitudinal or Natural History) Studies

In each RDCRN multi-site consortium clinical research projects are conducted at multiple sites that characterize and more completely define the disease and its course for the rare diseases that are encompassed in their consortia. These, in general, are observational (non-interventional) such as longitudinal or natural history studies of patients with the given disease. Many of these studies are clinical trial-readiness projects (e.g., development of biomarkers for clinical trials, clinical outcome measures, etc.) and/or clinical trials (at least two projects are required, and one of them must be a longitudinal study). The study design and objectives take into consideration what information regarding the rare disease population would be needed in order to pursue clinical trials in that rare disease. The longitudinal studies are approached with the question: what knowledge/tools are needed regarding the rare disease in order to design efficacy trials for this rare disease? Even if there are no treatments currently proposed for the rare diseases under study, the longitudinal study is designed with the consideration that if a treatment were available for this

Table 6.1 Rare Diseases Clinical Research Network Program

Consortium/diseases studied	Principal investigator/institution
Urea Cycle Disorders Consortium	Tuchman, Mendel, M.D.
N-acetylglutamate synthetase (NAGS) deficiency	Children's National Medical Center, Children's Research Institute, Washington, DC
Carbamoyl phosphate synthase 1 (CPS) deficiency	
Ornithine transcarbamylase (OTC) deficiency argininosuccinate synthetase deficiency (classic citrullinemia)	
Citrin deficiency (citrullinemia type 2)	
Argininosuccinate lyase deficiency (argininosuccinic aciduria)	
Arginase deficiency (hyperargininemia)	
Ornithine translocase deficiency syndrome (HHH)	
Clinical Research in ALS & related disorders for Therapeutic Development	Benatar, Michael, M.D., Ph.D
Amyotrophic lateral sclerosis (ALS)	University of Miami, Coral Gables, FL
Frontotemporal dementia (FTD)	
Henoch–Schönlein purpura (HSP)	
Primary lateral sclerosis (PLS)	
Progressive muscular atrophy (PMA)	
The Frontotemporal Lobar Degeneration Clinical Research Consortium	Boxer, Adam L., M.D., Ph.D.
Corticobasal degeneration syndrome (CBS)	Sandler Neurosciences Center, San Francisco, CA
Frontotemporal Lobar Degeneration (FTLD)	
Frontotemporal dementia (FTD)	
Primary progressive aphasia (PPA)	
Progressive supranuclear palsy syndrome (PSPS)	
Primary Immune Deficiency Treatment Consortium	Cowan, Morton, M.D.
Primary immune deficiencies: severe combined immunodeficiency (SCID)	University of California, San Francisco, CA
Wiskott-Aldrich syndrome (WAS)	
Chronic granulomatous disease (CGD)	
Porphyrias Consortium	Desnick, Robert J., Ph.D., M.D.
Porphyrias: Acute Intermittent Porphyria (AIP)	Mount Sinai School of Medicine of New York University, New York, NY
Variegate porphyria (VP), hereditary coproporphyria (HCP)	
Aminolevulinate dehydratase deficiency porphyria (ADP)	
Porphyria cutanea tarda (PCT)	
Eerythropoietic protoporphyria (EPP)	
North American Mitochondrial Diseases Consortium	Hirano, Michio, M.D.

(continued)

Table 6.1 (continued)

Consortium/diseases studied	Principal investigator/institution
Mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS)	Columbia University Medical Center, New York, NY
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	
Leber's hereditary optic neuropathy (LHON), LHON and dystonia, Leigh syndrome	
Encephalomyopathy	
ALS-like syndrome of encephalomyopathy	
Neuropathy, ataxia and retinitis pigmentosa syndrome (NARP)	
Maternally inherited Leigh syndrome (MILS)	
Familial bilateral striatal necrosis (FBSN)	
Leukodystrophy	
CoQ deficiency	
Encephalopathy	
Cardioencephalomyopathy	
Leukodystrophy/tubulopathy	
Fatal infatile encephalomyopathy	
Dystonia coalition	Jinnah, Hyder A., M.D.
Focal dystonias	Emory University, Atlanta, GA
Cervical dystonia	
Blepharospasm	
Spasmodic dysphonia	
Craniofacial dystonia	
Limb dystonia	
Genetic Disorders of Mucociliary Clearance Consortium	Knowles, Michael R., M.D.
Primary ciliary dyskinesia (PCD)	University of North Carolina at Chapel Hill, Chapel Hill, NC
Cystic fibrosis (CF)	
Pseudohypoaldosteronism (PHA)	
Nephrotic Syndrome Study Network	Kretzler, Matthias, M.D.
Focal and segmental glomerulosclerosis (FSGS)	University of Michigan, Ann Arbor, Ann Arbor, MI
Minimal change disease (MCD)	
Membranous nephropathy (MN)	
Brain Vascular Malformation Consortium	Lawton, Michael, M.D.
Familial Cavernous Malformations (CCM)	University of California, San Francisco, CA
Common Hispanic Mutation	
Sturge-Weber Syndrome (SWS)	
Leptomeningeal Angiomatosis	
Hereditary Hemorrhagic Telangiectasia (HHT)	
Brain Arteriovenous Malformation	
Brittle Bone Disorders Consortium	Lee, Brendan, M.D., Ph.D

(continued)

Table 6.1 (continued)

Consortium/diseases studied	Principal investigator/institution
Osteogenesis Imperfecta (OI)	Baylor College of Medicine, Houston, TX
Chronic Graft Versus Host Disease	Lee, Stephanie J., M.D., MPH
Cutaneous sclerosis	Fred Hutchinson Cancer Research Center, Seattle, WA
Bronchiolitis obliterans	
Late acute graft versus host disease (GVHD)	
Vasculitis Clinical Research Consortium	Merkel, Peter A., M.D., Ph.D.
Vasculitides:	Hospital of the University of Pennsylvania, Philadelphia, PA
Wegener's granulomatosis (WG)	
Microscopic polyangitis (MPA)	
Churg-Strauss syndrome (CSS)	
Polyarteritis nodosa (PAN)	
Takayasu's arteritis (TAK)	
Giant cell (temporal) arteritis (GCA)	
Rare Kidney Stone Consortium	Milliner, Dawn S., M.D.
Rare hereditary stone diseases:	Mayo Clinic College of Medicine, Rochester, MN
Primary hyperoxaluria,	
Cystinuria	
Dihydroxyadeninuria,	
Dent's disease	
Rett, MECP2 Duplications and Rett- Related Disorders Consortium	Percy, Alan K., M.D.
Rett syndrome	University of Alabama at Birmingham, Birmingham, AL
Prader-Willi syndrome	
Sterol and Isoprenoid Diseases Consortium	Rizzo, William B., M.D.
Smith-Lemli-Opitz Syndrome	University of Nebraska Medical Center, Omaha, NE
Sjögren-Larsson Syndrome	
Niemann-Pick Disease Type C	
Mevalonate Kinase Deficiency	
Hyperimmunoglobulinemia D Syndrome (HIDS)	
Mevalonic Aciduria	
Cerebrotendinous	
Xanthomatosis	
Sitosterolemia	
Autonomic Disorders Consortium	Robertson, David M.D.
Multiple system atrophy (MSA)	Vanderbilt University, Nashville, TN
Baroreflex failure, autoimmune autonomic neuropathy	
Pure autonomic failure (PAF)	
Hypovolemic postural tachycardia syndrome (hPOTS)	
Dopamine beta hydroxylase deficiency (DBHD)	

(continued)

Table 6.1 (continued)

Consortium/diseases studied	Principal investigator/institution
Consortium of Eosinophilic Gastrointestinal Disease Researchers	Rothenberg, Marc, M.D., Ph.D.
Eosinophilic esophagitis (EoE)	Cincinnati Children's Hospital Medical Center, Cincinnati, OH
Eosinophilic gastritis (EG)	
Eosinophilic colitis (EC)	
Developmental Synaptopathies Consortium	Sahin, Mustafa, M.D., Ph.D.
Autism spectrum disorder and intellectual disability (ASD/ID)	Children's Hospital Corporation, Boston, MA
Inherited Neuropathies Consortium	Shy, Michael E., M.D.
Inherited peripheral neuropathies: Charcot-Marie-tooth diseases (CMT) including	University of Iowa, Carver College of Medicine, Iowa City, IA
CMT1, the dominantly inherited demyelinating neuropathies,	
CMT2, the dominantly inherited axonal neuropathies,	
CMT4, the recessively inherited neuropathies	
Rare Lung Diseases Consortium	Trapnell, Bruce, M.D., M.S.
Hereditary Interstitial Lung Disease (hILD)	Cincinnati Children's Hospital Medical Center, Cincinnati, OH
Lymphangioleiomyomatosis (LAM)	
Pulmonary Alveolar Proteinosis (PAP)	
Alpha-1 Antitypes (Alpha-1)	
Lysosomal Disease Network	Whitley, Chester B., M.D.
Mucopolysaccharidosis (MPS)	University of Minnesota Twin Cities, Minneapolis, MN
MPS bone disease	
Pompe disease	
Niemann-Pick disease type C	
Glycoproteinoses	
Wolman disease	
Late infantile ceroid lipofuscinosis, (LINCL)	
Mucolipidosis type IV	
Hexosaminidase deficiency	
Fabry disease nephropathy	
Batten-Turner muscular dystrophy	
Data Management and Coordinating Center (DMCC)	Krischer, Jeffrey P., Ph.D.
	University of South Florida, Tampa, FL

rare disease, what knowledge (outcome measures, features of disease course, markers of disease or subpopulations of the rare disease that may alter disease course, etc.) about the rare disease over time would be important to have in order to design an appropriate treatment (efficacy) trial.

6.4 About RDCRN Program

Collectively, the RDCRN is studying 200 rare diseases in natural history and clinical trials at more than 400 clinical sites located in the US and in 24 countries. There are more than 90 active protocols (observational studies and clinical trials). Since 2009 more than 44,000 patients have enrolled in these clinical studies. Two hundred and sixty four young investigators have been trained through the training program. There are 3261 collaborative consortium members of this Network including principal investigators, multidisciplinary scientists, project coordinators, NIH ICs project scientists and representatives of PAGs. There are 144 PAGs as research partners that have collectively formed a Coalition of Patient Advocacy Group (CPAG). The RDCRN-CPAG looks over the issues common to rare diseases.

6.5 Value of PAGs as Research Partners

Research partnership with PAGs is a unique feature of RDCRN program. PAGs help with recruitment of patients in clinical studies. They participate regularly in all activities of individual consortium and provide educational materials for patients and many help with training of young investigators. Since 2004 PAGs within RDCRN program are involved in more than one of the following roles as research partners (Table 6.2).

6.6 The DMCC of RDCRN Program

The DMCC is an integral part of RDCRN and provides a coordinated clinical data management system for the collection, storage, and analysis of diverse data types from clinical researchers working on many different types of rare diseases [12]. The

Table 6.2 Expanded Roles of Various PAGs in RDCRN Program

Recruit patients for clinical studies, encourage participation in NHS.
Identify cohorts of patients with range of phenotypic expression.
Educate patients, public, media and health care providers.
Identify research efforts and translate research results to communities.
Organize and fund research based scientific conferences and meetings for patients/families/caregivers.
Provide financial support for research and training programs of RDCRN (consortia) and patient registries.
Provide financial support for *travel clinics* to facilitate patient access to investigators and studies.
Establish global partnership.

DMCC provides the administrative core to the whole network and statistical support to several consortia. It also makes available technologies, tools, on line protocol management system, and support of study design and data analysis. In addition, it provides clinical research expertise, operating policies and procedures, and monitors Network compliance while addressing privacy and confidentiality issues related to database management, and multi-level data sharing. To enhance recruitment in clinical studies the RDCRN consortia utilize a Contact Registry developed by DMCC [18, 19].

6.7 RDCRN Contact Registry

The RDCRN Contact Registry is an Efficient and Effective Tool for Conducting Survey Research Large numbers of rare disease patients can be enrolled in survey-based studies in a short period of time. The RDCRN Contact Registry has been utilized to conduct 14 studies. Median study duration is only 2.5 months and median enrollment is 296 rare disease patients. Three of the studies conducted through the RDCRN Contact Registry are described below:

- The Vasculitis Clinical Research Consortium (VCRC) conducted a study [3] on the reproductive health of men and women with vasculitis. The objectives of the study were to compare the rate of infertility with and without prior cyclophosphamide and to compare the rate of pregnancy complications in pregnancies delivered before and after vasculitis diagnosis. The study enrolled 467 participants in approximately 2 months.
- The Inherited Neuropathies Consortium (INC) conducted a study [10, 11] to identify the symptoms and issues which have the greatest impact on quality of life for patients with CMT in order to facilitate development of a disease-specific quality of life measure for adult CMT. A second objective of the study was to determine the frequency of muscle cramps in adult patients with CMT and their impact on quality of life. The first phase of the study enrolled 243 participants over approximately 3 months. The second phase of the study enrolled 168 participants over approximately 3 months.
- Another Consortium is currently conducting a study to explore the patient perspective of disease burden in a rare disease. The DMCC activated the protocol on June 8, 2016. Within 24 h, the original enrollment goal of 100 participants was achieved. Due to the overwhelming response, the protocol was amended to increase the enrollment goal to 300 participants, as the study team would like to achieve 30% (25–30 individuals) of the 2–4 age group in the rare disease Contact Registry population. As of early 2016, 275 participants were enrolled in the study.

RDCRN Program's Public Website The RDCRN Public Website (http://rarediseasesnetwork.epi.usf.edu/) serves as a portal for the rare diseases community, including patients and health care professionals, to provide information on research on rare diseases, consortium activities, RDCRN protocols and practice guidelines, the

individual consortia websites and the over 240 diseases currently available through the RDCRN Contact Registry. All consortia are publicly represented on the RDCRN public website through a web page dedicated to each consortium that contains key information such as: diseases being studied, open protocols, participating sites, site contact information and PAGs associated with the consortium.

RDCRN Program's Members' Website The RDCRN Members' Website is a secure, password-protected website for Network members that includes announcements, calendars, protocol management tools and electronic case report forms. Among the functions supported include systems for adverse event reporting and monitoring, research pharmacy drug management, biospecimen tracking, image processing, desktop videoconferencing, and automated reporting. Each Consortium has a dedicated page on the Members' Website.

6.8 Training Program Within RDCRN

Recognizing the need for an increased pool of well-trained physician-researchers to work on are diseases, the RDCRN consortia each have a training component. Each consortium is required to support and train at least two trainees over the 5 years an award period such as clinical fellows or advanced post-doctoral fellows, junior faculty (e.g. assistant professor rank, research faculty, instructors), or established investigators who wish to develop or refocus their careers on clinical research in rare diseases.

The training program at each consortium includes the policies, criteria, and processes for selecting candidates, and a mentorship program. Over two hundred and fifty trainees have been trained within various consortia of RDCRN program between its inception and 2016. .

6.9 Examples of Successful Collaborations/Scientific Advancements Within RDCRN Program

Through the RDCRN program new diagnostic methods have been generated, new gene identification has been facilitated and new therapies have been identified by creating collaborative multidisciplinary, multi-site research consortia consisting of PAGs, academic researchers from domestic and international sites and project scientists from NCATS and partnering NIH ICs as collaborators, the program has demonstrated that collaborative effort can accelerate clinical research.

The RDCRN program is an effective and working model for multi-site collaborative clinical research involving PAGs as research partners. Included below are some examples.

6.10 Three Products for Urea Cycle Disorders Brought to the Market: Collaborative Effort of RDCRN-Urea Cycle Disorders Consortium (UCDC)

Within the Urea Cycle Disorders Consortia [22] at Children's National Medical Center (then led by Dr. Mark Batshaw) 19 Academic Research Centers in USA and 2 International Sites and collaborations with European Registry, Network For Intoxication Type Metabolic Disorders (EIMD), Patient Advocacy Group – The National Urea Cycle Disorders Foundation, O'Malley Family Foundation, Kettering Fund, Rotenberg Family Foundation, and Dietmar-Hopp Foundation, ORDR/NCATS and NICHD in partnership with pharmaceutical industry (Ucyclyd Pharma, Recordati and Hyperion) three drugs (Ammonul, Carbaglu, Ravicti) were successfully approved and brought to market. In addition, ORDR/NCATS and NICHD (from NIH), provided support and scientific collaboration. This was not done in isolation by UCDC, but with active and efficient teamwork with all stakeholders.

6.11 The First Approval of a Drug Therapy Treatment for LAM: Study Performed by RDCRN-Rare Lung Diseases Consortium (RLDC)

In early 2015 FDA accepted for priority review a supplemental New Drug Application for (sNDA) Sirolimus (RAPAMUNE®) for the treatment of lymphangioleiomyomatosis (LAM). LAM is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal. This is an accomplishment of the Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) Trial conducted by Dr. Francis McCormack of RDCRN-RLDC in collaboration with LAM Foundation. The sNDA was based on results from the MILES Trial [13]. This is the first drug therapy approved for the treatment of LAM and was obtained through a collaborative effort.

6.12 A Consensus Document Published to Provide Diagnostic, Testing, Monitoring and Therapeutic Guidance to Primary Ciliary Dyskinesia (PCD) Clinical Centers: From RDCRN-Genetic Disorders of Mucociliary Clearance Consortium (GMDCC)

These recommendations (for PCD and Idiopathic Bronchiectasis) include airway clearance through daily chest physiotherapy, antibiotics for acute respiratory exacerbations, and receipt of vaccinations [20]. These recommendations will greatly

enhance clinical care by providing standardized guidelines for clinicians evaluating and treating PCD patients. This was a collaborative effort of PCD Foundation, a patient advocacy group affiliated with the RDCRN-GMDCC.

6.13 A Novel Treatment for Erthyropoietic Protoporphyria: Accomplishment of RDCRN-Porphyria Consortium

About a year and a half ago the RDCRN's Porphyrias Consortium published an article in New England Journal of Medicine [9] describing the safety and efficacy of Afamelanotide for the novel treatment of Erthyropoietic Protoporphyria that is a rare blood disorder (Table 6.3).

6.14 Discussion

The Rare Diseases Act Of 2002 mandated the development of centers of excellence for rare diseases and resulted in the establishment of the RDCRN program, which has conducted clinical studies and clinical trials for rare diseases with small patient populations under a common protocol. Through the RDCRN an expanded role for patients and PAGs with recognition of need to establish collaborative partnerships has been developed. The RDCRN program has also developed and demonstrated collaborative partnerships with the pharmaceutical industry, and with academic and government investigators and institutions. In addition, it has established a critical

Table 6.3 Accomplishments of RDCRN Program (Data as of May 20, 2016)

	1st Cycle 08/01/03–07/31/09	2nd Cycle 08/01/09–07/31/14	3rd Cycle 08/01/14–5/20/2016	Total
Consortia	10	17	22	
Activated protocols	38	99	31	168
Participants enrolled in studies	5544	22,767	9073	37,384
Participants joined the contact registry	5161	10,667	5974	21,802
Journal articles	257	907	284	1448
Books and book chapters	30	96	0	126
Conference papers	111	157	0	268
Conference proceedings	9	150	6	165
Trainees	48[a]	160	56	264
Audits	71	402	278	751

[a]Do not have trainee information for all RDCRN1 consortia

mass of investigators and connected them to research participants so that clinical studies could be completed in a timely fashion.

Results of first 13 years suggest that start up times and participant recruitment have improved. Patient advocacy groups in their expanded roles have been helpful in facilitating research, and in particular participant recruitment. Involvement of ten NIH ICs has resulted in increased number of consortia. In addition, clinical trials to meet regulatory requirements of new drug applications are possible and encouraged in RDCRN consortia and this has ultimately led to drug approvals.

There are several lessons learned through RDCRN program. A multi-site approach can be successfully implemented for rare diseases including those affecting multiple organs. Several separate areas of expertise can be coordinated in such a Network. The central coordination of recruitment sites is important, along with the standardization of data through a single DMCC or single capture platform (one consistent system) and data repository. Central training of investigators for good clinical practice is also helpful.

Career development/training of young physician researchers is essential to maintain a pool of workforce for clinical research. Collaboration with pharmaceutical industry, PAGs and academic investigators with global effort is needed.

There still are several challenges to address as we aim to further facilitate clinical research. Especially for very rare diseases, we need to find more efficient ways to collaborate with global sites.

SMART IRB To streamline study start up and the implementation of the new NIH single IRB policy, the DMCC has been working on the use of a single Institutional Review Board (IRB) for multi-site studies. More recently, the RDCRN program has begun collaborating with the Clinical and Translational Science Award (CTSA) Program single IRB initiative, termed SMART-IRB (streamlined, multi-site, accelerated resources for trials). The NCATS SMART IRB platform [14] offers a harmonized IRB reliance agreement that CTSA Program hubs are signing on to so that there is a shared agreement on which specific studies can built efficiently in order to relay on another institution's IRB. Having a single IRB review a protocol for multi-site studies is anticipated to accelerate the start-up time, and improve accountability and oversight for studies.

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Chapter 7
Rare Disease Biospecimens and Patient Registries: Interoperability for Research Promotion, a European Example: EuroBioBank and SpainRDR-BioNER

Yaffa R. Rubinstein, Manuel Posada de la Paz, and Marina Mora

Abstract Well-annotated and properly preserved specimens are crucial both for diagnostic purposes and for use in basic and pre-clinical research, and are especially important for rare disease (RD) studies. Several consortia have been established in the recent years in order to facilitate research and to maximise access to rare biological samples and data stored in rare disease biobanks and registries, among them the EuroBioBank network and the Spain National Rare Disease Registry (RDR) and Biobank (BioNER).

EuroBioBank, established in 2001, was the first network of RD biobanks to operate in Europe as a service distributing human DNA, cells, and tissue to the scientific community conducting research on rare diseases.

The Spanish RDR and BioNER were created for facilitating rare disease research and health-related matters. The coordination of these two bodies represents an example of great scientific value as biological samples donated by patients at BioNER are linked to clinical information collected in the RDR.

Rare disease biobanks and registries will need for the future to increase their effort to improve interconnection so to enable investigators to better locate samples and associated data, while protecting security of the data and privacy of the participants and adhering to international ethical and legal requirements.

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Keywords Biospecimens • Biological samples • Data sharing • GUID • Biobank • Registry

Rare diseases (RDs) are a clinically heterogeneous group of about 6000 disorders. In the USA the definition for rare disease is a disease or condition that affects less than 200,000 individuals in the USA at any given time [6], and in Europe when it affects less than 1 in 2000 people [1]. Although any one condition is rare, their cumulative public concern is substantial with 6–8% of the population (millions of individuals) having a rare disease at some point in their life. RDs are commonly diagnosed during childhood and often have deleterious long term effects and can be life threatening [5].

Many of the problems and difficulties associated with biospecimens for common diseases also apply to rare diseases biospecimens. In the latter, however, these problems are more acute, because of the additional challenges that uniquely pertain to research in rare diseases. Rare disease biospecimens, to the extent that they are available, are widely dispersed across geographical regions and among various government supported and private bio-repositories.

Biorepositories (Biobanks) can provide the fuel to stimulate collaborations between patients, researchers and industry to accelerate research to develop drugs, therapeutics and, hopefully cures for these rare diseases. Bio-specimens with well annotated clinical information are essential for medical research, specifically in the era of personalized and precision medicine. Because of the rarity of these biospecimens, global sharing and collaboration for standardization of high quality of samples with the associated data and interoperability between the different databases collecting patient's samples and data is important.

Unfortunately, this effort is being hampered due to a combination of many factors which includes lack of standardization in data collection and the quality of the samples. Also lack of a consensus on human subject issues, ethical, legal regulations (informed consent, ownership, and patient privacy), interferes with global sharing of material and the associated data,

For rare diseases the quality and the availability of the specimens are important factors that need to be taking into account whenever establishing a database that serves as a locator and a link to a network of biorepositories.

Since these samples for most cases are scarce and limited in number, there are two main questions to address; one is how to locate a collection of rare disease specimens and second what should be the basis of sharing these valuable samples. Regarding the latest point a question is arisen, should they be used only for projects with highly significant scientific and medical value, or be available and distributed to any request?

When it comes to the value of the specimen, one needs to realize that specimen with clinical annotation will accelerate research and lead to discovery of new biomarkers for targeted therapies that will lead to improve the quality of life for many patients.

Sample collection and biobanking should be incorporated in the infrastructure of any hospital or organization that collects patient clinical data, for example patient registries.

Somiari & Somiari [19] suggested, in a recent article, a grading system to define the value of the specimen and provide some gaudiness for distribution and sample sharing. This grading system with the accreditation system developed by CAP (College of American Pathologists) [11] and the best practices developed by ISBER (International Society for Biological and Environmental Repositories) [9] and NCI [3] collectively it can alleviate some of the difficulties and concerns about acquiring and distribution of rare and valuable sample including issues related to cost associated with manning these biobanks.

To accomplish that it will require a great degree collaboration of agreement, not only within the different scientific entities, but also on the level of private sector across many countries. Indeed, for rare diseases there is a growing international collaboration and agreement on the need to increase the access to data and biocpecimens to optimize their use [12].

In addition to the physical collection of the samples, in order to increase sample accessibility, there is a need for systematically listing the existing repositories around the world, that will enable investigators locate specific collection and foster collaboration worldwide. Networks of biobanks can also serve also as a biorepositories locator.

Biospecimens held in biobanks have enabled researchers and clinicians to understand the mechanism and underlying cause of RD for gene discovery and for development of diagnostic and therapeutic biomarkers. For example; DNA has been used to discover new genes and gene mutations, identify new diagnostic criteria, and genotype–phenotype correlations. Sera and plasma facilitated the identification of new biomarkers and protein profiles allowed the identification of disease. For Biospecimens users to be able to help handle and process samples in a standardized manner and to evaluate, interpret the data and compare it in a consistent manner, the Biospecimen Reporting for Improved Study Quality (BRISQ) was developed and an article submitted for publication. Authors submitting articles reporting on the use of biospecimens are required by many major journals to provide the information established by BRISQ [14].

For Biorepositories harmonization and interoperability with RD patient registries it is critical to promote clinical engagement and enhance diagnostic and therapeutic development for RD. To this regard, equitable and ethically grounded data sharing agreement through engagement in order to achieve consensus with patients, clinicians, institutions, and government agencies is essential.

In addition, collaborative research requires sharing and/or integrating data from various sources using a range of different terminologies, which requires semantic and syntactic interoperability [20]. The use of biobanks for research does not only depend on the availability and quality of the biomaterials, but also on the associated clinical data and personal characteristics, and the requirements to obtain time-specific phenotypic-genotype data. The development of precisely defined clinical Common Data Elements (CDEs) may help to ensure that clinical relevant data are

collected at each time interval. Clinicians should be encouraged to adopt common CDEs to facilitate their use in clinical research, patient registries, and other human subject research including in all omics fields. Thus, it is of an important need to link patient's clinical information collected through patient registries to the date associated with biospecimens donated by the same patient The integration of clinical phenotype data across centers and across diseases is essential for future progress. This is a critical problem in rare disease. To address this issue, major medical research institutes have joined in a global effort to foster collaboration in rare disease research and established The International Rare Diseases Research Consortium (IRDiRC) [8].

In order to facilitate research in the field of rare diseases, and to maximize access to rare biological samples and data stored in biobanks, several consortia have been established in the recent years. Here we discuss two major biobanks which made a tremendous effort to address the issues listed above; the EuroBioBank and the Spain RDR-BioNER.

7.1 The EuroBioBank Experience

The EuroBioBank (EBB), established in 2001, was the first network of RD biobanks to operate in Europe as a service distributing human DNA, cell, and tissue to the scientific community conducting research on rare diseases [15]. The EBB network obtained funding in 2002 under FP5, started operating in 2003 and was subsequently supported through the FP6 program TREAT-NMD. While financed by the European Commission, major milestones of the network were concerned with definition of common quality criteria; development of Standard Operating Procedures and ethical guidelines; adoption of standards for material transfer and biobanking; and development of a dedicated website [4] to offer services to the scientific community. A web-based catalogue was specifically designed to provide easy access to referenced samples and to allow for the presentation of the collections. This has been a key service that has made the EBB network highly valued within the scientific community during the last decade.

New partners have joined the EBB network, since its beginning: the network now includes 22 biobanks from 11 countries (9 European). Biobanks and biomaterial collections across the world can join EBB. The member biobank maintains the legal custodianship of samples, whereas the EBB acts as a clearing house or 'virtual' biobank with its online catalogue for locating samples. Researchers from anywhere in the world who locate a sample of interest through the catalogue can directly contact the biobank holding the sample. Sample distribution is governed by the conditions set out in the EBB charter and standardized material transfer agreements (MTAs).

Since its establishment, the reputation of the network has greatly increased making the EBB brand highly recognized, but EBB remains prominent mainly thanks to the support of the members, and without specific funding. Since its establishment,

more than 400 papers have been published using some of the about 130,000 RD samples available across the network.

Recently, EBB has joined the RD-Connect platform [20] a European-funded global infrastructure project whose main aim is to link up databases, registries, biobanks and clinical bioinformatics data for rare disease research. EBB, in this context, will become "the biobank" for RD-Connect. New incoming RD-Connect biobanks will be incorporated as part of the EBB network. The sample catalogue of each EBB partner will become part of a unique dynamic, updated, searchable catalogue of biological samples linked to clinical data from patient registries and to patients' 'omics' data, which will represent a major output of RD-Connect [13].

Furthermore, EBB will contribute expertise to promote high professional standards and best practices in RD biobanking and implement the integration with RD patient registries.

7.2 The Spain RDR-BioNER

The Spanish National Rare Disease Biobank [2] was created in 2013 to support national and international research, through collecting and storing biological samples of people affected by rare diseases, their relatives and controls. BioNER, coordinated by the Institute of Rare Diseases Research, Instituto de Salud Carlos III (IIER, ISCIII), participates both to the EuroBioBank network, being IIER, ISCIII one of the founding EBB members, and to the Spanish Network of Biobanks (60 biobanks collecting samples from all diseases). BioNER mission is to support national and international research, providing rare disease samples for research related to aetiology and preventive aspects, as well as to discovery of new treatments and prognostic factors.

BioNER, in addition, is strictly connected with the national RD Registry (RDR) that gathers health information on RD patients. The National RDR's main aim is to build a comprehensive platform where patient and population-based registries can be harmonized. It involves all health departments of the autonomous communities (regions) of Spain, the Spanish Ministry of Health, the Spanish Centre of Reference of People and Families affected by rare diseases (CREER), six Spanish medical societies, four research networks, pharmaceutical and biotechnological organizations, the Spanish federation of Rare Diseases (FEDER) and its foundation (FEDER Telethon Foundation), as well as the Institute of Rare Diseases Research (IIER) which acts as a coordinator and leader of the network. Patient registries addressed to patient outcome research, and population-based registries addressed to epidemiologic research and social and health system planning, are contributing to building RDR. More than 1 million people affected by RDs are listed in the Spanish RDR registry, representing about 94% of the RD population in Spain.

The interconnection of BioNER and RDR represents for Spain a great advance in the strategy aimed at facilitating RD research and health-related matters. In fact, the coordination of these two bodies represents an example of an optimal scientific benefit

and value when biological samples donated by RD patients at BioNER are linked to patient clinical information collected, using standard terminology, in the RDR, having as ultimate aim the collaboration and interoperability with other RD databases.

7.3 Future of Biobank and Registry Interoperability

Newly established biobanks as well as existing biobanks, will need to increase their effort to improve interconnection with registries and clinical datasets in order to provide well annotated high quality biospecimens linked to related clinical data, to produce complete dataset to enable high quality and meaningful research. Patient registry managers are now realizing the value and the need of collecting samples from their participants and linking the specimen's data to the participant's clinical information collected through the registry. The importance of this linking was reported by Rubinstein et al. [17] during an international conference. Institutions and government agencies may have to come up with some appropriate requirements to ensure that RD biospecimens be collected into biobanks that are incorporated in the infrastructure of any hospital or organization also collecting patient clinical data. Spain BioNER and RDR interconnection represents a perfect example of how such an issue can be addressed.

With regards to linking patient's clinical data to their donated samples, there is no one specific system yet that has been agreed upon and adopted by the international community. The NIH Global Unique Identifier (GUID) [16] which was developed to enable follow up on patients over time, in different studies or registries, can be used also to link the patient clinical data to their donated specimens. The NIH GRDR pilot project [18] suggested to use of the GUID as a mean to link the two data sets.

The GUID is a randomized, secured number that is generated from a few required data (elements) collected from the patients. The elements that are required to generate the GUID are embedded in the list of the GRDR CDEs that were developed for patient registries [18]. Any registry using these CDEs can generate the GUID and use it as a unique number attached to the patient clinical data and to the donated biospecimens while protecting the privacy of the patient. Other GUIDS or linkage systems may be used and available.

In addition, collecting phenotype data according to the Human Phenotype Ontology (HPO) [7] a standardized vocabulary of phenotypic abnormalities encountered in human disease, will greatly improve the interoperability between biobanks and registries. Thanks to the detailed terminology and semantic organization of the HPO, and the use of instruments such as PhenoTips, it will be possible to specify precise and detailed phenotypic profiles in a standardized computer-interpretable format.

As the demand for high quality and well annotated samples increases and the linkage and interoperability between clinical databases and registries, so is the complexity of data management, integration, sharing and access of metadata across institutes and organization around the globe [10]. The fast growing demand for interposable databases, requires the development of software that can handle

metadata. Examples for these type of software which already have been developed are i2b2, XTENS AND CaTissue,

In conclusion, the future of RD biobanks linked to registry from the global perspective, will require a well standardized and integrated system to enable investigators locate the sample and the associated data, collaborate and share samples/data while protecting the security of the data and the privacy of the participants and adhering to international ethical and legal requirements.

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Chapter 8
Data Quality in Rare Diseases Registries

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Abstract In the field of rare diseases, registries are considered power tool to develop clinical research, to facilitate the planning of appropriate clinical trials, to improve patient care and healthcare planning. Therefore high quality data of rare diseases registries is considered to be one of the most important element in the establishment and maintenance of a registry. Data quality can be defined as the totality of features and characteristics of data set that bear on its ability to satisfy the needs that result from the intended use of the data. In the context of registries, the 'product' is data, and quality refers to data quality, meaning that the data coming into the registry have been validated, and ready for use for analysis and research. Determining the quality of data is possible through data assessment against a

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number of dimensions: completeness, validity; coherence and comparability; accessibility; usefulness; timeliness; prevention of duplicate records. Many others factors may influence the quality of a registry: development of standardized Case Report Form and security/safety controls of informatics infrastructure. With the growing number of rare diseases registries being established, there is a need to develop a quality validation process to evaluate the quality of each registry. A clear description of the registry is the first step when assessing data quality or the registry evaluation system. Here we report a template as a guide for helping registry owners to describe their registry.

Keywords Rare diseases registries • Quality assurance plan • Data quality indicators • Public health registry • Clinical research registry • Validity

8.1 Introduction

Patient registries are considered key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to collect a critical mass of data to increase the understanding of natural history of rare conditions, and to support the feasibility of the clinical trial. Therefore high quality data of rare diseases registries is considered to be one of the most important element in the establishment and maintenance of a registry. Quality is a much more complex term than it appears. Many definitions and interpretations exist depending on the goal, use and intent of the registry [9, 21, 36]. In broader terms, the term "quality" is defined as the totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs [15] (ISO 8402:1994 2004). Quality evaluation of registry is considered to be one of the most important element in the establishment and maintenance of a registry. It is desirable that every registry should have a "builtin" a Quality Assurance Plan that should be implemented at every stage of the registry, from inclusion of new cases to dissemination of the final data analysis reports. As Brooke states, "every year an enormous quantity of medical statistics is compiled and published, and very little is known about the quality of the data on which these statistics are based" [4]. Before embarking on the quality evaluation of a registry, it should be determined whether the entire registry system (its total quality), or only part of it, will be assessed. The last guidelines on patient registry developed by the Cross-Border Patient Registries Initiative, a Joint Action Project funded by the European Union, identified numerous "quality influencing factors" that categorised the total quality of the registry into four groups. These categories should not be viewed separately when assessing the overall quality of a registry. Together these categories capture all the aspects of registry quality that are important to data end-users [38]. These categories are: (1) Registry governance; (2) Data quality; (3) Information quality; (4) Ethical issues (including security and privacy). The aim of this article is to focus on and address only the data quality aspects of a registry.

8.2 Data Quality

Data quality can be defined as the totality of features and characteristics of data set that bear on its ability to satisfy the needs that results from the intended use of the data [1]. The term "quality" refers to the degree of excellence, as in, "a quality product". In the context of registries, the 'product' is data, and quality refers to data quality, meaning that the data coming into the registry have been validated, and ready for use for analysis and research. Data characteristics must altogether satisfy the intended needs of the registry purpose. In fact, the success of a registry will ultimately be judged on its ability to meet the goals it was created for.

Determining the quality of data is possible through data assessment against a number of dimensions. Data quality dimensions can be defined as "a set of data quality attributes that represent a single aspect or construct of data quality" [37]. By identifying different aspects or constructs of data quality it is then possible to measure the quality of data against those aspects or constructs identified.

Some dimensions of quality have been well discussed and defined in other area of disease registries [3, 22].

The dimensions provided are applicable for different registry types with different purposes, however not all may be equally important. The importance of a particular quality dimensions depends on the set objectives of the registry.

According to the objectives they are interested in, Registries are classified in the following categories:

- Public health registry/surveillance registry (disease registry): focus on disease occurrence (estimate incidence prevalence, temporal trends geographical distribution in relation to person, place, time); source of cases could be various and multiple; data collected are "basic" and refer to demographics, outcomes such as mortality; non longitudinal data are collected and tempestive information is required; the principal uses of data are disease burden measure, disease descriptive epidemiology, disease aetiology and risk factors, public health surveillance; health planning generate hypothesis for epidemiological research; the advantage and disadvantage are that data are "basic" but representative and can provide population disease occurrence; the denominator is well defined and the population or geographical coverage is comprehensive (population based registry). Example of public health registry/surveillance rare diseases registry are the Italian National Rare Diseases Registry [33, 34], Spanish Rare Diseases Registry [39], French National Rare Diseases Data Bank [20].
- Clinical/genetic research registry (patient registry): focus on the study of natural history of disease, understand cause of disease, risk factor, prognosis or treatment effect; sources of cases are clinical units; data collected are "clinically rich" and refer to diagnosis, prognosis, clinical outcome measures; the principal uses of these types of data are for clinical research, patient care and disease management. The follow-up is essential and tempestive data information is not

fundamental; the advantage and disadvantage are that data are "clinically rich" but not representative of the residing population, thus cannot provide epidemiological estimates of disease at population level; the denominator is not well defined and the population or geographical coverage may not be comprehensive (non population based registry). Furthermore, depending on the initial research question posed, there will be clear inclusion/non-inclusion and exclusion criteria defined before starting collecting data, which will exclude cases. Example of such clinical registry are TREAT-NMD DMD Global Database [2] and RaDiCo cohort databases (RaDiCo is the French Programme on Rare Disease Cohorts coordinated by Inserm is funded by the French National Research Agency under the specific programme "Investments for the Future", Cohort grant agreement ANR-10-COHO-0003): www.radico.fr).

- Treatment registry focus on safety of monitoring for post-marketed drugs or devices products; services health technology assessment; mainly collect clinical and anthropometric data, information about medication, devices and health services, and Patient-Reported Outcomes [26].
- Combination registries

While each of the dimensions may be considered equally important, there may be instances where the relative importance of one dimension is greater than another.

For Public health registry/surveillance registry, that is used to calculate incidence rates of diseases, it is essential to include all existing patient cases, therefore the completeness dimension is of critical importance. On the other hand, in registries used for infectious disease, timeliness may be extremely important. For clinical registry, to satisfy the accuracy dimension, it may be necessary to sacrifice some elements of completeness or timeliness. In fact for clinical registries, exhaustive enrolment of all existing cases in the study and geographical coverage is not required, because only reaching an acceptable statistical power matters to perform the subsequent analyses.

Regardless of the type of registry, the high quality of the data is usually associated with a good oversight and governance mechanism, a secure and modern/adaptable information system, and with durable funding and would benefit from support in organizational aspects and management, innovation activities in information technology, epidemiology and statistics [6].

8.3 Dimensions of data quality and definitions

The data dimensions outlined in this article are: completeness of case ascertainment; completeness of the items; prevention of duplicate records; validity; comparability; accessibility; usefulness; timeliness.

8.4 Completeness of Case Ascertainment

Completeness of case ascertainment, known as external completeness, is the extent to which all patients occurring in the population are included in the registry database and applies to surveillance registries. A high degree of completeness of case ascertainment will ensure that the calculated incidence and prevalence rates are closed to their "true value". There are two kinds of methods to assess the case completeness: qualitative and quantitative [7]. The qualitative approach is to observe the trends in incidence/prevalence rates that can be a manifestation of changes in completeness of case registration. Implausible trends in incidence/prevalence may reflect incompleteness in recording events. Furthermore, failure to register deaths (and cause of death) will lead to overestimation of prevalence and of patient survival.

The quantitative methods may allow numerical evaluation of the completeness. Linkage with independent sources such as hospitals or national death certificates databases may be useful to estimate the number of cases missed by the registry [11, 16, 23]. These are less sensitive but inexpensive methods too. An independent survey with case ascertainment, however, gives a more accurate information on registry' completeness [12, 27]. Besides, though it is expensive, it makes possible a subsequent examination of case selection bias, a point that needs to be examined particularly when registry are incomplete. Otherwise, one will never know if those registered cases are characteristically different from the missed ones.

Two statistical methods have been suggested by David H Stone to quantify completeness of a registry: pooling method and screening method [32]. In the latter case (Table 8.1), we just use the alternative information source as a gold standard with which we compare the registry.

Therefore, cases identified by both will be true positives, and we will have false negatives (sensitivity) and false positives (positive predictive value) depending on which one of the two sources has the cases. With the pooling method (Table 8.2), all cases identified by the registry and the alternative information source, excluding the repeat ones, are put together and the proportion of those identified by the registry is calculated as an estimate for completeness of the registry. Thus, by establishing a cut-off, it could be possible to see if a registry is reasonably complete.

Table 8.1 Screening method

		External source (gold standard)		
		Cases	Non cases	Total
Registry	Cases	a	b	a + b
	Non cases	c	d?	c + d?
	Total	a + c	b + d?	?

Sensitivity = a/a + c
Positive predictive value = a/a + b

Table 8.2 Pooling method

Alternative information source	= A
Registry	= B
Pooled data	= C ➔C = (A ∪ B) – (A ∩ B)
(Set C is equal to the union of set A and set B minus their intersection)	

These methods are quite good particularly for assessing completeness of a population-based registry where the alternative information source might give us the possibility of identifying almost all cases diagnosed. However, in the case of population-based registry, it is too difficult to know all the individuals with that particular disease, and it is not easy to estimate how many of these are missed by both the registry and the alternative information source. Thus, the two methods mentioned above would not tell us how truly complete our registry is. This is an important point to be considered when we are interested in estimating in precise manner disease frequency in a target population.

Besides the methods mentioned above, there is a third and more accurate method to assess the completeness of a registry – a capture recapture method [5, 28, 29]. It is a relatively complex technique which requires a special software and the necessary know-how. It gives the opportunity to estimate the actual morbidity rate in the target population regardless of how complete the registry is. In brief, it is a method that helps to estimate those cases that are identified neither by the registry nor by the alternative source. By doing so, it completes the fourth cell of our 2 × 2 table and gives an estimate of the total number of cases in the target population.

Assessing completeness of a registry, is a relatively complicated process and becomes more difficult in the case of population-based registries. One can try hard to maximize its coverage but there is no way to assure inclusion of all cases in the registry. Complete case ascertainment mainly depends on peoples' demand of medical care, accessibility of health care, health service utilization rate and health workers' capacity to identify the illness (cases).

8.5 Completeness of the Items

Completeness of the items known as internal completeness is the proportion of registered cases with missing values (or unknown) for different variables.

When registries collect large amounts of variables, it is important, in the perspective of data quality, to take into account the specific purpose of the analysis and to distinguish for this specific analysis items deemed to be 'essential' from those deemed to be 'non-essential'. It may be reasonable to focus the objective of full completeness on the essential items only [7]. The missing value must be very low for variables which are critical to a specific analysis; for population based cancer registry the gold standard for missing value for critical variables <= 2% [13].

A registry of good quality should have a high percentage of item completeness throughout the course of its existence. If the collection of data is based on electronic data capture and data management tools (eg eCRF and e-query systems), simple automatic rules, professional and continuous data management support for making sure that critical items are completed and may help to support completeness of the registry.

8.6 Validity

Validity refers to the proportion of cases in a dataset with a given characteristic, which truly have the attribute. Lack of validity is referred to a bias or systematic error [24]. Validity depends on the precision of source documentations on the level of expertise in data classification and coding; on the registry "protocol" (explicit definitions, good coding systems, documented rules limitation of free text fields, preference for pre-defined list of possible information items; data coherence rules, continuous data management for validating entered data before final integration in the registry).Validity has both an internal and an external dimension [8].

- **Internal validity** relates to the extent of errors within the system. It depends on the following errors: – misdiagnosis: health outcomes with unspecified symptoms in the absence of laboratory confirmation; – miscoding: health outcomes which were not reported because the coding system doesn't include a specific and appropriate code; – misclassification: health outcomes reported with inappropriate case definition category; no clear case inclusion/exclusion criteria including diagnosis criteria. Moreover limitation of free text fields, preference for pre-defined list of possible information items; data coherence rules, continuous data management for validating entered data before final integration in the registry improve the internal validity of item.
- **External validity** is the ability to generalize study results to a more universal population. It is the degree to which the conclusions in a study would hold for other persons in other places and at other times. One indication that a study lacks external validity is if the sample is not representative. Evaluating validity implies a registry indicator measured against a 'gold standard' value. An agreement between the registry under examination and an alternative information source in all the items of a single case is recommended. Cases can be selected at random from the registry and entries of each item can be compared with the alternative information source. This can be patients' clinical record, laboratory records, etc. We may quantify their agreement in terms of percentage, and depending on the purpose of our interest we can establish cut-offs. Some authors use also the kappa coefficient, a statistical measure commonly used in testing the reliability of diagnostic tests, to see the agreement between the two information sources on specific variables [14, 35].

8.7 Coherence and Comparability

Coherence reflects the degree to which data can be successfully brought together with other statistical information within a broad analytic framework and over time. Coherence covers the internalconsistency of data collection as well as its comparability both over time and with other data sources [38]. Comparability is the extent to which the data collected can be analyzed to make a comparison with other registries or over time. This is very important in the analysis of geographical and temporal distribution. Standardization of definitions, use of standard clinical vocabularies, terminologies, classifications and ontology, is the only sure way to achieve the international comparability [31].

8.8 Timeliness

Timeliness refers to the rapidity at which a registry can collect, process and report sufficiently reliable and complete data, for producing results or outcome for action (report and/or research article and/or public health action) [3]. This timeliness is determined by the time between the various steps in the registry information chain and depends, also on the aims of the registry. If a registry has a role in quality improvement of health care or immediate public health action, the time period needed to produce results for feedback to clinical centres is a crucial point.

Couchoud et al. [7] propose four indicators to evaluate the timeliness. (1) Time until receipt: time from the clinical event to the record in the registry. (2) Process time: the time from the presence of the record to its availability for research (available in the 'frozen' database after quality control procedures). (3) Time to availability: sum of the two previous times. (4) Number of patients or data recorded in the registry after the database was 'frozen' to produce an annual report or a scientific paper. These cases or items are found the year after, in a new 'frozen' database [7]. An other indicator of timeliness is also timelines of patient visits and adherence to them in a given longitudinal study. If you consider a surveillance registry, you need only one capture of the "case"; if it is a clinical research registry, you need to make sure all planned visits (ex: 2 visits per year during 5 years are respected for all included cases.

Other prerequisites of data quality are accessibility, usefulness and prevention of duplicate records.

8.9 Accessibility

Accessibility is defined as availability of aggregate data, publication of periodic reports and/or literature in peer-reviewed journals, and clear framework and procedures (including at the technical level) for accessibility to external researchers of anonymized patient-level data. Registry data accessibility presents an opportunity

for sharing and more productive collaborations to collect relevant data, implement quality and standardization procedures, and provide broad access to comprehensive aggregate information and anonymized patient-level data to facilitate the advancement of research and improvement of patient care [19].

8.10 Usefulness

Usefulness refers to the extent to which an information system or its output provides any benefit or value. The usefulness of a registry can be perceived differently by different stakeholders. Government institutions are likely to value systems from public health point of view: for example, evaluate the population health status; planning health services; provide data on declining disease incidence. On the other hand, the scientific community will find it useful when disease registry data offer new insights in the discovery of disease knowledge and its natural history, or reveal new phenomena, which will help to generate new hypotheses. For clinical registry, the level of usefulness is intended for example how to use data registry in subsequent clinical trial and study design; participation in awarded grants; several publications through peer-reviewed publications.

One more feature closely linked to usefulness is the registry's overall adaptability or its capacity to include new data items (eg to address specific research subprojects in partnerships with potential data end-users such as pharma companies).

8.11 Prevention of Duplicate Records

Duplicate records refer to the multiple registration of the same patients into the registry database. This might due to patient mobility, which often refer to more than one doctor and more than one hospital; jumping from paediatric care to adult care management or related to registration errors (spelling mistake in family name (or very long family names not entered the same way by two clinicians in the same of different hospitals). Specific methods to detect those duplicate should be in place, otherwise, incidence and prevalence rate may be overestimated. Identifying duplicate case records can be difficult, and a common set of criteria needs to be employed to prevent their generation. They can be detected with a series of deterministic/probabilistic matches using the personal identification number, or by a match in other identification variables such as name and surname if allowed, birth month and year, sex and etc. Records matching exactly in all of these fields are automatically assigned to the same patient. In some cases the diagnosis needs to be managed because a patient could have two different RD and the rest of the variables will match but this is not a real duplicate record. This only happens in wider registries where several diseases are registered. It is important that the registry needs to have in place procedures for handling duplicate registrations in order to avoid having duplicate patients entered into the registry and to calculate regulatory the percentage of duplicate records found in the whole database.

8.12 Factors Influencing the Data Quality Dimensions

Considering that data quality is part of a complex system, as many others factors may influence the quality of a registry: development of Standardized Case Report Form (CRF) and informatics infrastructure.

8.13 Development of Standardized Case Report Form

Case report form (CRF) (paper or electronic based) is the initial step in translating the protocol into standard questionnaires. The CRF must comprise all variables that are necessary to answer the research questions planned in the design phase and it has to use standard definitions of items and variables. Standard development of CRF using standard guidelines helps the collection of consistent and valid data [10]. Problematic CRF include: unclear questions (e.g. when acronyms, complex words or abbreviations are used; poor ergonomics and no use of branching logics and conditional fields systems resulting in too long reporting form); poor ergonomics and no use of branching logics and conditional fields systems (resulting in too long reporting form); no logical order of questions (e.g. clinical and laboratory sections not clearly separated or mixed-up); meaning of question is unclear [30]. In addition, scientific expert are encouraging the use of Patient-Centered Outcome Measures form (PCOM), as a relatively new concept, to be integrated with CRF. The use of PCOM form, which are potentially of relevance for rare diseases, are the instruments that can be used to measure real benefits for patients and from their perspective. The International Rare Diseases Research Consortium (IRDiRC) strongly recommend that the insertion of PROs into the design of rare diseases registries is necessary to fully evaluate their natural history [25].

A "library" of standard reporting form are elaborated by the National Institute of Neurological Disorders and Stroke (NINDS) (https://cde.nlm.nih.gov/home) with the aim of standardizing the collection of investigational data in order to facilitate comparison of results across studies and more effectively aggregate information into significant metadata results.

8.14 Informatics Infrastructure

The successful implementation and use of a registry depends on a thoroughly and accurate planning and construction of a suitable IT infrastructure [8].

The IT infrastructure for user authentication, data entry, data management, storage and subsequent analysis should be:

- Web-based for data entry through Secured-cloud-based for data storage and backup (information on a case or series of cases is entered into a data entry mask on a secured web page). Advantages are that this technology is common, cheap.

- Interface-mediated data retrieval before integration in the registry if data are initially collected or recorded in an external system. It may be possible to wholly automate data import/export by developing an interface (data warehouse) and machine readable forms (Extract, Transform, Load (ETL approach).
- Interface-mediated data management system, allowing for instance to implement pre-defined automated control rules in the forms as well as query messaging system between the data manager and the clinical unit participants for continuous (if not real time) control and validation of entered data.
- Open-source software. The great advantage of an open-source software that enables scientists to build a registry for a specific rare disease even without special IT knowledge. The downside is that the software is not supported in an enforceable way, i.e. by a legally binding contract.
- Secure-certified following regular security audits, to prevent from malicious/unauthorised interventions
- Adaptable to technological evolutions (resistant to obsolescence) and to the rise of "big data" needs.

Determining which information system architecture to use and how to design the system is an essential question when setting up a registry system [8].

The choice of server hardware and database solution can have a marked effect on data quality. Server hardware varies in levels of stability, maturity and speed and the choice of database software can affect data quality. To mitigate risks caused by the choice in soft- and hardware, the validity of data needs to be thoroughly monitored.

Based on a systematic review of the literature, Doris Lindoerfer et al. [17, 18]. developed a checklist for patient registry software systems (CIPROS) which supports developers to assess requirements of an existing system. It also supports the reporting of patient registry software system descriptions in papers and it can be a first step to create standards for patient registry software systems.

8.15 Conclusion

With the growing number of registries being established, there is a need to develop a quality validation process to evaluate the quality of the each registry.

As stated earlier, the quality of a registry refers always to the objective for which it was meant.

It will be important to –provide tools for registry managers and to elaborate on the quality indicators so they can conduct self-evaluation. This helps them to continue what they are doing if they are on the right track or to rethink and restructure their registry activity if they are having some problems. Accordingly, a questionnaire is developed as an initial tool for assessment of a registry. A clear description of the registry is the first step when monitoring data quality or the registry evaluation system. Here we report a template as a guide for helping registry owners to describe

their registry. It is necessary to update regularly this template description. Ideally all the questions of the questionnaire should be answered positively, before going ahead with the analysis of data quality (Table 8.3).

Table 8.3 Example template for registry description

Indicate the date when you are filling out the template	date: dd/mm/yyyy
1. Contact information	
Name of the registry (and acronym)	
Name of registry database owner (responsible legal entity for data management)	
Name of registry contact person	
Registry address	
Registry telephone number	
Registry fax number	
Registry email address	
Registry web home page	
2. Registry organisation	
Year of establishment	
Registry language(s)	
Membership of other international networks (yes/no, if yes specify the name of the network)	
Indicate the registry funding source	
Describe staff working in the registry which may include: PI (e.g. management, financial sustainability), Registrar (e.g. collection, registration, data management and monitoring); Informatic personel (e.g. maintenance in operational condition, backoffice/helpdesk and bug resolutions, automation and output); Statistician/epidemiologist (methods, analysis, interpretation) Medical (e.g. pathology, coding), Administration (e.g. secretarial support) and etc.	
3. Type of registry	
According to the objectives they are interested in, Registries are classified in the following categories:	
1. Public health registry focus on disease occurrence (estimate incidence prevalence, temporal trends geographical distribution in relation to person, place, time); the principal uses of data are disease burden measure, disease descriptive epidemiology, disease aetiology and risk factors, health planning;	
2. clinical/genetic research registries focus on the study of natural history of disease (understand cause of disease, risk factor, prognosis or treatment effect); the principal uses of data are for clinical research, patient care and disease management,	
3. treatment registry focus on safety of monitoring for post-marketed drugs or devices products; services health technology assessment	
4. combination registries.	
4. Objectives	
The objectives of the system indicates why the system exists	
List the principal and secondary objectives of the registry	

(continued)

Table 8.3 (continued)

5. List of diseases under registration
When preparing for the evaluation of registry system, all diseases covered by the system should be listed. The disease under registration could be specific (example: Prader-willy syndrome) or group of diseases (haemoglopinopathies, primary immunodeficiency). It is recommendable to use the list of diseases included to the Orphanet classification of rare diseases diseases (http://www.orpha.net/consor/cgi-bin/Disease_Classif.php?lng=EN).
6. Inclusion/esclusion criteria
The registry team should specify so-called eligibility or inclusion criteria that are a set of conditions that a patient must meet to be eligible for inclusion in a registry, and generally include geographic (e.g. hospitals in a particular region of the country), demographic (e.g. age, gender, ethnicity), disease-specific (e.g. a certain diagnosis, stage of disease), time-specific (e.g. specification of the included dates of hospital admission), laboratory-specific, and other criteria (e.g. size of the hospital in terms of number of patients). Exclusion criteria, on the opposite side, are those criteria that disqualify subjects from inclusion in the registry.
7. Data sources and data flow
A data source for a registry system can be defined as a place where the initial information on the disease to be reported is collected. Genetic laboratories and hospitals are the most common sources of information for registry. Other source (general practitioners electronic health record, administrative data, Patient Reported Outcomes PROs, connected devices generated data) may also be included in the registry system.
A clear flowchart for a generic case reporting system is necessary and the following elements should be considered in order to describe data flow: (1) Data providers or data sources as described in the previous section; (2) Processes for clinical diagnosis, case confirmation, and gathering of additional information; (3) Public health institutions (data recipients) that provide feedback information to participants of the case reporting process, public health professionals, and the general public. (4) data management entity.
8. Populations under surveillance of registry system
The population under surveillance can be defined as the general population or targeted groups. The targets can be based on specific age categories (e.g. children under five years of age) or other determinants.
9. Geographic coverage
The geographic coverage represents the geographic unit (municipality, region, country or any other pre-definedgeographic area) where disease registry is conducted.
Based on geographical coverage registry could be classified in:
1. population-based registries, which refer to a geographically defined population and aim is to register all cases in that population. For public health registry this information is of critical importance.
2. non-population-based registries are based on selected bodies, clinical Centers or other types of structures where the population coverage may not be comprehensive. The majority of research clinical registry are non-population based as this information is less relevant. The geographical coverage of disease surveillance is linked to the concept of representativeness of the registry system.
10. Specification of the information to be reported
List all Variables included in the registry.

(continued)

Table 8.3 (continued)

11. Registry's regulatory status
List all ethical and regulatory approvals obtained/country covered for the registry implementation.
12. Collaborative framework status
Is there a clear governance in place? yes/no if yes describe.
Please list any contract (eg consortium agreement) existing between all registry-participating institutions.
13. Informatics infrastructure (software and hardware)
Determining which system architecture to use and how to design the system is an essential question when setting up a registry. Give details of your computing system and software for data entry, data storage and data analysis, type of architecture; server selection.
14. Data management procedure/quality control
Is there a data management procedure in place? Yes/No if yes describe staff and procedures in place to manage registry data and its quality (Data management plan, (DMP), Data validation Plan (DVP) automatic rules in eCRF, continuous data management versus periodic controls, electronic data correction, query system, site visits and monitoring, etc.
15. Security standards and procedures
Describe any security measures in place (frequency of security audits, certifications obtained) and procedures (Active directory for user rights management, login authorisation procedures, history logs, back-ups, etc.).

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Chapter 9
Preparing Data at the Source to Foster Interoperability across Rare Disease Resources

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Abstract The ability to combine heterogeneous data distributed across the globe is critically important to boost research on rare diseases, but it presents a number of methodological, representational and automation challenges. In this scenario, biomedical ontologies are of critical importance for enabling computers to aid in information retrieval and analysis across data collections.

This chapter presents an approach to preparing rare disease data for integration through the application of a global standard for computer-readable data and knowledge. This includes the use of common data elements, ontological codes and computer-readable data. This approach was developed under a number of domain-relevant requirements, such as controlled access to data, independence of the original sources, and the desire to combining the data sources with other computational workflows and data platforms.

Keywords Ontologies • FAIR approach • Linkable data • Data integration • Standardization • Semantic model

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9.1 Introduction

Rare diseases present a driving use-case for the development of methods that help to efficiently combine data from disparate and dispersed resources (clinical and physiological data such as blood pressure and phenotype; molecular data such as gene expression and genotype; biobank data; and model organism/disease model information). The ability to do this efficiently with data distributed across the globe is critically important to boost research on rare diseases (RD).

Correctly combining data from disparate, heterogeneous sources presents a number of challenges that broadly split into three types: methodological challenges, representational challenges, and automation challenges.

With respect to methodological challenges, these generally relate to the act of gathering the original data. For example, what measurements were performed and how? Were the same methods or instruments used in all locations? Do instruments share identical calibrations? Were survey results collected using the same questions? If measurements were not exactly the same, at what level may they still be compared? For instance, if smoking habits were measured differently, is there a unifying measure of smoking that the datasets can be mapped-to for comparison?.

Representational challenges relate mainly to the data's "transparency" and encoding. For example, is it clear what data from each source is, in fact, comparable? Which spreadsheet columns contain which type of data? If a clinical coding system is used, is that same coding system used by both datasets? For example, can a data analyst be absolutely sure that a '2' under the column header 'smoking habit score' in one data file is equivalent to the '2' in another data file under the header 'smoking score'? This may seem trivial, but is a source of many errors. Data analysts lose a lot of time correcting mistakes and redoing analyses because they misinterpreted the meaning of the data in disparate datasets. It is important to see that if the encoding between data sets is ambiguous, the harmonization of data gathering methods is rendered futile.

The methodological challenge and the representational challenge are both aspects that relate to data quality, and high-quality data will meet both of these challenges. We might use the Orphanet database as an example. Orphanet is curated according to a set of Standard Operating Procedures (SOPs) to ensure optimal and consistent quality of its data about rare diseases [13, 15]. These SOPs address both the methodological and the representational challenge. However, if Orphanet had not focused on the representational challenge, and its curators had chosen to use French disease names to represent diseases in their database, then the data would be nearly unusable for many data scientists. Orphanet addressed this representational challenge by providing orphacodes linked to the Orphanet Rare Disease Ontology (ORDO) to uniquely identify diseases for applications across the globe. Thus, this database is both methodologically rigorous, as well as representationally transparent, and as such, is highly reusable by other researchers.

The third challenge relates to the need to combine numerous data sets. To achieve the scale of data integration required by the rare disease case, the number of datasets that must be interpreted and parsed quickly scales beyond the ability for manual

manipulation. In that case we need computers to 'know' what the structures and values in the data represent, in order to combine them correctly. For example, a row in a table with motor score, phenotype, and gene expression, does not explicitly state how motor score, phenotype, and gene expression are related to a person and to each other. This may be obvious when an expert inspects a table, and a data analyst can ask the expert who drafted a table, but that is too time consuming and error-prone for more than two or three data sets. Achieving clarity on what data means for both humans and computers is therefore a critical challenge in speed and quality-control in rare disease research. Lack of such clarity can even entirely block the reuse of the data if the person who created and managed a data set is no longer available for assistance. As such, this third challenge requires that the data be computer readable (structurally) and computer interpretable (semantically). It extends the representational challenge by requiring that all data and their interrelationships are available in a form that conforms to a global framework for data linking.

Fortunately, the technology experts of the World Wide Web have had to address this challenge before and created such a framework: the Resource Description Framework (RDF). This framework enables, for example, linkage of the information in a specialized registry on ring-14 syndrome in Italy to the curated information in Orphanet in Paris, and to relevant biobank information stored in Graz. This occurs when all three sites use the Web address of the code for ring-14 disease, defined by Orphanet. Sharing common codes, based on their Web addresses, also referred to by as Uniform Resource Locators (URLs), enables a study on the symptoms of epileptic attacks across all three data sources without the need to explicitly coordinate between them. In this way, we 'virtually augment' the potentially sparse ring-14 data in the specialized registry with the highly curated and detailed information in two remote knowledge bases. We note that in practice, this layer of interoperability is often added as a complement to a more local data representation. It is also important to point out that RDF reuses Web technology, but without any implication that this makes data open or public. Data encoded by URLs is still data, and is as safely stored as it was without URLs.

It is our observation that while the first challenge is well-understood by the rare disease researcher or registry/biobank host, and the second challenge is becoming increasingly recognized as 'best practice' by this community, the third challenge poses problems that are unfamiliar to rare disease domain experts. Nevertheless, the interlinking between related Web data and knowledge resources, and the 'virtual augmentation' that results, ensures that each participating data host is maximally useful, both for their local users, and for the broader rare disease research community. As such, we have worked with the rare disease community to establish some guidelines and workflows that will simplify this third challenge, hopefully to the point that the data hosts are comfortable undertaking this challenge on their own.

In summary, in this chapter we present an approach to prepare data for integration by enabling rare disease data to be exchanged on the basis of a global standard for computer-readable knowledge and data. We explain how this enables cross-resource research and creation of a robust infrastructure of rare disease data resources that are Findable, Accessible, Interoperable, and Reusable for humans and computers – FAIR [24] – *at the source*.

9.2 The Bio-ontology Forest

Ontologies play an important role in the scenario described above. 'Ontology' is an ancient concept in philosophy that has been adopted by computer scientists to describe a particular approach to making knowledge computer-readable. Real-world concepts are represented by a concept hierarchy where each concept is called a "class" and the subclasses – those further down the hierarchy – become increasingly more specific (e.g. humans are a more specific subclass of mammals). It is a best practice to publish ontologies that cover a specific part of reality. For instance, the Human Phenotype Ontology (HPO) covers only human phenotypes. As such, there are numerous ontologies; effectively, one for every top-level concept in the domain. For example, in the rare disease domain there would be ontologies describing disease symptoms, genetics, hospital staff, diagnostic equipment, etcetera. Things in the real-world – for example, individual researchers, or individual pieces of equipment, are called "instances" of these classes. Properties (also referred to as relations or predicates) describe how instances of these classes relate to each other. For example: one of the authors of this chapter is an instance of the class 'Researcher' and has a relation 'hasSurname' with 'Roos', which is an instance of the class 'Family Name'. Thus, a machine could, without human intervention, find these two instances in the database, and know that one instance is a 'Researcher', and that the researcher has the family name 'Roos'. A full record of the researcher 'Roos' would, therefore, have facets encoded by a wide range of ontologies, spanning multiple kinds of data such as medical history, address information, and various identification numbers. Globally defined and shared properties enable these ontologies to be unambiguously connected, such that a functionally interlinked knowledge network can arise. It is important to realize that the current consensus is that an ontology should cover a facet of reality in depth, and be linkable to other ontologies to cover the breadth of an application. For example, it makes little sense to expect concepts for drugs or genes in HPO, as they are not human phenotypes. Thus, so-called 'application ontologies' or 'semantic archetypes' select a subset of terms and properties from a number of ontologies to cover the breadth of an application [9].

Numerous ontologies already exist for the biomedical community. Although general search engines such as Google may be used to create a list of existing biomedical ontologies, the easiest way to locate them is the use of public ontology repositories. Ontology repositories are usually more specific than search engines and they offer tools that may be focused on the type of applications the repository was designed for. The leading repository of biomedical ontologies is the BioPortal (http://bioportal.bioontology.org/) [23], developed by the National Center for Biomedical Ontology (NCBO), which is one of the National Centers for Biomedical Computing funded under the NIH Roadmap Initiative. BioPortal provides access to a library of biomedical ontologies and terminologies via the NCBO services. Ontologies from a number of different groups are published in BioPortal, including the Consultative Group on International Agriculture Research, the Open Biomedical Ontologies (OBO) Foundry (http://www.obofoundry.org) [20], the WHO Family of International Classifications,

the Cancer Biomedical Informatics Grid, the Proteomics Standards Initiative, the Clinical and Translational Science Awards, the Biodiversity Information Standards and the Unified Medical Language System. The Web services allow multi-layered access to the ontology content, spanning functionality such as getting all terms in a ontology to retrieving the definition of a single term.

Two of the most important domains of ontology for RD clinical medicine and research are those defining phenotypic or clinical features (signs, symptoms, and findings of diseases), and ontologies defining specific disease classifications or groups. Beyond these critical core ontologies, additional ontologies and standards will be required for various RD data repositories depending on their data collection process, potentially including ontologies or standards for mutation nomenclature, biobanking, clinical trials, natural history, as well as for RD medications and treatments [4].

Given the large number of ontologies which currently exist, and given that RD data hosts will generally lack experience in exploring ontologies and selecting terms, it would be useful to highlight a set of reference ontologies to facilitate the selection of ontological codes to use in the registry/biobank. The OBO Foundry is a collaborative experiment involving developers of science-based ontologies who are establishing a set of principles for ontology development, and creating a suite of reference ontologies in the biomedical domain. Ontology developers have agreed to work together on an evolving set of design principles that can foster interoperability between ontologies, and ensure a gradual improvement of quality and formal rigor, in ways designed to meet the increasing needs of data and information integration in the biomedical domain. The OBO Foundry also works to minimize overlap and redundancy between ontologies, encouraging members to share and reuse terminologies within their specialist domains, rather than creating new, but redundant ontological classes. In so doing, there is community convergence on a single reference ontology that already assists in finding and selecting the best ontological term. Nevertheless, it would be useful to undertake an additional filtering step to more precisely define the optimal ontologies for the rare disease domain. This is an area of active investigation in this field. For example, we propose to share ‘semantic archetypes’: small models comprised of terms and properties from different ontologies that are selected by ontology experts for encoding a specific set of related data elements, such as for the data gathered by a case report form [17].

9.3 Preparing Data at the Source for Analysis Across Resources

Preparing data for integration can be viewed from different perspectives. For instance, health professionals may see this as a matter of harmonizing operating procedures and/or clinical measurement protocols (the methodological challenge), while IT (“Information Technology”) professionals may wish to agree on data elements and their exchange format (the representational challenge). Attention to both

of these is critical for accurate integration, but here we will focus on the latter, as the former perspective is best managed by health experts.

From the IT perspective, we divide the problem into three distinct considerations, according to the aforementioned challenges: (i) what is measured or observed and how (methodological challenge), (ii) how measurements (observations) are encoded in data collections (representational challenge), (iii) how we make data computer-readable (automation challenge). We note that these three considerations pertain only to preparing data for integration. Downstream analyses will likely require additional data transformations (e.g. R will require data in the form of R data frames for statistical analysis); however, analyses can often not begin until the data from multiple sites has been accurately located, retrieved, and integrated, so that is our focus in this chapter. We also note that the considerations are, in effect, hierarchical, and we will present them as such.

9.3.1 Consideration 1: Consensus on Common Data Elements

It is typical for specialist communities to reach consensus on what should be measured and how, but the importance of this step cannot be understated. Deciding on common data elements (CDEs) across resources is mostly a social process, and is common practice in consortia that are formed to perform a large study, for instance a GWAS (Genome-Wide Association Study) consortium. It is the first step towards integrative analyses within the consortium for the duration that it is funded.

Consensus, however, has limitations with respect to reusing the data outside of the consortium and/or beyond its lifespan, which is usually coupled to a grant. For instance, if a consortium of cystic fibrosis researchers reaches consensus on measuring forced expiratory volume in 1 s (and how), this may differ from the consensus of measurements and methodology in a primary ciliary dyskinesia consortium. Nevertheless, comparison of these very similar diseases could lead to significant insights.

Striving for *g*lobal consensus between all researchers in all domains to accommodate all future uses of data is unrealistic and overly rigid (different domains legitimately have different requirements). While lack of widespread consensus does limit the ease and power of cross-resource data comparisons and analyses, it does not thwart it completely. Applying the solution proposed in Consideration 2, below, mitigates this problem by moving the requirement from consensus to compromise with respect to the way that these common data elements are encoded. This will clearly be more acceptable, and therefore effective, than attempting to enforce a rigid set of common data elements that *all* resources *must have*.

9.3.2 Consideration 2: Ontological Encoding

Health research has a long history of the use of nosologies (classifications of diseases). Similarly, healthcare organizations use coding systems both for patient care as well as for billing and other administrative tasks. Biomedical ontologies are very similar to these familiar approaches to knowledge capture and classification, with the extension that contemporary ontologies utilize formal logics in their code definitions, and are thus able to be processed and interpreted by machines. Consideration 2, therefore, proposes the use of globally unique identifiers [10] and ontologies when exchanging data elements. For instance, when HPO identifiers are used as the codes for phenotypes in disparate disease databases, then phenotypic features in these databases can be unambiguously compared and, when commonalities are found, the data may be selected for integration. Resources in different countries may have used different terms or languages, but the agreement to use HPO codes as the unifying descriptor – the "Rosetta Stone" – can easily reveal that two entries are referring to the same concept, regardless of language. Ontologies, therefore, play a key role in rare disease data collections. They provide standard terms by which the common data element values can be compared. 'HP:0002072', the identification number for the concept which is, in English, called "chorea", is the same in all resources that use the HPO to define phenotypes. One caveat remains: codes for phenotypes such as HPO codes are by themselves not necessarily uniquely identifiable across the globe if the codes do not conform to some globally defined schema. For instance, without the context of knowing that we are discussing diseases, we cannot tell if the string of characters "HP:0002072" refers to the HPO term for 'chorea' or perhaps to some Hewlett and Packard component number. This particular requirement is addressed in the next level of the hierarchy, Consideration 3. The technology that we add to ontological encoding enables data to be made unambiguous. The positive consequence of this is that, if a data element is unambiguous, and shared between multiple resources, it becomes unambiguously linkable with those resources, much like the shared keys between database tables. Thus, it eliminates the need/desire to explicitly combine data in one central warehouse separately from the sources, an undertaking that is costly in terms of finances, human effort, and risks to privacy.

9.3.3 Consideration 3: Machine Readable Data and Knowledge

This consideration pertains to making data, and the meaning of the data, computer-readable using a structured data representation model combined with a more formal approach to representing ontological (and other) concepts. The purpose is to enable computers to aid in combining data from multiple rare disease resources across the globe.

To prepare data for integration at the source, we advise the framework that is recommended by the Semantic Web initiative and the 'Linked Data' principles – Resource Description Framework (RDF). Both of these integrative initiatives reuse the core technology that underlies the World Wide Web itself (i.e. the HTTP protocol). The use of RDF together with HTTP allows machines to "surf" the Web in a *meaningful* way; much like how grammatical rules define how words can be assembled into meaningful sentences, RDF explains how to structure ontological concepts, and other entities such as individual patients and their specific interventions or treatments, into relationships whose meaning can then be interpreted by software. This requires, simply, that all aforementioned codes (for specific phenotypes, diseases, genes, etc.), but also data types such as the general class 'Human phenotype' for all human phenotypes, patient identifiers, and relation types such as 'binds to', are represented by a Uniform Resource Identifier (URI). Biologically and clinically meaningful statements are then constructed using "Triples" of URIs. For example, in RDF 'chorea *is-a-manifestation-of* Huntington's Disease', becomes an unambiguous statement – a Triple – understood by both humans and machines, because each element of that Triple is represented as a URI, and all parties, globally, use the same URI to refer to the same concept or relationship. If the ontological concepts and relationships within these "sentences" are further formalized in description logics, they can be even more powerfully processed by computers, where, for example, a computer could automatically define the category for a new data entry, or could infer consequences from certain combinations of data points that were not explicitly entered into the database. Defining relations between data elements in terms of these Triples further mitigates the need for a rigid set of globally common data elements. The encoding by description logics allows any inferable commonality at any level to be exploited, instead of only the values of pre-defined common data elements. Nevertheless, it does not replace the solutions for Considerations 1 and 2. URIs and Triples of URIs only *represent* what researchers have decided to measure, encode and define relations between, such that computers can help to perform accurate analysis across any number of data sets. The stack of solutions is most powerful when all three levels are addressed.

9.4 Requirements for Preparing Rare Disease Data for Integration

We constrain our pursuit of an integrative solution by the following requirements and desiderata [17]:

1. When access to data is granted, 'link*able* data' must be trivial to query and/or analyze across (large numbers of) independent data sources, by both humans and machines.
2. All originating sources must retain their independence; i.e. the solution-space cannot depend on centralized data warehouses or portals.

3. Data sources should be easily combined with existing computational workflows and data platforms such as those developed by the RD-Connect project [21]. The solution should avoid proprietary or *de novo* interfaces and formats (data silos).
4. The technology that we propose to make rare disease data linkable should *complement* existing technologies and protocols being used at-source, and not interfere with them.

These desiderata and requirements impose certain challenges. The first requirement –the ability to dynamically integrate large numbers of potentially linkable resources- poses significant demands on the knowledge representation that we apply, confirming the aforementioned representation and automation challenges. Effectively, at larger scales, human assessment of the meaning of the data in each of the resources should not (and cannot) be required. The second desiderata, that all sources should remain independent, does not *exclude* the use of global services to facilitate data integration scenarios, such as initiatives that make it easier to find and access registries and biobanks through creating centralized indexes [7]. It does, however, exclude the wholesale warehousing and *en masse* integration of the data, as has been the norm in the biomedical domain for many years, *in lieu* of retaining the data at its original source.

We point-out, in addition, that these requirements surpass simply *finding* data. Making data discoverable is often considered lower-hanging fruit, because it requires only the information *about* the data source in a standard form ('metadata'). Examples are the disease that a data set pertains to, how many subjects it contains, the type of material that was collected, etcetera. Our driving research questions, however, require more than information *about* data. For instance, finding tissue samples of patients with ring-formation in chromosome 14 (the defining feature of ring-14 syndrome) requires interrogation of the specific karyotype of a patient, which goes beyond simply knowing that karyotype information was collected. Furthermore, we need to enable researchers to exploit relevant biomedical information. For example, information associated with the ring-14 karyotype may be the link to rich sets of information about model systems that researchers can exploit to find new treatments for the disease.

9.5 Backbone: Linkable Data and Ontologies

The backbone for our approach to make data linkable and computer readable at the source is, as we noted in Consideration 3, provided by the recommendations of the World Wide Web Consortium (W3C): Linked Data principles [1], Ontologies, and the Resource Description Framework (RDF). RDF is a generic data model that was designed with the objective of creating qualified networks of data, upon which increasingly complex domain models can be overlaid to assist with interpretation of that data. For instance, the Human Phenotype Ontology and the Orphanet Rare Disease Ontology are available in RDF, as are most ontologies in the biomedical

domain. We therefore consider this the best way to facilitate integrative biological and translational research across rare disease resources. In addition to tools that exploit the use of ontologies, such as the Exomizer [19], MatchMaker Exchange (MME; [14]), and Monarch [11], we see an increasing amount of life science data resources that use RDF to support data linking, such as the RDF platform of the European Bioinformatics Institute (EBI; [6]) and the Open Phacts [25]. RDF is capable of representing disease specimen identifiers, patient/disease personal and clinical information, and molecular data, thus the choice of this singular technological framework helps reduce the overall cost of data integration for rare disease resources.

9.6 Building on the Backbone: A Reference Model for Data Integration

The process to prepare data for analysis across resources entails recoding values by ontology codes, adding ontology terms to describe the meaning of values, and adding relation terms (also from ontologies) to define how values are related and what they represent. This is not a trivial process. While many ontologies exist in the biomedical domain, choosing the appropriate ontology terms requires substantial understanding of ontologies, and substantial understanding of what the data represents. We recommend consulting an ontology expert to collaboratively choose the correct terms. However, this in itself does not guarantee that the same ontology terms will be used by all resource providers. There are often multiple ontologies that appear to have appropriate, even identical terms. Moreover, to increase efficiency for the large amount of data resources in the rare disease domain, it is important that we can reuse the ontology choices of one resource for other resources with similar data.

To mitigate these issues, our approach entails the development of reusable reference models for data integration ('semantic archetypes') that are composed of terms from recommended ontologies. These models differ from typical ontologies in that their purpose is to provide a common schema for multiple types of data for a particular application, not to conceptualize a particular part of reality. Publishing these semantic archetypes, for instance via FAIRsharing.org, allows reuse of previous effort and thereby stimulate greater commonality between ontology-based data sets.

As an example, we have created a first version of a semantic archetype for a subset of identifier types in rare disease databases for the purpose of enabling answering questions across patient registries and biobanks. We constructed the model as a stack of modules to cater for increasingly complex applications of the archetype (Fig. 9.1; [17]). The model and our selection of ontologies can subsequently serve as reference for new cases that involve similar data.

9.7 Composition of the Prototype Reference Model

The starting point for crafting the semantic reference model was to list the core set of identifiers that will likely exist in RD registries/biobanks (the dark grey semicircle at the center of Fig. 9.1). These are:

- Biobanks
- Patients
- Sample donors
- Experiments
- Samples (biological specimens)

The next task ('rdc-meta' in Fig. 9.1) was to provide a model that describes the meaning of these identifiers and their interrelationships in computer readable terms. The following ontologies contain classes that could be used to add meaning to the kinds of identifiers above:

Ontology for BIoBanking (OBIB; [2]):

- Human being
- Patient/donor role
- Identifier
- Object properties

Open Archives Initiative Object Reuse and Exchange (OAI-ORE; [8]):

- Aggregation
- Aggregate properties

EMBRACE Data and Models, an ontology of bioinformatics operations, types of data, data identifiers, data formats, and topics (EDAM*; [5]):

- Specific types of identifiers (e.g. biobank ID, stock accession ID, person ID)
- Standard terms for genes, proteins, DNA, and other biological entities
- Standard terms for analytical methodologies

Information Artefact Ontology (IAO*; [3]):

- Specific types of identifiers (e.g. biobank ID, stock accession ID, person ID)

** EDAM and IAO both provide an identifier class. Including them both in the semantic archetype increases the reusability of the model. While EDAM is widely used, IAO provides the convenient link to the OBO Foundry suite of ontologies.*

Dublin Core ontology (DC; [22]):

- Identifier properties
- Authorship and other contact information
- Basic descriptive information

Simple Knowledge Organization System (SKOS; [12]):

- Mappings (for instance, to SNOMED terms)

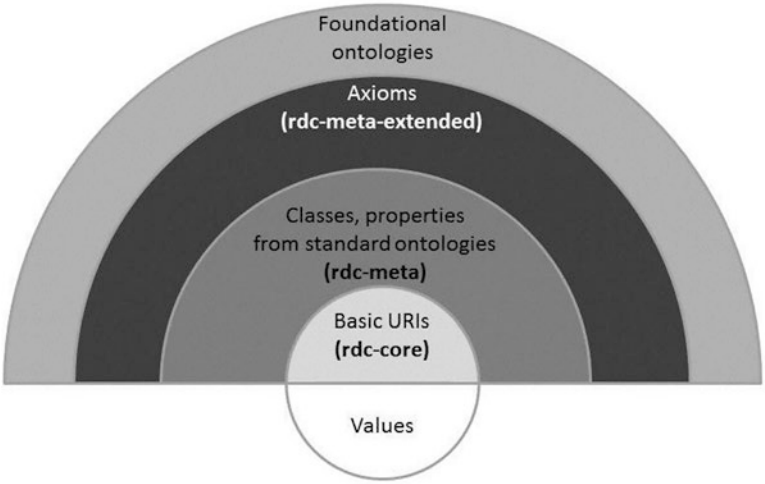

Fig. 9.1 Semantic archetype for rare disease data integration. The model is constructed hierarchically from modules that can be used for increasingly complex cases. From bottom to top: 'Values' represent data in multiple resources; 'rdc-core' provides simple classes for database identifiers; 'rdc-meta' supplies immediately relevant classes and properties to denote the meaning of identifiers and their interlinks; 'rdc-meta-extended' provides logical definitions from the reused ontologies as needed for computational reasoning; the top semi-circle represents the 'foundational ontologies' that the reused ontologies refer to (they are not directly part of the semantic archetype)

From these ontologies, the following semantic modules were created (see the layers in Fig. 9.1):

1. **rdc-core**: the minimal set of classes and properties to map to the data in the sources. Because of the task at hand the focus is on identifiers. Rdc-core represents little more that the lowest level types of the identifiers.
2. **rdc-meta**: the minimal semantic model, defined as much as possible using the aforementioned ontologies (Fig. 9.2). Ontology experts will note that this module lacks the complete set of logical definitions (so-called axioms) to be able to use the concepts.
3. **rdc-meta-extended**: this module includes the axioms and the extra subclasses and properties that are required to reason over the semantic archetype if and when required by computational scientists [18].

These modules (and others currently under construction) provide support for the stepwise migration of data in RD registries/biobanks. Each module provides a constrained set of ontological choices, based on the task-at-hand, and on the most prevalent data types encountered in RD data repositories. For example, in Fig. 9.2, "Phenotips patient ID" is one of only six options provided for the data-type "Identifier"; however, the original ontology from which these six options were derived (EDAM) has many dozens of additional options. We believe that constrain-

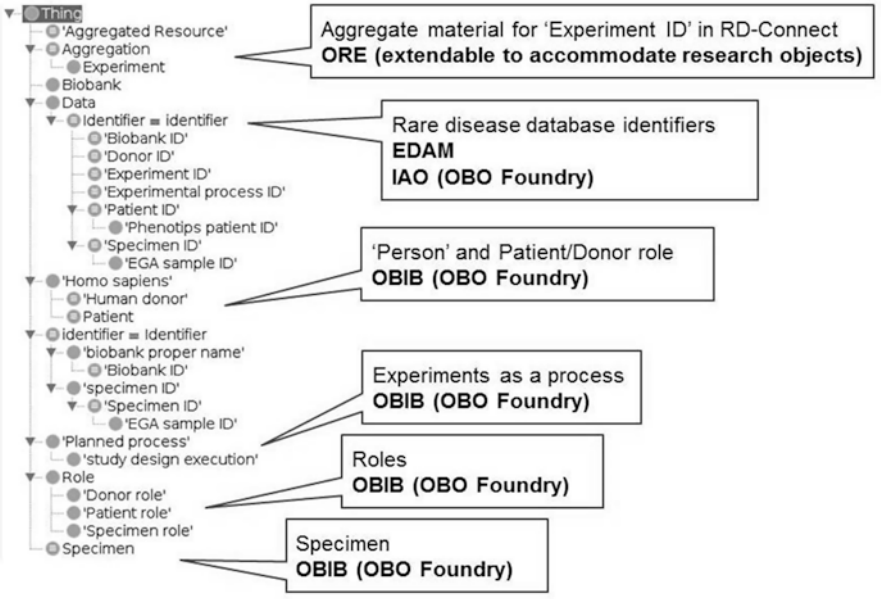

Fig. 9.2 Semantic archetype for enabling questions across registries and biobanks (the class hierarchy). The call-outs indicate the ontologies from which the classes were used. The complete ORE can be found on https://www.openarchives.org/ore/. The complete versions of the other ontologies can be found on http://bioportal.bioontology.org/

ing the choices to only a few possibilities specific for RD data sources will dramatically ease the burden of making RD data interoperable. We hope that, with proper tools, we can arrive at the point where RD registry/biobank owners can undertake this task without expert assistance.

9.8 Summary

What we present here is a general approach for preparing data for integration that enables to address the current driving research questions, but also future applications beyond the scope of a single project. Compared to projects where, for instance, data is prepared for integrative analysis in R or SPSS, it adds an intermediate step. This is undeniably extra work, but it makes the harmonization effort of a project reusable. It quickly becomes the more efficient approach when we desire data collections to be used many times, realizing that without preparation at the source, the harmonization step is carried out by each user of the data again and again with high risk of errors.

Ontologies are of critical importance for enabling computers to aid in information retrieval and analysis across data collections. They play a key role in speeding

up the overall research process towards better understanding of a disease, new treatments, and diagnostic biomarkers.

Linked Data with strong ontological underpinnings, and a clear model for achieving proper access control, is our first ambition for preparing the relatively small, but numerous and disparate, rare disease data sets for wide-scale data integration. Sharing and reusing semantic archetypes developed by ontology experts mitigates an immediate and major bottleneck: the current sparsity of expertise in the community to make informed decisions about which ontological concepts to use for their data annotations. Searching for a concept, e.g. in NCBO's bioportal or EBI's ontology lookup service, typically returns too many "hits" for a non-ontologist to choose-from. Specific ontologies may be advised by experts, but the breadth of data types across data sets is large. For example, in a recent workshop [16] organized for RD patient registries owners and computer experts, we could easily list at least 10 ontologies relevant for just a subset of a registry's data, and not all of these are included in the BioPortal or EBI search services. Here, we propose finding a middle-ground and providing an early workflow towards that goal. Domain experts first select a subset of the most appropriate and common ontological classes used for each of the data types encountered in a rare disease resource that we need to make FAIR, such as for the data types of a typical rare disease registry. Only these limited (but relevant) options are presented to the data curator, in a stepwise, and contextually-sensitive manner, as they undertake their data transformation.

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Part IV
Orphan Drugs and Therapies

Chapter 10
Incentivizing Orphan Product Development: United States Food and Drug Administration Orphan Incentive Programs

Tran T. Le

Abstract Over 30 years ago, the United States (US) Congress passed the Orphan Drug Act (ODA) to encourage the development of products for rare diseases or conditions ("orphan products"). The Act provided incentives to sponsors for developing products with orphan designation and established a grant program to fund studies of orphan products. Since its enactment in 1983, the ODA has been credited for bringing more than 590 orphan drugs to the market, inspiring the implementation of orphan legislation globally, and enabling the creation of other programs that extend existing knowledge of the natural history of rare diseases and stimulate the development of medical devices for children and patients with rare diseases. This chapter provides a brief overview of the main features and successes of 5 of the orphan incentive programs administered by the US Food and Drug Administration (FDA): the Orphan Drug Designation Program, the Humanitarian Use Device (HUD) Designation Program, the Orphan Products Clinical Trials Grants Program, the Pediatric Device Consortia (PDC) Grant Program, and the Orphan Products Natural History Grants Program.

Keywords Rare Diseases • Orphan Products • Orphan Drug act (ODA) • Orphan Drug Designation Program • Humanitarian use Device (HUD) Designation Program • Orphan Products Clinical Trials Grants Program • Pediatric Device Consortia (PDC) Grant Program • Orphan Products Natural History Grants Program • Food and Drug Administration (FDA) • Office of Orphan Products Development (OOPD)

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10.1 Introduction

Rare diseases, although individually rare, collectively affect approximately 30 million Americans of all ages and millions more throughout the world. To date, more than 7000 rare diseases have been identified, and many of these are chronic, progressive, life-threatening, and/or fatal [1]. As rare diseases represent a substantial health burden, there is a recognized need to improve the detection, diagnosis, and treatment of these diseases [1]. However, many challenges complicate efforts to develop products for rare diseases. These challenges include difficult enrollment (due to the rare and heterogeneous nature of each disease), lack of natural history data, and lack of validated biomarkers or clinical endpoints. Combined with these challenges are those encountered in the United States (US) prior to 1983 in which the high cost of drug development and the low return on investment discouraged development of products for extremely small patient populations. Recognizing the dire need to provide more treatment options for patients with rare diseases, the US Congress passed the Orphan Drug Act (ODA) in 1983 to encourage the development of products for rare diseases [2]. The ODA provided financial and regulatory incentives to sponsors of drugs and biologics that are "designated" as "orphan drugs" and established a grant program to fund research of orphan products [1, 3–6]. Since its enactment in 1983, the ODA has been widely recognized as being successful in stimulating the development of orphan products. Between 1973 and 1983, only 10 drugs had received Food and Drug Administration (FDA) marketing approval for the treatment of rare diseases [3, 4, 7]. Since implementation of the designation and grant programs in 1983, more than 3900 drugs and biologics have been designated as orphan drugs, and more than 590 of these have received full marketing approval for the treatment for more than 250 rare diseases. Orphan products now represent roughly 40% of all new drugs approved by FDA. Of all the drugs and biologics that have received marketing approval, more than 10% of these had received grant support from the Orphan Products Clinical Trials Grants Program.

Since enactment of the ODA, additional legislation has been passed to not only strengthen the ODA, but also to stimulate other rare disease and pediatric product development, including for example, the development of medical devices for children and patients with rare diseases through the creation of the Humanitarian Use Device (HUD) Designation Program and the Pediatric Device Consortia (PDC) Grant Program. The newest program designed to stimulate orphan product development is the Orphan Products Natural History Grants Program, which funds studies that extend existing knowledge of the natural history of rare diseases. This chapter provides a brief overview of the main features and successes of 5 of the orphan incentive programs administered by FDA.

10.2 Designation Programs

The designation programs specific to rare disease product development are administered by the Office of Orphan Products Development (OOPD), within FDA's Office of Special Medical Programs. OOPD currently administers both the Orphan Drug Designation Program and the Humanitarian Use Device (HUD) Designation Program. These programs grant special status to drugs, biologics, or medical devices for the treatment, diagnosis, or prevention of rare diseases or conditions.

The Orphan Drug Designation Program was established in 1983 following passage of the ODA. The program grants "orphan designation" to drugs and biologics intended for the safe and effective treatment, diagnosis, or prevention of rare diseases or conditions. Orphan designation qualifies the sponsor of the drug for various development incentives, including tax credits for qualified clinical testing, an exemption from marketing application fees, and the potential for 7 years of marketing exclusivity.

10.2.1 Program Features

A sponsor (most often a company) seeking orphan designation for a drug must submit a request for designation to OOPD; this request may be submitted at any time during product development as long as it is before the submission of the marketing application for that drug for the rare disease or condition. In the request for orphan designation, the sponsor should (1) describe the disease or condition that the drug is proposed to treat or prevent; (2) submit evidence that the prevalence of the target population is less than 200,000 in the US; and (3) provide scientific rationale supporting the drug's promise for the proposed use. Under the ODA, if the target population is more than 200,000 in the US, a drug may still qualify for orphan designation if the sponsor can demonstrate that the drug will not be profitable within 7 years of approval in the US. Given the inherent challenges of demonstrating a lack of profitability, sponsors have rarely relied on this provision when seeking orphan drug designation [8].

The regulations related to orphan designation are designed to promote rare disease drug development in a variety of ways. For example, a sponsor may request orphan designation of a drug that has not been previously approved for any use, or for a new use of an already marketed drug ("repurposing"). Moreover, a sponsor may also obtain orphan designation for the same drug for multiple rare diseases or conditions; conversely, numerous sponsors may acquire orphan designation for the same drug for the same rare disease or condition. However, when a sponsor submits a designation request for the "same drug" as one that has already received marketing approval for the proposed orphan indication, like a different formulation, the sponsor must provide a plausible hypothesis as to why its formulation may be clinically superior to the approved product by means of greater effectiveness, greater safety, or that it provides a major contribution to patient care (MC-to-PC). This requirement

ensures that the incentives afforded under the ODA are reserved only for those products that are better than the products that are currently available on the market.

Once a drug receives orphan designation, OOPD posts the information on its website to notify the public about products potentially being studied for rare diseases. Drugs designated as orphan are subject to the same standard for approval as common drugs; the granting of an orphan designation does not alter that standard. Like drugs for common diseases, drugs for rare diseases must provide substantial evidence of safety and effectiveness through adequate and well-controlled studies. However, in recognition of the challenges associated with rare disease drug development, FDA exercises flexibility in determining how much evidence is sufficient to meet this standard. Although orphan drugs must meet the same standard for approval as common drugs (because most orphan drugs are used to diagnose, treat, or prevent serious or life-threatening diseases or conditions), they are typically eligible for one or more expedited pathways for review, including breakthrough therapy designation, priority review, fast-track designation, and/or accelerated approval.

10.2.2 Incentives

Once orphan designation is granted, the sponsor of the orphan designated drug is eligible to receive various financial and regulatory incentives to develop the product. First, the sponsor can claim tax credits for up to 50% of clinical trial costs associated with studying an orphan designated drug. Considering the current high costs of conducting clinical trials, these tax credits can and do amount to significant savings for a sponsor. Second, the sponsor is exempt from the user fee when they submit a marketing application (either a New Drug Application [NDA] or a Biologics License Application [BLA]) for an orphan designated drug. User fees for an original NDA or BLA are now set at approximately $2 million. A waiver of this $2-million user fee represents a significant cost-saving benefit, particularly for smaller startup companies. Lastly, and perhaps most importantly, the sponsor of an orphan designated drug may be eligible for 7 years of market exclusivity upon approval if that drug or biologic is the first of its kind to be approved for that rare disease. During this 7-year period, FDA may not approve a marketing application for the same drug for the same use from another sponsor unless the sponsor holding exclusivity provides consent or cannot assure the availability of sufficient quantities of the approved drug. This exclusivity ensures predictable and often significant revenue from sales due to the lack of competition from other sponsors. Interestingly, when the ODA was contemplated, rare disease stakeholders believed that the tax credits would be the most important incentive to industry; they did not contemplate that there would be multiple companies vying for the same market space. Now, over 3 decades later, the 7-year market exclusivity is considered to be one of the biggest drivers of orphan drug development.

10.2.3 Successes

The Orphan Drug Designation Program has been successful in stimulating development of drugs for rare diseases. Since 1983, FDA has received over 5600 designation requests, granted more than 3900 designations, and promoted the development and marketing of more than 590 drugs for rare diseases. Designation continues to be a highly sought after incentive, not just for the financial benefits that are offered through the ODA, but because the moniker of designation has been tied to other benefits unrelated to the ODA in subsequent legislation. In 2015 alone, FDA received a record number of over 460 requests, when just 8 years prior, less than half that number were received. FDA also designated and approved more orphan drugs in 2015 than in previous years; over 350 drugs were designated and 54 were approved, including both novel and repurposed drugs. In fact, more than 40% of all new drugs approved by the Center for Drug Evaluation and Research (CDER) were for the treatment of rare diseases in 2015, an increase of almost 10% from just 5 years prior. Many of these orphan drug approvals have been for new and innovative products and for patients with unmet needs.

10.3 Humanitarian use Device (HUD) Designation Program

The Humanitarian Use Device (HUD) Designation Program was established in 1990 following passage of the Safe Medical Devices Act. The primary goal of the program is to stimulate the development of medical devices for rare diseases. The program grants "HUD designation" to medical devices intended for the treatment, diagnosis, or prevention of rare diseases or conditions. Unlike the Orphan Drug Designation Program, the HUD Designation Program does not provide financial incentives. Instead, the program allows designated devices to be eligible for an alternative marketing pathway known as the Humanitarian Device Exemption (HDE) pathway [9, 10].

10.3.1 Program Features

A sponsor seeking HUD designation for a medical device must submit a request for designation to OOPD; in the request, the sponsor should (1) describe the disease or condition that the device is proposed to treat or diagnose; (2) submit evidence that the incidence of the target population is not more than 8000 per year in the US; and (3) describe the device and discuss the scientific rationale for use of such device for the rare disease or condition.

Within 45 days of receiving the HUD designation request, OOPD will either approve the request, request additional information (i.e., issue a deficiency letter), or disapprove the request.

10.3.2 Incentives

HUD designations, unlike orphan drug designations, are not associated with financial incentives. Rather, HUDs are eligible for an alternative marketing pathway known as the HDE pathway. This pathway is less stringent than the standard premarket approval application (PMA) pathway. Under the PMA pathway, the sponsor must demonstrate a reasonable assurance of safety and effectiveness for the device in order to receive marketing approval. Under the HDE pathway, the sponsor of a HUD must demonstrate safety similar to the PMA pathway; however, rather than having to demonstrate effectiveness, the sponsor of a HUD is required to demonstrate only "probable benefit" in order to receive marketing approval. The probable benefit standard was established based on the notion that determining effectiveness for devices to treat or diagnose diseases affecting small populations is difficult.

The probable benefit standard established for the HDE pathway has allowed FDA to exercise a high degree of flexibility in its review of HDE applications. Analyses of HDE approvals from 2007–2015 revealed that while all approved applications included clinical data, the level of scientific evidence accepted for approval varied widely, ranging from retrospective analyses of prior clinical studies to prospectively conducted clinical trials. Furthermore, clinical trials for HDE approvals were relatively small compared to those for PMA devices, and most were open-label, single-arm trials. As FDA continues to exercise flexibility in all HDE reviews with the ultimate goal of providing treatment options to patients with serious or life threatening rare diseases, sponsors are encouraged to communicate with FDA early in the development process to best facilitate device development and to ensure a least burdensome approach to obtaining marketing approval for these devices.

Because the probable benefit standard represents a lower standard of approval, HDE devices are subject to certain profit and use restrictions. First, HDE devices cannot be sold for profit, except in narrow circumstances. Second, HDE devices can be used in a facility only after an IRB has approved their use in that facility, except in certain emergencies [11].

10.3.3 Successes

Given that HUD designation does not provide financial incentives like orphan drug designation, and in light of the fact that HDE devices are subject to profit and use restrictions and face reimbursement challenges due to the lower standard of approval, the HUD/HDE program is understandably smaller than the Orphan Drug Designation

Program. Even so, since the program's inception in 1990, more than 370 HUD applications have been submitted to OOPD; more than 240 of those have been designated, and more than 65 have received HDE approval. These devices range from cardiovascular devices to treat congenital defects and pediatric heart failure to ophthalmic devices to treat blindness. Some examples include the Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD), which provides mechanical circulatory support as a bridge to heart transplant in pediatric patients; the Argus II Retinal Prosthesis System, which improves visual function and produces the sensation of light in patients with advanced retinitis pigmentosa who have bare or no light perception; and the PDGFRB FISH assay, which is used for the qualitative detection of PDGFRB gene rearrangement to aid in the selection of patients with myelodysplastic syndrome/myeloproliferative disease (MDS/MPD) for whom imatinib mesylate (Gleevec®) treatment is being considered. HDE devices are vital to public health and often serve very vulnerable patient populations with unmet medical needs.

10.4 Grant Programs

OOPD currently administers 3 grant programs: (1) the Orphan Products Clinical Trials Grants Program, (2) the Pediatric Device Consortia (PDC) Grant Program, and (3) the Orphan Products Natural History Grants Program. These programs provide grants to support the development of products for patients with rare diseases or for pediatric patients.

10.4.1 Orphan Products Clinical Trials Grants Program

The Orphan Products Clinical Trials Grants Program (formerly known as Orphan Products Grants Program) was established in 1983 following passage of the ODA. The program provides competitive grants to fund clinical studies of safety and/or effectiveness that will result in, or substantially contribute to, market approval of orphan products. The goal of the Orphan Products Clinical Trials Grants Program is to accelerate the clinical development of products for use in rare diseases where no current therapy exists or where the proposed product will be superior to existing therapy. The program has an estimated fiscal year funding of approximately $14 million ($4 million of which funds new awards and $10 million funds noncompeting continuation awards). At any given time, the program typically funds 60–85 ongoing projects.

10.4.1.1 Program Features

Orphan Products Clinical Trials grants are available to a wide range of applicants, including for example, any foreign or domestic, public or private, and for-profit or nonprofit entities, as well as state and local governments; federal agencies and organizations that engage in lobbying activities are not eligible to receive grant awards. Studies that qualify for this grant program are clinical studies that facilitate or result in FDA approval of a product (drug, biologic, medical device, or medical food) used in the treatment, diagnosis, or prevention of a rare disease or condition. Funding levels vary depending on the type of study proposed. In general, phase 1 studies are eligible for up to $250,000 in total cost per year for up to 3 years, and phase 2 or 3 studies are eligible for up to $500,000 in total cost per year for up to 4 years. Orphan drug designation or HUD designation is not required to be eligible for the grant program; however, grant applications must include appropriate documentation to support the population estimate.

An applicant seeking funding for a study must submit a grant application electronically through www.grants.gov. The application must contain documentation to support the estimated prevalence of the rare disease or condition and an explanation of how the proposed study will either help gain product approval or provide essential data needed for product development. Complete submission requirements and review criteria are available in the Request for Application (RFA) that is published annually in the Federal Register, the National Institutes of Health (NIH) Guide, and on OOPD's website [12, 16].

10.4.1.2 FDA Assessment of Applications and Ongoing Grants

All applications received are reviewed by grant management and OOPD for responsiveness. Responsive applications are subsequently reviewed and evaluated for scientific and technical merit by an ad hoc panel of at least 3 independent experts from outside the FDA in the clinical specialty area of the specific application. A unique aspect of the application review process is that FDA representatives from the relevant review divisions ("FDA Review Division") are invited as non-scoring participants to provide their perspective on any potential regulatory issues with the study proposals as well as whether a proposed study will provide acceptable data that could contribute to marketing approval. A score is then assigned to each application based on the scientific/technical review criteria.

If an application is funded, a Project Officer within OOPD will work with the grantee to help ensure that the grantee meets enrollment goals and regulatory requirements (e.g., IND annual reports, Institutional Review Board approvals) through quarterly updates and annual reports; provide feedback on how projects can be improved (e.g., adding study sites, modifying inclusion/exclusion criteria); and serve as a liaison with the FDA Review Divisions. OOPD also conducts site visits of funded studies to monitor the performance of those studies for consistency with the terms of the grant agreement.

10.4.1.3 Successes

The Orphan Products Clinical Trials Grants Program is a highly competitive program that has successfully fostered the development of many rare disease products. Since the program's inception in 1983, OOPD has received over 2500 applications (generally, about 100 applications/year), reviewed over 2200, and funded over 590 studies. The Orphan Products Clinical Trials Grants Program has been used to bring more than 55 products to marketing approval. Some of the Program's successes include the funding of studies involving scorpion antivenom (Anascorp®), lomitapide (Juxtapid®), and ivacaftor (Kalydeco®). In the case of scorpion antivenom, the program funded approximately $558,000 to support a study evaluating safety and effectiveness of the product in the treatment of scorpion envenomation in the primary care setting. In the case of lomitapide, the program funded approximately $1 million to support a single-arm, open label study evaluating safety and efficacy of the drug as an adjunct to other lipid-lowering agents in the treatment of homozygous familial hypercholesterolemia. And in the case of ivacaftor, the program funded approximately $350,000 to support a preliminary study evaluating endpoints and dosage selection for the drug in the treatment of cystic fibrosis. While the funds provided by the program alone can cover only a portion of the total clinical trial costs for studying these products, orphan product grants are often used to fill critical funding gaps and help secure additional funding.

10.4.2 Pediatric Device Consortia (PDC) Grant Program

The Pediatric Device Consortia (PDC) Grant Program was established following passage of the Pediatric Medical Device Safety and Improvement Act of 2007 (PMDSIA). The program was established to address the challenges of developing medical devices for pediatric patients (e.g., small market size, need for multiple pediatric sizes, expensive trials, barriers to enrolling children, lack of pediatric device trials infrastructure). The PDC Grant program is unique in that it does not directly fund individual device projects. Instead, it funds networks of pediatric medical device advisors with broad expertise in pediatric device development who are able to provide a platform of experienced regulatory, business planning, and device development services (e.g., intellectual property advising; prototyping; engineering; laboratory and animal testing; grant-writing; clinical trial design) to help foster and guide the advancement of medical devices for pediatric patients. The goal of the PDC Grant Program is to support the development of these nonprofit consortia in an effort to promote medical device development for pediatric patients. Although the program is intended to encompass devices that could be used in all pediatric diseases or conditions (not just rare diseases), many devices for pediatric patients are used in those with rare diseases [14].

10.4.2.1 Program Features

PDC grants are available to any domestic, public or private, or nonprofit entity, including state and local governments. A successful PDC brings together individuals and institutions that can support pediatric medical device progression through all stages of development: concept formation, prototyping, preclinical, clinical, manufacturing, marketing, and commercialization. Application budgets are limited to $750,000 in total cost (direct costs plus indirect costs) per year for up to 5 years, with a maximum of 10% indirect costs. Complete submission requirements and review criteria are available in the Request for Application (RFA) that is published in the NIH Guide and on OOPD's website [13].

10.4.2.2 FDA Assessment of Applications and Ongoing Grants

Responsive applications are reviewed and evaluated for merit by an ad hoc panel of independent experts. Similar to the Orphan Products Clinical Trials Grants Program, OOPD is kept informed of the progress of these projects through quarterly updates and annual reports. Information including project progress, problems, adverse events, changes in consortium leadership and planned activities, and any applicable regulatory compliance are reviewed. In addition, FDA conducts periodic site visits with officials from the consortia organizations. Since consortia are typically funded for 5 years, after 2.5 years, consortia grantees undergo a mid-cycle evaluation. This evaluation takes into account the number of projects assisted, the depth and extent of the consortium's involvement in advancing pediatric device projects, and feedback from innovators who have received assistance.

10.4.2.3 Successes

To date, the PDC Grant Program has funded 10 consortia for a total $23 million; these consortia have assisted in the development of over 450 proposed pediatric medical devices, over 100 of which are still being actively managed or mentored. Most of the active device projects supported by the consortia are in the early stages of device development, including the initial concept-generating stage, prototyping (designing models of a device idea), and preclinical (bench and animal testing) stages. Over $69 million of additional outside funds have been raised to advance consortia projects.

A number of devices assisted by the consortia are now commercially available, including:

- The Buzzy (a device that combines ice and vibration to relieve pain associated with needle sticks)
- The Rhinoguard (a device that assists in naso-tracheal intubation)

- The TIVA (a needle-free blood collection device that allows blood draw through peripheral IV)
- The SleepWeaver Advance Pediatric CPAP Mask (a device that provides an interface for noninvasive Continuous Positive Airway Pressure [CPAP] ventilation)
- The EKO stethoscope (a specialized stethoscope that records and electronically amplifies, filters, and transfers heart sounds, cardiac murmurs, bruits, respiratory, and abdominal sounds)
- The Geiger Pyloric Immobilizer (a surgical tool used in pyloromyotomy)
- The Abriiz (a computerized asthma-management tool)
- The Dynamic Compressor System (an external brace for the treatment of pectus carinitum).

Another device assisted by the consortia that is under development but not yet commercially available is the tracheal splint, a biodegradable splint designed and manufactured using patient imaging and a laser-based 3D printing system, intended for use in the treatment of tracheomalacia. With continued congressional appropriations, it is anticipated that the critical work of developing medical devices for children will continue with assistance from the PDC.

10.4.3 Orphan Products Natural History Grants Program

The Orphan Products Natural History Grants Program is the newest program administered by OOPD. Established in 2016, the program is a unique funding source that provides competitive grants to support natural history studies of rare diseases. The program was established to address one of the most common and urgent issues hindering the development of products for rare diseases: the lack of natural history data. Because a thorough understanding of the natural history of rare diseases serves as a foundation for drug development (e.g., by helping to identify biomarkers and drug targets as well as guide clinical trial design and selection of clinically meaningful endpoints), and because the lack of sufficient funding for natural history studies has been identified as an important gap, OOPD has committed approximately $2 million to fund 2–5 natural history studies. The goal of the Orphan Products Natural History Grants Program is to support studies that advance rare disease medical product development through characterization of the natural history of rare diseases or conditions, identification of genotypic and phenotypic subpopulations, and development and/or validation of clinical outcome measures, biomarkers, and/or companion diagnostics [15].

10.4.3.1 Program Features

Orphan Products Natural History grants are available to any foreign or domestic, public or private, and for-profit or nonprofit entities, as well as state and local governments; federal agencies are not eligible to receive grant awards. Studies that qualify for this program are natural history studies of a disease or condition that affects fewer than 200,000 people in the US. Qualified studies include but are not limited to those that characterize the natural history of rare diseases or conditions, identify genotypic and phenotypic subpopulations, and develop and/or validate clinical outcome measures, biomarkers and/or diagnostics. Examples of qualified studies include but are not limited to prospective studies involving clinical visits, retrospective studies such as chart reviews, and survey studies. Funding levels vary depending on the type of study proposed. In general, prospective natural history studies are eligible for up to $400,000 in total cost per year for up to 5 years, and retrospective natural history studies or survey studies are eligible for up to $150,000 in total cost per year for up to 2 years.

An applicant seeking funding for a study must submit a grant application electronically through www.grants.gov. The application must contain documentation to support the estimated prevalence of the rare disease or condition. The application must also include a discussion of the landscape of the disease (e.g., existing natural history data, current treatment options, barriers or progress in product development) and how the proposed study will extend existing knowledge, provide essential data needed for product development, or help support product approval. Complete submission requirements and review criteria are available in the Request for Application (RFA) that is published in the Federal Register and on OOPD's website.

10.4.3.2 FDA Assessment of Applications and Ongoing Grants

All applications received are reviewed by grant management and OOPD for responsiveness. Responsive applications are subsequently reviewed and evaluated for scientific and technical merit by an ad hoc panel of experts in natural history studies and in the subject field of the specific application. A score will be assigned to each application based on the scientific/technical review criteria. The review panel may advise OOPD about the appropriateness of the proposal to the goals of the grant program.

If an application is funded, a Project Officer within OOPD will work with the grantee to help ensure that the grantee meets enrollment goals and regulatory requirements. OOPD also conducts site visits of funded studies to monitor the performance of those studies for consistency with the terms of the grant agreement.

10.5 Conclusions

The designation and grant programs established following passage of the ODA and subsequent legislations have in general been heralded as a success [4, 6]. Since the inception of these programs, more than 590 products have received marketing approval for more than 250 rare diseases for which very few or no effective treatments were available. The success of the ODA has over the years inspired the implementation of orphan legislation outside the US to address the treatment needs of rare disease patients worldwide [4]. While much has been accomplished, a great need still remains, as most of the 7000+ rare diseases still need safe and effective treatment. FDA continues to encourage the development of products for rare diseases and remains committed to ensuring that more safe and effective therapies are available for the millions of patients living with such diseases.

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Chapter 11
Post-approval Studies for Rare Disease Treatments and Orphan Drugs

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Abstract Drug development involves a multi-stage process of drug discovery, animal studies and human clinical trials to assess the safety and efficacy of new medications. Rare disease drug development involves a much smaller number of affected patients, a predominance of pediatric patients and more complicated disease presentation. Post-approval studies are designed to address several limitations associated with the rare disease clinical trials.

National and international regulatory agencies in the US and Europe have adopted similar approaches to requirements post-approval data for rare diseases and orphan drug indications. The US FDA published guidance in 2011 and the European Medicines Agency in 2015.

Post-approval studies for rare diseases include observational studies, pragmatic trials and randomized controlled studies. Observational studies include both original data collection studies and the use of secondary data (retrospective studies). Original data collection can address limitations of retrospective studies resulting from incomplete information in secondary data sources. Disease registries focus on detail about a broad range of patients with a rare disease while product-related registries focus on specific health care outcomes associated with a single product and may incorporate a comparator of an alternative therapy or therapies.

Rare disease patients can be difficult to find and enroll in a registry using conventional physician based driven recruitment. The study process also needs to recognize changes in the patient's disease and lifestyle and adapt both the study design and methods over time. Many rare diseases have strong patient advocacy groups that can in aid the design and execution of rare disease registries.

Keywords Rare diseases • Orphan drugs • Post-approval studies • Phase 4 studies • Post-marketing surveillance • Regulatory requirements • Pharmacovigilance • Pharmacoepidemiology • Risk evaluation and mitigation strategies

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11.1 Introduction

Drug development involves a multi-stage process of drug discovery, animal studies and human clinical trials to assess the safety and efficacy of new medications. Over the past 10 years, this process has been expanded to include data collected to describe the effect of drugs on patients in actual clinical practice.

Rare disease drug development involves a refinement of this process arising from a small number of affected patients, the occurrence of many rare diseases in pediatric patients and often, a more complicated presentation of the disease. This refinement results in combining multiple objectives within a single human clinical study and conducting these studies with smaller sample size. The final clinical data package is usually substantially smaller than would be produced through the clinical testing of drugs targeting more common diseases. Consequently, post-approval studies play a larger role in understanding the overall therapeutic value of new orphan medications.

Post-approval studies are designed to address several limitations associated with the clinical trial package submitted for drug approval. These studies are usually larger than the trial population to provide the ability to observe uncommon side effects over time, including a broader population to evaluate drug safety in patient groups not studied in clinical trials. These groups may include patients with greater disease severity, concomitant medications, pregnancy or large numbers of co-morbid conditions.

Post-approval studies are often designed to provide additional efficacy information to supplement that obtained in clinical trials. The drug approval process is based on accepted standards of therapeutic efficacy which have been established through experience gained by regulatory authorities in multiple drug approvals for a specific disease. This process generally requires confirmation of drug efficacy in two randomized, blinded control clinical trials. However, the small populations associated with rare diseases make it both practically and ethically difficult to conduct multiple confirmatory efficacy trials. In the case of many rare diseases, there may be no established treatment standards so the design of the registration studies may involve observation of changes in clinical status over time rather than comparisons of drug effect relative to a placebo or comparator therapy.

11.2 Regulatory Requirements for Post-approval Studies for Orphan Drugs and Rare Diseases

National and international regulatory agencies in the US and Europe have adopted similar approaches to requirements for additional post-approval data for new medications, including those for rare diseases and orphan drug indications. In the US, the Food and Drug Administration (FDA) has the ability to require additional studies after drug approval to more fully understand the mechanism of the medication,

monitor the safety and provide additional information about the longer-term efficacy of the medication based on Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. The FDA published guidance related to post-marketing studies and clinical trials in 2011 [8]. This guidance describes the types of post-marketing studies and clinical trials that will generally be required under the legislation as Post-marketing Requirements (PMRs) and those that will generally be agreed-upon as Post-marketing Commitments (PMCs) because they do not meet the new statutory criteria for required post-marketing studies and clinical trials. Previously, in 2005, the FDA provided guidance to describe good practices in pharmacovigilance and pharmacoepidemiologic assessment [7]. This document provides guidance to industry on best practices in the use of observational data regarding drugs, including biological drug products (excluding blood and blood components). It describes different types of non-randomized observational studies, guidance on the required elements of study protocols and the strengths and weaknesses of various study designs.

In addition to post-approval studies related to evaluation of drug safety, sponsors may be required to conduct additional activities to reduce the risk of potential medication adverse events. The FDA has developed the concept of Risk Evaluation and Mitigation Strategies (REMS) to provide a systematic framework for drug manufacturers to follow when these activities are required by the FDA. These guidance documents outline the requirements and expectations, but not the explicit approach that companies will need to use for a specific product [6, 9]. The basic elements of REMS programs include mechanisms to inform healthcare providers about appropriate use of medications, describe product risks to patients and control access to products through risk screening (i.e., questionnaires), diagnostic testing and use of national specialty pharmacies. Companies selling products with a REMS program also have to commit to the evaluation of the effectiveness of these risk control measures at regular intervals following the launch of the drug. All of these activities are monitored and approved by the Office of Surveillance and Epidemiology within the Center for Drug Evaluation and Research.

In Europe, the European Medicines Agency (EMA) has developed a multi-chapter set of guidance documents, Good Pharmacovigilance Practices (GVP), to outline sponsor requirements for all aspects of drug safety reporting and monitoring including both post-approval studies and risk management programs. In this set of 16 GVP guidance documents, post-marketing studies are described in the module related to Post-authorization Safety Studies (PASS) [3].

There is additional complexity for Risk Management Plans (RMP) in Europe due to the multi-layered pharmaceutical regulatory environment. The EMA has responsibility for the approval of most new products in the European Union (EU) and will approve a specific risk monitoring and control program as specified in the required European Risk Management Plan (EU-RMP), but the implementation of this program will occur and be regulated separately by each individual European Union country. The practical result is that additional risk control activities may be required at an individual EU country level even after drug approval by the EMA. EMA guidance on risk management systems is provided in modules 5 and 16 [2, 4].

European drug law also provides a definition of Advanced Therapy Medicinal Products (ATMP's) which includes gene therapy, somatic cell therapy, and tissue engineering. These products are governed under EU regulation 1394/2007. The EMA has provided a draft guidance document including information about required post-approval efficacy and safety studies for these types of products [5]. This guidance indicates that these studies have to include all patients being treated when this product is used for treatment of an orphan indication.

11.3 Voluntary Post-approval Studies

Post-approval studies can also be conducted voluntarily by biopharmaceutical companies. Rare disease medications may be prescribed by a relatively small number of physicians so a post-approval drug registry provides an opportunity to include a relatively large proportion of patients using a new medication. Physicians may decide to participate to understand how their patients' conditions are responding relative to the total patient population using the medication. Voluntary post-approval studies are also sponsored by biopharmaceutical companies to describe the amount of drug use in specific populations to aid in the budget impact assessment for health care payers. The process of reimbursement for rare disease is often complicated by the relatively high price of these medications. Pay-for-performance programs have been conducted jointly between biopharmaceutical companies and health care payers in the US to provide conditional drug reimbursement based on the achievement of specific outcomes at both the individual patient and total patient population levels. These health outcomes often relate to maintenance of effectiveness for an extended duration, reduction in health care utilization and/or achievement of high levels of patient compliance [1]. For example, United Healthcare, a large US health insurance company, agreed to reimburse the Oncotype Dx test for 18 months while it and the manufacturer, Genomic Health, monitored the results. If the number of women receiving chemotherapy exceeded an agreed upon threshold, even if the test suggested they did not need it, the insurer would negotiate a lower price [10].

11.4 Study Designs for Post-approval Studies of Rare Disease

Many different study designs are used for post-approval studies for rare diseases. These study designs include observational studies, pragmatic trials and randomized controlled studies. Observational studies include both original data collection studies (prospective studies) and the use of secondary data (retrospective studies).

Retrospective studies reuse existing sources of health care information to construct patient cohorts that can provide detail about how patients' conditions change

over time. Patient disease or drug treatment cohorts can be constructed to follow patients from the time of diagnosis or initiation of treatment. Case-control studies are a specific type of retrospective study used to investigate risk factors associated with rare diseases. These studies collect historical information about specific risk factors being investigated on a sample of patients with a rare disease (cases) and group of non-affected control patients selected from the same region or population catchment area. This catchment area could also be a network of physicians treating rare diseases.

Retrospective studies can be based on data obtained from medical records or electronic health care databases based on health care claims or electronic health records. As many rare diseases are treated by a small number of physicians, it can be efficient to use medical records if these physicians can be identified. Large health care databases may also be a useful tool for finding patients with rare diseases to construct retrospective cohort studies. A major limitation of health care databases based on health care claims, however, is that the disease may be misclassified as a more common disease and thus, no additional data are available to further refine the disease classification.

Original data collection provides a method for addressing the limitations of retrospective studies resulting from the lack of homogeneity of information available from secondary data sources. Disease registries focus on detail about a broad range of patients with a rare disease while product-related registries focus on specific health care outcomes associated with a single product and may incorporate a comparator of an alternative therapy or therapies. Several hundred rare disease patient registries are currently ongoing to collect clinical and patient reported information to help describe the overall impact of these diseases to inform health policy and medical care. Table 11.1 provides a description of several organizations that catalogue and support rare disease registries, investigators interested in rare disease research and patient groups.

Biopharmaceutical companies may provide sponsorship for disease registries but their primary involvement is with sponsorship of product-focused registries to satisfy regulatory post-marketing requirements. A major challenge in the construction of product-focused registries in rare diseases is the selection of an appropriate control population. Rare diseases are often orphan indications with no existing therapies to treat the condition. As a result, control populations are based either on historical information from disease registries or based on a concurrently enrolled patient population using ‘standard care.’ Although the same information is collected on a concurrently enrolled population, standard care may have substantial variation in approaches if the registry is based on data from different regions within a specific country or among countries.

Table 11.1 Basic resources for rare disease research

Name	Description	Services provided
TRND	*Therapeutics for Rare and Neglected Diseases.* Within NIH and NCATS Division of Pre-Clinical Innovation.	Aims to encourage and speed new drug development for rare and neglected diseases. Stimulates research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses. http://www.ncats.nih.gov/research/rare-diseases/trnd/trnd.html
GRDR	*Global Rare Disease Patient Registry and Data Depository*. Within National Institutes of Health (NIH)	A data repository by patients for patients to improve the quality of life for millions suffering from rare diseases. Provides the rare disease community a resource of standardized aggregated de-identified patient information to accelerate research and advance therapeutic development. http://www.grdr.info.
ORDR	*Office of Rare Diseases Research.* Within NIH. Integrated with National Center for Advancing Translational Sciences (NCATS) since 2011	Resources of interest to the rare disease community such as social networks, online medical reference Web sites, rare disease events, etc. Links to genetic resources, testing and treatments. http://rarediseases.info.nih.gov/resources/2/rare-diseases-resources
NORD	*National Organization for Rare Disorders.* A 502(c) (3) organization, a federation of voluntary health organizations.	Dedicated to helping persons with rare diseases and assisting the organizations that serve them. Supports innovative research, fair and consistent government policies, and access to medically necessary treatments. http://www.rarediseases.org.
CORD	*Canadian Organization for Rare Diseases*	Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. www.raredisorders.ca
EURORDIS	*The Voice of Rare Disease Patients in Europe.* Non-governmental, patient-driven alliance of patient organizations.	An alliance representing 561 rare disease patient organizations in 51 countries covering approximately 4000 rare diseases-the voice of 30 million people affected by rare diseases throughout Europe. http://www.eurordis.org
ORPHANET	A European database; a consortium of about 40 countries led by French INSERM team.	A reference portal for information on rare diseases and orphan drugs, for all audiences. Orphanet's aim is to help improve the diagnosis, care and treatment of patients with rare diseases. http://www.orpha.net.
ICORD	*International Conference on Rare Diseases and Orphan Drugs*	ICORD is an International Society for all individuals active in rare diseases and/or orphan drugs, including health care, research, academic, industry, patient organizations, regulatory authorities, health authorities, and public policy professionals. www.icord.se

11.5 Challenges in Conducting Post-approval Registry Studies

There are several challenges that are specific to rare diseases when conducting post-approval studies focused on product safety and effectiveness. Rare diseases often represent a diverse disease spectrum that may present with symptoms for many years before a definitive diagnosis is obtained. This disease heterogeneity affects the ability of the study to obtain a representative sample of patients. One potential solution is to conduct this study within the infrastructure created for an ongoing disease registry to allow for patients using the new drug to be followed or recruited from the ongoing registry. The limitation of this approach is the ability to obtain the data needed for the study using either the current data or requesting additional data fields from the sites contributing to the ongoing registry. Biopharmaceutical companies have statutory requirements to collect and report in a relatively short time frame all adverse events that occur in patients taking their drugs; they also need to provide additional data about the physician's judgment if the event is possibly related to drug use and additional data about dosage, concomitant medications, and patient condition. This information is usually provided as a case report for each event of interest. When companies sponsor post-approval safety studies they usually need to ensure that these conditions for safety reporting are met for events observed in the patients enrolled in the study. Most ongoing disease registries cannot comply with this requirement because they obtain data only periodically reported by patients to a central database coordinating center. Data may also be provided to this center in de-identified fashion so that tracking back to the medical record of a specific patient to obtain additional detail about the specific case is impossible. As a result, sponsor companies either have to secure approval from regulatory authorities that this limitation is acceptable or set up studies that involve original data collection from investigators treating patients in actual clinical practice.

Investigator recruitment into rare disease registries can be challenging because physicians may not see many patients with rare diseases in their practice. Once identified, patients may be reluctant to become involved with the registry if they perceive it as burdensome, and thus may lose interest and be difficult to retain if the registry continues over a long period of time.

Many rare diseases have strong patient advocacy associations which can be very helpful in overcoming these potential problems. Patient organizations often maintain extensive lists of affected individuals and their family members who may be interested in participating in a rare disease registry. These individuals are often very motivated to help further the development of new treatments and the understanding of patient burden associated with the disease. These associations are also usually aligned with medical specialists who treat patients with the rare disease. These medical specialists are generally experts in the rare disease and may be willing to participate as expert advisors on the study design, data analysis and clinical interpretation, and help with the identification of other study investigators.

Once enrolled, there are a variety of strategies that can be used to enhance patient retention over the course of the study. The use of study-specific communication about progress, press releases and patient-specific and aggregate study data can be motivating to help patients see the value of their continued participation in the study. The use of phone, email and smartphones as patient engagement tools also provide a way of creating a staged and dynamic process of continued engagement with patients in the study to avoid communication fatigue and loss of participation.

The study process also needs to recognize changes in the patient's disease and lifestyle and adapt both the study design and methods over time. Most rare diseases are diagnosed in children, whose parents or caregivers provide consent for their participation in the study. If the study continues for many years, these children will need to be re-consented as adults in order to continue participation in the study. In addition, the use of variable means of patient and alternative contact information and communication is particularly important for long-term studies because over time patients may move and begin seeing a physician in their new location.

11.6 Summary

Post-approval studies play a key role in the development and use of new orphan medications to treat rare diseases. These studies help to address the concerns of patients, physicians, drug regulatory agencies and health payers about the safety and efficacy of these medications. Rare disease product-related registries are more challenging to conduct due to a number of factors including small patient numbers. It may be possible to adapt the existing infrastructure of an ongoing rare disease registry to conduct a post-approval product-related registry if drug safety reporting requirements can be met. Engagement with patient advocacy groups for a rare disease can be a primary success factor in the execution of disease registries and product-related post-approval registries.

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Chapter 12
Evidence-Based Medicine and Rare Diseases

Simon Day

Abstract This chapter discusses the meaning of evidence-based medicine and where it relates to randomised controlled trials, but also where it does not. The need for good quality evidence is stressed through a discussion of high failure rates in drug development and arguments against access to unlicensed (and largely untested) treatments are set out (despite the good intentions of those who advocate such access to treatments).

Good quality, reliable evidence does not always have to come from clinical trials. Other forms of evidence are discussed. Meta-analyses of individual trials may help to resolve the problem that, in rare diseases, it may be very difficult or impossible to do adequately powered clinical trials – but that does not imply those trials have no value at all.

The importance of patients' choices is stressed but the difficulties of making choices and the general poor understanding of risk can make patients and caregivers, as well as healthcare professionals, very vulnerable to making poor decisions. All stakeholders need to be adequately guided through the evidence to make proper informed decisions.

Keywords Bias • Bradford Hill • Evidence • Meta-analysis • Patient preference • Precision

12.1 Introduction

This chapter covers both the production of, and use of, best evidence about 'treatments'. Although discussion is in the context of therapeutic treatments, essentially very similar ideas and concepts also apply to evidence concerning such things as vaccines, medical devices, diagnostics, patient management, palliative care, and so on. The context is within that of rare diseases (although rare covers an enormous

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range from 10s to tens or even hundreds of thousands). Importantly, whilst there is nothing inherently different about evidence-based medicine for rare diseases as opposed to more common diseases, often the rarity, severity, and lack of alternative therapies bring with them some new and special problems. 'Rare' and 'serious' need not necessarily be linked: there are many quite rare conditions that are not too serious and there are undoubtedly many serious and life threatening diseases that are frighteningly common: heart disease and lung cancer, for example; but also malaria in some regions of the world (although typically this is still considered a rare disease in many other areas of the world). Rarity and severity do, however, in many cases, go hand in hand – particularly in cases where infants are born with rare congenital disease. The severity of the disease often results in a limited life span so that the *prevalence* (total number of cases) remains low. This also implies a disproportionate distribution of young patients with rare diseases. The combination of rarity, severity and children makes this a particularly emotive topic.

12.2 What Is Evidence-Based Medicine?

Various definitions of evidence-based medicine exist. It is probably impossible to definitively identify when evidence-based medicine began but its major development was during the 1980s and 1990s and was epitomised by the work of such people as David Sackett and Gordan Guyatt at McMaster University. Sackett *et al*. [27] defined evidence-based as:

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

They also comment that, through increased expertise of the treating physician, there can be 'more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care.'

Po [25] built on Sacket *et al*. and described evidence-based medicine in the following way:

> Evidence-based medicine has been defined as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'… [Sackett and colleagues] also states that the practice of evidence-based medicine means integrating individual clinical expertise with the best available external evidence from systematic research. However, the term evidence-based medicine is now used much more generally to mean systematic, explicit and judicious use of best evidence in patient care.

So he narrows the focus and takes out the aspects of patient preference. It is probably true that most people's use of the term 'evidence-based medicine' *does* centre on getting reliable evidence, assuming, perhaps, that treatments shown to be best in good quality research will naturally be the patient's first choice. But this seems unfortunate and such may not always the case. Not only do patients (or sometimes their carers) decide on something other than what is apparently the current best

option (according to current best evidence), but patients' choices for a treatment, in the *absence* of reliable evidence, are critically important to incorporate into the scope of evidence-based medicine. Otherwise, how else will such patents suffering from one of the nearly 8000 rare, but currently untreatable, diseases be cared for?

In this chapter we clearly differentiate between the two aspects of *evidence* and *patient choice*. We begin by considering what is good quality evidence about which therapies to use for treating patients of a certain type who have a particular disease. Interpreting and evaluating what is best evidence and producing that best evidence are, of course, the same problem simply viewed from a different angle. In treating a patient, the physician will know what types of evidence (s)he would ideally like to see; it is the researcher's task to get that evidence, whenever possible. When ideal (or 'gold standard') evidence is not available, still the aim of the physician will be to use the best evidence that there is (however good or bad that might be)−why would they use anything other than the best? It is a happy luxury that using the best evidence typically is not associated with any more cost or effort than using poor evidence (assuming we are going to some effort to get evidence). Similarly, it is the task of the researcher also to present the best evidence that they can, even when gold standard evidence may not be obtainable. And this is so often the case when researching treatments for rare diseases when there are simply not enough patients to produce the quantity of evidence that we might generally wish to see. It must be realised though that in contrast to *using* best evidence, *producing* that best evidence may often involve considerable time, effort and expense. So pragmatism in all forms of research (common diseases or rare ones) is always necessary, it is not just in the domain of rare diseases. It is, however, important to understand where pragmatism and compromise still allow reliable evidence to be produced and where the degrees of compromise lead to unreliable and potentially misleading evidence.

We want to strive for the best possible evidence but when patients are a very scarce resource and it is not easy to get much evidence (so we compromise), it seems even more important to get the very best evidence that we can (so no compromise here). These aspects of *quantity* of evidence and *quality* of evidence both contribute to our understanding of the benefits and harms of treatments and we need to proactively work on the quality of evidence (which will mostly include data) as a means to help balance for the inevitable limitations on quantity. Whether the quantity, quality or persuasiveness of the evidence matches what we might expect in (for example) major cardiovascular randomised controlled trials that might recruit tens of thousands of patients is really not relevant. Because we cannot get a similar *quantity* of evidence should not in any way prevent us trying to get similar *quality* of evidence and, consequently, it may sometimes be that the results from small studies can be just as persuasive as those from large studies.

12.3 Evidence-Based Medicine and the Randomised Controlled Trial

'Evidence-based medicine' and 'clinical trial' are not synonymous terms. Even setting aside the aspects of clinical experience and judgement, and that of patient preference, the pure 'evidence' aspect of evidence-based medicine still does not necessarily equate to a randomised controlled clinical trial. Elsewhere in this book, Köpcke and Gerss have written specifically on clinical trials and so in this chapter we will not dwell on aspects of their design, management, analysis and interpretation but rather their context as a research tool.

There are often objections put forward to carrying out randomised controlled trials in rare – and often life threatening – conditions. The most frequent objection put forward is that of 'no other treatment option' and a compelling, compassionate argument to give patients any hope that there is of a cure, extension of and/or improved life, relief of symptoms, or some other endpoint. There are, perhaps, three counter arguments to this position.

Firstly (and a somewhat brutal argument) is that most new experimental treatments sadly do not work – or, even if they do work, their overall benefit-risk balance [20] is not positive. Surveys of pharmaceutical industry success rates (or, more specifically, attrition rates) of compounds as they move through the development pipeline bear this out. Pearson [22] showed that of all compounds entering phase I trials in man, 90% of them never make it to market. Why might this be? Di Masi [7] presented evidence on why drugs fail during development (for the periods 1981–1986 and 1987–1992): about 30% of candidate drugs were discontinued for 'commercial' reasons, between 30% and 40% were discontinued for lack of efficacy, and about 20% discontinued because of adverse safety findings. Similar data from 1991 and 2000 are presented by Kola and Landis [15]. They showed some differences between the 2 years but still about 30% of treatments failed due to lack of efficacy, just over 10% because of adverse safety findings and 11% (1991) and 20% (2000) failed for adverse toxicology findings. Interestingly, they report that in 1991 only about 5% of products were withdrawn from development due to commercial reasons but this rose to 20% in 2000. Of course, insufficient efficacy or excessive side effects may impact on commercial viability – but even setting aside the commercial reasons for discontinuing, in both studies (which cover the period from the early 1980s–2000), an unfavourable balance of benefits and risks accounted for more than 50% of attrition. Put another way, more than half the experimental drugs offered to patients in clinical trials have a benefit-risk profile that is *worse than placebo*.

A second reason often put forward (more often on behalf of patients rather than by patients themselves) is that of 'no other treatment options.' In many cases this will, indeed, be true. But does that mean it is therefore unethical to carry out a randomised controlled trial – even against placebo control? If a general standard of care exists (whether that be evidence-based or not, whether it be based on controlled clinical trials or not) then it would likely be unethical to withhold such care, except

in the case of minor and reversible outcomes [36] but an "add-on" trial design [13, 14] would likely be of most interest anyway. (We should note, however, that there are cases where even the 'assumed' best care has been shown to be harmful [26].) Where there is not even a general consensus of best care – so that there really are no other treatment options available – placebo would be an ethically justified control. The argument is put forward that patients randomised to placebo are being disadvantaged and denied the new therapy, but if these patients were not in the proposed trial, they would either receive no treatment or, at best, would receive the (assumed) best standard of care. So no patient is worse off by being in the trial than if they were not. Though, of course, some patients might be worse off being in the trial than not: as noted above, more than half the experimental treatments trialled on patients are worse than placebo. Spodick [31] has even argued that patients deserve the chance to get the best therapy – which might mean *not* to get the new medicine:

> [it is always possible to do a randomized trial]… in the search for a real answer, and ensures an ethical approach that gives every patient a 50–50 chance to get best treatment, that is, not to get the new medicine at a time when its precise effects and risk-benefit ratio are not understood.

Putting this argument aside, at least here, the fall-back position is that it is not an obviously unethical approach to randomise patients to *not* receive a new experimental medicine when no other treatment options exist. As Sir Austin Bradford Hill [11] noted:

> …frequently, we have no scientific evidence that a particular treatment will benefit the patients and … we are often, willy-nilly, experimenting upon them. It may well be unethical, therefore, *not* to institute a proper trial.

A third reason in favour of carrying out randomised controlled trials (although strictly it applies to getting reliable evidence, not necessarily from trials) is the importance of the question and the importance of answering it properly. There is an irony in this. All of us like working on important issues; all of us would like to work on the development of truly new and beneficial therapies. So why would anyone want to introduce a treatment that, in fact, did not work? Yet this is the very risk from poor quality evidence. The risk is partly that useful therapies will be missed but also that useless, or even harmful therapies will not be seen for what they are. Some people may still fall back on the argument of 'nothing to lose', even if – in fact – a new treatment does not work as well as we thought it did. Sadly, there is plenty to lose. First and foremost, it gives very desperate patients false hopes. This matters little for a new treatment for relief, say, of mild headache. Patients will not be harmed and they will soon find something else to use instead. But it matters a lot when the treatment might be an only hope and possibly where use of the treatment may preclude use of any alternative treatment (for example in acutely life-threatening conditions). It also (partly because of legislative incentives around market exclusivity but also when directing research effort to needed areas) prevents or discourages other researchers – including those who might (but don't know it) have a treatment that works – from entering the research arena. It is harder to justify using experimental treatments in patients when an existing treatment already exists than when

there is no alternative. It may become impossible for follow-on researchers with genuinely useful treatments to test them and so patients continue to use ineffective treatments, realising they are not 'wonder cures' but still holding on to hope that they are believed to be better than nothing. Chalmers has addressed this point in a series of three articles [2–4] (first questioning, then stating, then demanding) that even the very first few patients who try experimental treatments should do so in a randomised trial, before hints of evidence, grossly exaggerated in uncontrolled settings, become assumed common knowledge. Uncontrolled trials are notoriously unreliable. Booth *et al.* [1] in writing about development of anti-cancer compounds refer to the 'dramatic unpredictability of single-arm, uncontrolled Phase II trials…'. Arguments to short-cut or circumvent well-established means of finding out *if* treatments work, *if* they are sufficiently safe, *how much* they work and *how safe* they are, (such as has been attempted in US Federal regulations [8]) are undoubtedly based on compassion for desperate patients. The consequential dangers need to be thoroughly understood [21, 30].

12.4 Other Forms of Evidence

Accepting that clinical trials are important in evaluating therapies (they have often been referred to as the gold standard for doing so), how else might we evaluate benefits and harms of therapies? We might consider what there is *in addition* to trials; we might consider what there is *instead* of trials.

Regarding, particularly, *additions* to trials the most obvious addition is more trials and, hence, the use of meta-analyses (see, for example, Sutton *et al.* [32], Whitehead [35]). This poses a potential problem when researching treatments in rare diseases when it may be very difficult to get enough patients for even one adequate trial, let alone more than one. Such constraints, however, can be used to advantage. Ideally, it seems that complete world-wide cooperation to recruit enough patients into a trial might be desirable but that is, of course, very difficult. Good international collaboration does exist (paediatric cancer trials perhaps being one of the highlights of this collaboration) but it is not easy and not universal. Whilst competition between trialists [28] is probably counterproductive, replication of evidence is of enormous value. Meta-analyses, particularly pre-planned meta-analyses, of more than one trial can be particularly helpful.

It is often questioned whether it is better to have one 'large' study, or a meta-analysis of two (or more) smaller studies. As a particularly special case, it is debated whether one trial of 100 patients (say) is better than two trials of 50 patients, or five trials of 20 patients. This is then seen as a statistical question relating to efficiency, power, and so on, but there is a broader (although perhaps still statistical) issue about the value of replication of evidence. Probably every clinical trial ever carried out has some degree of bias inherent in it. Often the biases will be small and inconsequential – but typically we may have little idea of how large they might be, often we cannot even guess in which direction they might go. So, immediately, two

different, independent trials would seem to protect us to some degree over just one trial. Similarly, several trials might protect us even more. Different trials, organised by different research groups in different regions of the world offer some protection against something going wrong with 'the one and only' trial. But meta-analysts and clever statisticians cannot mix apples and oranges (despite the fact that computer software can!) This is why pre-planning a meta-analysis is so beneficial. It means we can plan independent studies knowing that, although they may have differences, they are also sufficiently similar that combining their results can lead to a meaningful conclusion that is clinically interpretable and useful. In this context it is noteworthy that in a hierarchy of evidence described by the Committee for Medicinal Products for Human Use [5], although meta-analyses were put above individual randomised controlled trials, the phrase actually used was 'Meta-analyses of good quality randomised controlled trials that all show consistent results', this being to stress that poor meta-analyses, and meta-analyses of poor trials, are not useful. Meta-analyses do not automatically give the 'right' answer and there are many poor meta-analyses published. The full hierarchy described by CHMP was:

- Meta-analyses of good quality randomised controlled trials that all show consistent results
- Individual randomised controlled trials
- Meta-analyses of observational studies
- Individual observational studies
- Published case-reports
- Anecdotal case-reports
- Opinions of experts in the field.

Similarly, twenty years earlier, Green and Byar [10] listed a suggested hierarchy. Although the 'other way up' from that of CHMP, it corresponds very closely:

- Anecdotal case reports
- Case series without controls
- Series with literature controls
- Analyses using computer databases
- Case-control observational studies
- Series based on historical control data
- Single randomized controlled clinical trials
- Confirmed randomized controlled clinical trials.

The obvious difference is the lack of explicit mention of meta-analyses by Green and Byar. Although the term was relatively new in 1984, the concept was not and Green and Byer's highest (or strongest) level of evidence – 'confirmed randomized controlled clinical trials' – is really the equivalent non-technical term for CHMP's meta-analysis.

Both of these hierarchies stress the value of meta-analyses but also include other, much less stringent, types of evidence (i.e. the 'what else *instead* of trials'). Both have, for example, anecdotal case reports low (or bottom) of the hierarchy; CHMP went a step further and listed expert opinion as of even less value – but not of *no*

value. Note there are no solid lines cutting off 'acceptable' from 'unacceptable' levels of evidence (or, at least, none published) and nor should there be but many people do have their own unpublished doted lines; their own (private) thresholds of what level of evidence is convincing. However, different treatments in different indications (and particularly considering different expectations of disease progression and different degrees of efficacy) warrant different considerations of what types of evidence are adequately convincing. To make things even more difficult, the pattern of expected prognosis may change over time as diagnosis improves and background standard of care improves. So the value of one type of evidence may change with time.

'Strength of evidence' is only the first part of the problem. What matters more is what we actually do with that evidence and how we make decisions [6]. To consider this, it is helpful to look, for example, at the views of the GRADE Working Party [9] on 'Grading quality of evidence and strength of recommendations' and Schünemann *et al.* [29] on 'Interpreting results and drawing conclusions.' They give an analytical breakdown of how evidence of different strengths might lead to recommending implementation of a treatment (or diagnostic or screening procedure) but also discuss clearly how different people (or regulatory agencies, or reimbursement committees) might legitimately make different decisions based on the same evidence (or same data). The GRADE approach is summarised in Tables 12.1 and 12.2.

Unfortunately, in summary form they can be misleading and may get used as *criteria* rather than as *guidance*. For example, a series of uncontrolled cases seemingly offering symptomatic relief for a naturally self-remitting disease (or at least naturally fluctuating disease) might, indeed, be seen as very low quality evidence (classed as level 3) and, consequently only a grade D recommendation. In contrast, substantially extended survival in a similarly uncontrolled series of patients with a confirmed diagnosis of an acutely life-threatening condition may be seen as

Table 12.1 Levels of evidence

Level	Description
1++	High quality meta-analyses or systematic reviews of randomised controlled trials (RCTs) or of RCTs with very low risk of bias
1+	Well conducted meta-analyses or systematic reviews of RCTs or of RCTs with very low risk of bias
1–	Meta-analyses or systematic reviews of RCTs or of RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal
3	No analytic studies; only case reports, case series
4	Expert opinion

Table 12.2 Grades of recommendation

Grade	Description
A	At least one meta-analysis, systematic review or randomised controlled trial at 1++ and directly applicable to the target population;
	Or
	A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated 1+, directly applicable to the target population and demonstrating overall consistency of result
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results;
	Or
	Extrapolated evidence from studies rated 1+ or 1++
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results;
	Or
	Extrapolated evidence from studies rated 2++
D	Evidence level 3 or 4;
	Or
	Extrapolated evidence from studies rated 2+

much more convincing than simply a grade D recommendation, yet the evidence level would still only be level 3.

Further to considering what else there might be instead of randomised controlled trials, it is also helpful to consider what constitutes useful evidence from an observational (or as some might say, epidemiological) point of view. For this, the classic text and continually re-quoted 'criteria' come from Bradford Hill in 1965 [12]. The comment made here about continuously 're-quoted *criteria*' is apposite, for Bradford Hill never considered them as *criteria*. In the paper in which he first published them, he wrote:

> What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect.
>
> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer which is more likely than cause and effect?

The nine items, 'viewpoints' in his terminology (listed below) were not to be used (and should not be used today) in a simple tick-box approach to causality (either of an environmental factor causing disease or of a therapeutic agent 'causing' relief of illness, extension of life, etc.).

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient

6. Plausibility
7. Coherence
8. Experiment
9. Analogy.

Bradford Hill's nine viewpoints should also not be used as excuses to 'make do' with lesser levels of evidence when better evidence is necessary. Difficulty and necessity are separate. Difficulty may be a reasonable *excuse* but it is never an adequate *substitute* for higher levels of evidence when they are needed. We should always strive for high quality (or high grade) recommendations, but the levels of evidence (as detailed above) need not always be the same across different therapeutic options, in order to make those same high grade recommendations.

Any new study should usefully add to the existing evidence base. If there is a lot of evidence already, new studies need to be bigger or better than those that already exist. If very little evidence exists, then even small studies will add useful information and it is possible to explicitly and analytically determine, before a study starts, what benefits such a study might bring. Tan *et al.* [33] have done this from a scientific perspective; Phillips [23] has done it from an economic perspective. Small clinical trials (however 'small' is defined – and it must be allowed to differ in different situations) are not necessarily bad or of no value, although arguments for and against can be found in, for example Matthews [18] (in their defence), and Piantadosi [24] (citing concerns). Importantly, 'How much evidence already exists' does *not* equate to the current *sample size* of all existing studies, even though the two issues may be linked. But equally important is that there probably is an ethical case for objecting to a 'small' study when a 'usefully larger' one *could* be achieved.

12.5 Quality Always Matters

Perhaps a foremost approach should be that any data are better than none and good and reliable quality data are better than poor quality and unreliable data. Avoidance of bias (particularly in the way in which studies are designed and data are collected) is possibly one of the most critical features. Bias is very difficult to measure (although its existence is often easy to identify). So, some bias may exist but having no idea of its size (sometimes not even its direction) leaves us in very uncertain terrain.

Bias and precision are often illustrated in introductory statistics texts in pictures of arrows or bullets fired at a target, as in Fig. 12.1. Clearly the most desirable situation is in caption D where all the bullets are close to each other (there is high precision) and they are all just about on target (no apparent bias). Note that 'close to each other' is partly measured by the size of the target; it is closeness in a relative sense, not necessarily in an absolute sense. Of course, the situation in caption A (all the bullets are close to each other so there is high precision but there is an obvious bias) could be of use to us. If we know how far off target our gun fires, then we can

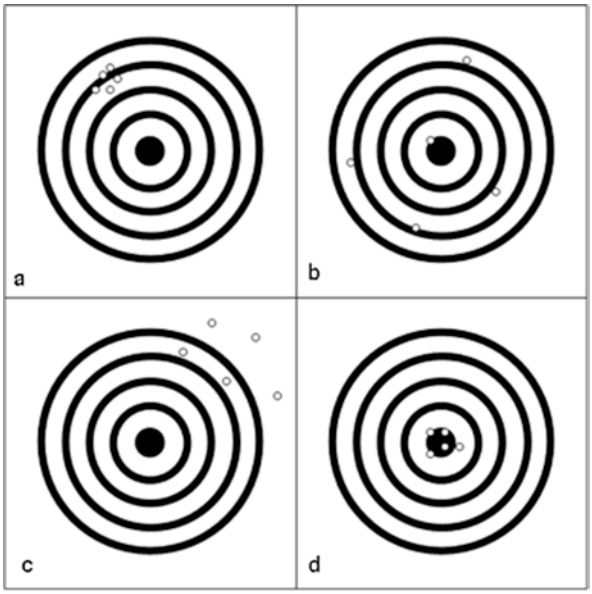

Fig. 12.1 Illustration of bias and (lack of) precision. (**a**) high precision (low variance) but biased. (**b**) low precision (high variance) but no overall bias. (**c**) low precision (high variance) and biased. (**d**) high precision (low variance) and no bias

Fig. 12.2 Illustration of real situation of collecting data. We have no idea if the bullets (the 'data') are on target or not (no idea of bias); and we have no idea if the bullets are closely packed relative to the size of the target (no idea of relative precision)

correct for that with our aim. But this illustration is only of any value if we know where the target is – that is, we know the 'right answer'. When we collect data – whether it be in a cohort of patients receiving a treatment (perhaps to try to determine an absolute response rate), or in a randomised controlled trial (to establish a relative effect, over and above the standard of care)—we do not know what the answer is; we do not know where the truth lies; we do not know where the target is. So, by analogy, the situation we have is more like that in Fig. 12.2. We can see the data (the bullets) but instead of assessing how close to the target we shot, we are using these bullets to try to infer *where the target is*.

We need an instrument (in this case a study of some type) that we can rely on to be sufficiently unbiased. Precision can, to some extent, be addressed with sufficient sample size and quality of measurements. Good clinical trials can often eliminate biases but it is not always necessary to perform randomised controlled trials to get

useable evidence. The United States Code of Federal Regulations [34], for example, lists '…placebo concurrent controls, dose comparison concurrent controls, no treatment concurrent controls, active treatment concurrent controls, historical controls' as acceptable control groups – not all situations necessarily need randomised controlled trials. Clearly, in Fig. 12.2 we have no idea where the target is. We do not even know its size, so we cannot even determine if we have (relatively) high or low precision.

12.6 What Else Matters? The Place of Personal Experiences

We turn, finally, to two elements of evidence-based medicine (encompassed in its definition) that often get forgotten. These are the expert opinions of the treating physician relating to the individual patient and – most importantly – the opinions and wishes of that patient.

As illustrated above, most new treatments in early phases of clinical development are probably worse than placebo. This is a sad fact but a realistic one. Of course, every patient will have a different perspective on treatment options and what matters to them. Some of us will clutch at any straw of hope; others will feel the emotional and physical burdens of an experimental toxic treatment (possibly after several earlier options have failed) are too much to bear. A patient suffering with a life-threatening disease, might argue that nothing can be worse than the inevitable disease prognosis. Put in slightly more scientific terms of benefit-risk assessment, if survival is the efficacy endpoint, then almost any and all adverse effects tend to be of secondary importance to mortality (of course, in less severe conditions, the adverse effects can easily outweigh the clinical benefits).

Patients' wishes, therefore, may often over-ride the data. To what degree should this be respected? The easy answer is 'always' but in some cases those wishes cannot be respected: unlicensed medicines, for example, are simply not available and often the only means of access will be in a trial (when there may be less than a 100% chance of being allocated to that treatment anyway). In other situations, patients may need to be protected against their own over-enthusiasm (and that of their physicians). As Moyé has stated [19] 'It is difficult for physicians to keep in mind how bad things may be with an untested intervention, in the face of the reality of how bad things are without it.' Often this may apply to patients too. The understanding of risk is generally poor and similar risks are interpreted differently depending on the context – both by patients [17] and professionals [16]. Hope in desperate situations is important but the distinction between hope and expectation is blurred. Even in randomised controlled trials, randomisation is not well understood and many patients enter trials knowing there may be a 50/50 chance of receiving placebo but still believing that they will get the (supposedly) active treatment.

Finally, recall from the definitions of evidence-based medicine that although treatment choices (and the name suggests this) should be driven by *evidence*, expert insight should not be ruled out completely. Often it is very difficult to formerly combine all sources of information and knowledge to arrive at a formal

decision-making procedure. The school of Bayesian statistics tries to amalgamate all sources of knowledge and expert experience [6] – but it is not straightforward. Expert opinion of experienced physicians should not be ruled out completely, just because it is anecdotal opinion and not well controlled and objective data.

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Chapter 13
Health Technology Assessment and Appraisal of Therapies for Rare Diseases

Georgi Iskrov, Tsonka Miteva-Katrandzhieva, and Rumen Stefanov

Abstract Innovative rare disease therapies and health technology assessment (HTA) share a lot of similarities. Both represent cases of interaction of epidemiology and health economics. Both are relatively new topics in public health practice. And both pose a lot of challenges to rare disease stakeholders who are currently looking for tools to support the timely access to innovative treatments while putting budget spending in order. This is why optimisation of assessment and appraisal of new rare disease therapies is a fundamental issue in rare disease health policy. Rare disease patients and caregivers expect prolonged life expectancy and improved quality of life and they perceive innovative health technologies as a rightful way to achieve these objectives.

Multi-criteria decision analysis (MCDA) provides a structured, transparent approach to identify preferred alternatives by means of combined calculation of relative importance of different criteria and performance of the alternatives on these criteria. The labyrinth of competing interests and numerous stakeholders involved is why innovative rare disease health technologies make an excellent case study of the integration between HTA and MCDA. This kind of formalisation of decision-making is perceived as fair and legitimate, leading to a balance and agreement. MCDA provides a stage for a debate of policy priorities, health system specifics and societal attitudes, while also addressing the impact of rarity on all criteria and considerations.

Keywords Innovative therapies • Health technology assessment • Appraisal • Reimbursement decision-making • Multi-criteria decision analysis • Cost-effectiveness • Budget impact

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13.1 HTA and Rare Disease Therapies: Interaction Between Epidemiology and Health Economics

Rare disease therapies, especially both orphan and non-orphan designated drugs, present an excellent case study of the interaction of economic and epidemiological factors in rare disease field [8]. From an economic perspective, these therapies would be highly unattractive under standard market conditions. Small number of patients cannot financially justify investing resources into rare disease therapy research and development. Rare disease patient populations are small and research costs must be recouped by increasing product price. From epidemiological perspective, the fewer number of patients makes conducting clinical trials extremely hard. And good, large-scale trials are essential for generating high quality evidence. Evidence-based medicine is very often non-working in rare disease field. Lack of experience and expertise puts health authorities and payers in an environment of great uncertainty when assessing and appraising new rare disease therapies [12].

It has been acknowledged that, while regulatory incentives have globally stimulated research and development of medicinal therapies for rare diseases, availability and accessibility of market approved drugs remain a problem. Access greatly varies among different countries. Furthermore, it is not an unusual situation to have contradictory reimbursement recommendations about the same medicinal product in different jurisdictions [18]. Economic and epidemiological issues are central in the process of assessment and appraisal of these therapies at national level. In times of fiscal austerity however, it is not a question whether to prioritise rarity, but to create legitimate mechanisms for measuring these product's value in accordance with public needs and preferences [20].

Health technology assessment (HTA) is now a well-established approach in public health reimbursement decision-making. Although it is not really a new concept, recent growing pressure on health care spending has formalised HTA as a standard paradigm in health policy. Introduction of advanced technologies, increased expenditures and greater public scrutiny over reimbursement decisions have pushed governments to balance needs and resources, expectations and costs [30]. HTA is evidence-based medicine par excellence. It weights epidemiological, clinical and economic data, combining all these considerations into an incremental cost-effectiveness ratio (ICER). ICER has been long regarded as the final outcome of the HTA process, making it a key point in reimbursement decision-making [4].

Despite being recognised for fostering informed decisions, HTA is nothing more than a technical tool. Reimbursement recommendations are made by health authorities, who must take into account various other factors as well [27]. Epidemiological and health economic evidence is not the only consideration that shapes reimbursement decision-making and health policy in general. Political context plays a major role in all public health decisions. Health authorities may not always tend to be benevolent maximisers of social welfare [14]. As a result from the influence of different stakeholders, decision-makers are more likely to use intuitive or heuristic approaches to simplify the complexity of assessment and appraisal of new therapies

[2]. Political pressure is now an essential constraint within which public health systems have to operate. It is not surprising, because effective public health leadership needs citizen engagement and support [24]. HTA process does have real-life political consequences, thus making it difficult to avoid such considerations.

In fact, rare disease therapies and HTA share a lot of similarities. Both represent cases of interaction of epidemiology and health economics. Both are relatively new topics in public health practice. And both pose a lot of challenges to health policy stakeholders who are currently looking for tools to support the timely access to innovative rare disease treatments while putting budget spending in order. Thus, optimisation of assessment and appraisal of new rare disease therapies is a fundamental issue in rare disease policy. Rare disease patients and caregivers expect prolonged life expectancy and improved quality of life and they perceive innovative health technologies as a rightful way to achieve these objectives [12].

13.2 Current Approaches to Assessment and Appraisal of Rare Disease Therapies: HTA and Its Methodological Challenges

HTA systematically explores the properties and effects of a health technology, evaluating direct and intended effects, as well as indirect and unintended consequences. These considerations include safety, efficacy, effectiveness, cost, cost-effectiveness, as well as expected social, legal, ethical and political impacts [5]. Balance between the value of a health technology and the effective access to it represents a fundamental issue of modern health policy. Appraisal of innovative therapies is, however, a debate of political priorities, health system specifics and societal expectations. This process does require trade-offs, as resources are limited in all health care systems and all countries. Two specific factors – cost-effectiveness and budget impact – are notorious for shaping the assessment and appraisal outcome for new rare disease health technologies [8, 32].

Cost-effectiveness is a leading consideration in all economic evaluations, with ICER being its main outcome measure. This decision factor is crucial, because it aims to ensure achievement of the biggest possible benefits to the widest range of users. ICER is defined as the ratio of the change in costs of a therapeutic intervention (compared to the alternative) to the change in effects of the intervention [4]. It has been long recognised that rare disease therapies can not meet this criterion. This is not a pure methodological pitfall, but rather a direct result from these therapies' epidemiological and economic specifics – high price and evidence uncertainty [12].

Whether or not to implement an explicit ICER threshold in reimbursement decision-making is a highly disputed topic. Public demand for scrutiny in resource allocation and priority setting is a natural catalyst for the introduction of fixed ICER thresholds. Application of such a benchmark in assessment and appraisal of health technologies provides advantages, such as reduced burden of responsibility upon

decision-makers, consistency and transparency of the decision-making process. Nevertheless, the concept of ICER is a very sensitive issue from both political and ethical points of view. ICER benchmarking requires comparisons and rankings under strict conditions that are often unavailable in practice. There is no such thing as constant, context-independent willingness-to-pay for any health benefit gained [4]. Health authorities and stakeholders tend to give different priority to different health technologies. Implementation of a clear-cut ICER threshold deprives them from the opportunity to take into account any ad hoc considerations, which may be substantial in the case of rare diseases [8].

The fact that there are very few practical examples of ICER thresholds is further illustrating these concerns. UK's National Institute for Health and Care Excellence (NICE) is often mentioned as using, albeit implicitly, ICER thresholds. Nevertheless, this institution has repeatedly denied these allegations [17]. Furthermore, the single universal focus on ICER as a reimbursement decision-making benchmark is detrimental [25]. ICER is a measure for cost-effectiveness, not for social justice. Cost-effectiveness has been increasingly criticised for limiting patient choice and health care rationing. Concentrating on ICER could eventually marginalise other decision points, such as whether the characteristics of the rare disease or patient population receiving the treatment would lead to value the produced health gain more highly than the analytical estimate, whether the characteristics of the rare disease therapy are such as to require to give due weight to innovativeness, whether other benefits to society are such that it is socially desirable for the rare disease treatment to be made available [12, 17].

Reimbursement decision-making for a new health technology requires a budget impact analysis. Budget impact is the other example of combined economic and epidemiological challenge in assessment and appraisal of rare disease therapies. While cost-effectiveness allows decision-makers to evaluate the effectiveness of health technologies, budget impact is measuring the financial impact of the adoption and use of a new technology within the health system. This indicator represents an assessment of the accessibility of a new health technology. Given the increasingly stringent budgetary frameworks, regulators and payers are paying more and more attention to this measure. Economic analyses may provide a basis for a favorable reimbursement recommendation, but it is the budget impact analysis which is ultimately determining what resources would be needed to actually implement this decision [21].

It is exactly these fiscal considerations that have been blamed for undermining the rational application of the cost-effectiveness criterion and HTA in general [21]. Budget impact is a substantial decision-making point because health authorities attach great importance to the sustainability of the health care system. With regard to innovative therapies for rare diseases, they fear that these costs would be significant and may trigger substantial changes in resource allocation. Practice clearly demonstrates that health technologies with a high budget impact are much more likely to be rejected for reimbursement or to be subject of access restrictions than technologies with a limited impact [16].

In case of rare disease therapies, budget impact considerations are further complicating the HTA process [15]. Data on the size of patient population, secondary costs, degree of market penetration are often difficult to predict. Use of health care information is traditionally fragmented [3]. Health care costs are usually divided into several different budgets and distributed among a number of payers. Reimbursement recommendations are often made at product level, without considering the spillover effect. An orphan therapy may significantly increase the costs for treatment, but at the same time it could also reduce the costs for other health and social services [8].

Rarity as a factor is obviously affecting the assessment and appraisal of rare disease therapies. These technologies' performance on economic and epidemiological decision criteria is poor. Reimbursement recommendations are, however, not automatically bounded on HTA outcomes. There is an increasing consensus among all stakeholders on the importance of balancing all factors, which are determining the combined impact of a health technology on the health system, patients and society [27]. Innovative rare disease therapies are intended to treat serious, life-threatening or chronically debilitating conditions, where other therapies are often not available. These health technologies are expensive on an individual patient basis, but are supposed to have limited impact on the health budget as a whole, since patients with a specific rare disease are very few. Cost-effectiveness and budget impact are important considerations, but health authorities and payers need to take into account the social value of these therapies, their innovativeness and future potential in non-rare indications [8, 32]. There is a strong need to address this divergence between the added value of orphan drugs and the public demand for efficiency in health care expenditure.

13.3 MCDA: A More Transparent and More Inclusive Approach in Reimbursement Policy

Multi-criteria decision analysis (MCDA) provides a structured, transparent approach to identify preferred alternatives by means of combined calculation of relative importance of different criteria and performance of the alternatives on these criteria [6]. In this way, MCDA enables the exploration of stakeholder preferences, as well as the comprehensive organisation of broad range of criteria on which real-world decisions are actually based. MCDA's main elements include decision context, alternatives to be appraised, criteria against which alternatives are appraised, scores reflecting the value of alternatives' performance on criteria and criteria weights that measure the relative importance of each criterion. Designing and constructing these components into a single MCDA reimbursement decision-making framework could be done through various methods – value measurement, outranking, reference-level models, etc. [28]. These approaches vary in terms of complexity, with the first one being the most discussed and practically applied technique [31]. Under the value

measurement procedure, individual scores are developed for each criterion and then multiplied by the respective criterion weight. Overall value or the degree to which one alternative is preferred over another is the sum of the weighted scores of all criteria.

Identification of the set of decision criteria is a crucial stage of MCDA, as this defines what would be considered important when appraising the value of a health technology [27, 28]. Decision criteria should be relevant to the specifics of the local health care system – its mission, priorities, but also funding mechanisms. It is obvious that jurisdictions cannot directly transpose a set of reimbursement decision-making criteria from others [11]. This is because public health resources, needs and expectations strongly differ across nations. These differences impact the relative importance of the individual criteria, making any MCDA framework unique to its own public health settings. Decision criteria may be the same, but local public health considerations are different. Political interests and societal preferences strongly vary as well [14].

When defining the set of criteria, it is a must to find a balance between different stakeholders, limited budgets and increased expectations, formal requirements and informal constraints. Inclusion of efficiency criteria like cost-effectiveness and budget impact is, of course, mandatory. These two indicators answer the fundamental public health questions of whether a health technology presents a value for the money and what resources will eventually be needed to implement this decision. Nevertheless, efficiency criteria need to be combined with equity factors, namely to ensure fair distribution of health benefits within society [11, 19]. Reimbursement recommendations have to be in line with overall health policy goals, including availability, accessibility and affordability of relevant health technologies to populations in need in a timely and adequate fashion. Equity considerations are, in effect, a strong mechanism for citizen involvement and patient empowerment. Appropriate recognition and inclusion of these values could increase the likelihood of meaningful health policies and enhance the satisfaction with the national health systems [9].

Overall, transparency and consistency are MCDA's two paramount advantages. Transparency actually means consistency of reimbursement recommendations over time. Indeed, any appraisal methodology needs to justify how different decisions are made by different people at different times. Appraisals of new health technologies often include some forms of access restrictions. These limitations are most accepted when they are transparent and consistent. They should foster sustainable population health by recognising societal priorities and fiscal constraints while giving due weight to the rights and claims of individual patients who seek health care. When societal and individual priorities considerably diverge, ethic principles require sound arguments why health needs are left unmet [22].

13.4 MCDA in HTA for Rare Disease Therapies: Opportunities and Real-World Examples

Reimbursement decisions are complex not only because of the multiple aspects considered, but also because of the potential gaps in evidence. It is more often the evidence vacuum, not the economic considerations, that makes health authorities and payers set up restrictions on access to new rare disease treatments [23]. Public acceptance of these limitations represents the real test for the credibility and feasibility of any reimbursement recommendation framework. The perceived transparency and consistency of these decisions could greatly enhance or undermine the overall rare disease policy.

The labyrinth of competing interests and numerous stakeholders involved is why innovative rare disease health technologies make an excellent case study of the integration between HTA and MCDA [29]. And this is no longer a purely theoretical experiment, as many jurisdictions are now either considering or implementing such an approach in assessment and appraisal of rare disease treatments [32]. MCDA's multidisciplinary nature enables the explicit understanding of trade-offs in reimbursement decisions, while addressing the impact of rarity on all decision criteria and considerations.

One of the very first examples of integrating HTA and MCDA in case of rare disease therapies was a study by Sussex et al. from 2013. Authors identified a list of criteria through a literature review. A linear additive MCDA model was constructed, consisting of eight non-monetary attributes – four concerning the disease being treated and four concerning the treatment itself. Then, weights and scores of individual decision criteria were elicited at consensus-building workshops with rare disease stakeholders. Results showed that these two categories of criteria weighted equally – for a half of the total assessment score. While the different contributors in this research generally agreed on the criterion weights and scores, patient representatives gave greater value than did the others to quality of life issues. Both authors and participants were satisfied with the way MCDA works and recommended it for use by payers and health authorities [26].

Two recent studies confirmed these outcomes. A study by Kolasa et al. explored the potential impact of MCDA on orphan drug pricing and reimbursement in Poland. Ten decision criteria were selected through a literature review and merged into a linear additive MCDA model again. Here, however, weights and scores were directly assigned by the researchers – 0 points at the worst outcome and 2 points at the best outcome for each criterion. Authors applied their model to a number of orphan drugs and then compared the total assessment score to the real-life reimbursement recommendations. Substantial disagreement was found in a considerable number of cases, the majority of which related to positive HTA guidance for negative MCDA outcomes. Nevertheless, this study confirmed that criteria of cost-effectiveness and budget impact tended to play a less important role in MCDA appraisal compared to the HTA process. In other words, MCDA was effectively balancing these two health economic considerations against other characteristics of the orphan drugs in question [13].

Another study by Iskrov et al. constructed an MCDA value measurement model to assess and appraise orphan drugs. Unlike the previous two examples, here, the set of decision criteria was made through a survey among four rare disease stakeholder groups (medical professionals, patient representatives, health authorities and industry representatives), resulting in three distinct criterion categories – health technology's characteristics, indicated disorder's characteristics and public health aspects. Elicitation of weights and performance scores was done through another survey and the MCDA framework (using again linear additive model) was piloted during a focus group discussion. Decision criteria that describe the health technology's characteristics were unanimously agreed as the most important group of reimbursement considerations, weighting for 44 points out of 100 assessment points in total. The results of this study suggested that the strength of evidence may be a key criterion in assessment and appraisal of new rare disease therapies. Evidence is used not only to shape reimbursement recommendations, but also to lend legitimacy to policies implemented [10].

These examples, as well as a number of extensive methodology analyses and systematic reviews on MCDA in HTA seem to fully support the use of this approach in assessment and appraisal of rare disease therapies [1, 7]. Above-mentioned cases highlight two important issues about the ongoing fusion of MCDA and HTA for rare disease therapies. First, simple value measurement represents the most preferred MCDA technique. Sure, there are more sophisticated methodologies, especially regarding weight and score elicitation. Nevertheless, they impose a higher level of complexity, unnecessarily increasing the burden for all participants. The approach applied in the cited cases does allow for a comprehensive collection and analysis of preferences of various groups of people on multiple criteria. This procedure is greatly consistent with the way people usually make decision aggregations. Second, the overall MCDA framework, including criteria, weights and scores, needs to be consensually agreed by all rare disease stakeholders – health authorities and payers, medical professionals, patient associations and industry representatives. As these groups may often present divergent perspectives, it is crucial to find out a common ground between what is good for the society and what is good for the individual. The right approach here is to foster cooperation and collaboration through consensus-building tools, such as a focus group discussion. This helps explicitly understand the trade-offs that are inevitable in the assessment and appraisal of rare disease therapies.

13.5 Conclusion

Rare disease patients view prolonged life expectancy and improved quality of life as the most essential indicators for a successful rare disease policy. Access to innovative therapies is regarded as a rightful step to pursue these objectives. Here, however, standard paradigm of HTA is not working due to scarcity of good epidemiological and economic evidence. This is why health authorities are more

unlikely to adopt a positive reimbursement recommendation. In all countries and health care systems, choices regarding the allocation of resources are necessary. Decision-making is a complex process. Despite best efforts, it is difficult to reconcile all competing interests. These considerations explain the uptake of value-based pricing and reimbursement. MCDA plays a major role in this policy shift. This kind of formalisation of decision-making is perceived as fair and legitimate, leading to a balance and agreement among the different stakeholders.

Lack of rigorous evidence is extremely complicating the assessment and appraisal of new rare disease therapies. Limited data make funding these highly expensive health technologies controversial in times of fiscal austerity. Closing the evidence gap is a crucial point for the timely access to innovative rare disease therapies. It is not a question to prioritise rarity, but to elaborate a decision-making framework that would be capable of formally detecting and quantifying all the values that mirror the impact of new treatments to patients, society and payers. Theory and practice now clearly demonstrate that MCDA is capable to provide a transparent and consistent reimbursement decision-making methodology for addressing this problem. Health authorities in partnership with all rare disease stakeholders need to pursue a multidisciplinary analysis on a range of criteria, ensuring a clear-cut understanding of the trade-offs for decisions on eligibility of reimbursement. Dialogue and collaboration in MCDA result in rational and consensual reimbursement decisions, which promote wise use of health care resources and allow for equal treatment of rare disease patients.

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Chapter 14
New Therapeutic Uses for Existing Drugs

Bobbie Ann Austin and Ami D. Gadhia

Abstract Eighty percent of drugs that enter human clinical testing are never approved for use. This means that for every five drugs that make it into the clinic, there are four that failed to show effectiveness for treating the disease or condition the drug was designed to treat.

This high failure rate means there are many existing, partially developed therapeutic candidates with known pharmacology, formulation, and potential toxicity. Finding new uses for existing experimental drugs or biologics "repositioning" builds upon previous research and development efforts, so new candidate therapies can be advanced to clinical trials for a new use more quickly than starting from scratch.

Federal funding initiatives in the U.S. and UK started to support pre-clinical /or early stage trials for repositioning existing experimental drugs or biologics (therapies). This chapter covers some of the process issues that have been solved and the remaining challenges that are still in need of solutions. The chapter is primarily written from a U.S. federal funding perspective. The general concepts could be applied more globally to benefit rare and neglected disease populations. The drug development and process bottlenecks are the same for both rare and common disease.

Keywords Drug repurposing • Drug repositioning • Drug development • Public private partnerships • Crowdsourcing computational strategies • Early stage trials • Pre-clinical studies • Experimental drugs • Pharmacology • Off-label use • Drug partnership

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14.1 Introduction

Therapeutic development is a costly, complex and time-consuming process, mainly due to bottlenecks in the development process. The average length of time from target discovery to approval of a new chemical entity ranges from 10–17 years [6]. Eighty percent of drugs that enter human clinical testing are never approved for use. Since existing therapies already have been tested in humans, detailed information is available on their pharmacology, formulation and potential toxicity. Repositioning builds upon previous research and development efforts, so new candidate therapies can be repositioned and advanced to clinical trials for a new use more quickly than starting from scratch. Pre-clinical testing, chemical optimization, formulation, and early development can often be bypassed in a repositioning program [1]. By repositioning existing drugs the timeline is shortened to 3–12 years [6] (Fig. 14.1).

14.2 General Concepts

Drugs are often repositioned from their initial use when they failed for business reasons, scientific reasons, or any other reason besides a toxicity reason that precludes the therapy from being safe to use in humans.

14.2.1 Drug Repositioning Advantages

Advantages of repositioning an existing drug include shorter development timelines and reduced risks [2]. Generally, drugs are repositioned to take advantage of the investments that were already made for experimental therapies. While therapeutic

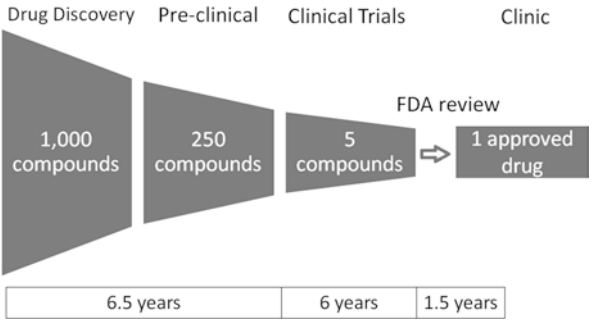

Fig. 14.1 Therapeutic development pipeline (Therapeutics development currently is a slow, costly and failure-prone endeavor. Figure depicts how many assets enter each stage of the drug development process, how long it actually takes at each stage, and how many compounds actually enter clinical trials and eventually make it to the clinic)

development for a new chemical entity requires a large infrastructure, starting with a partially developed asset can "bypass ½ the costs by eliminating pre-clinical assessment" [10]. Some of the risks are reduced, when studies are already complete for determining the safety, toxicology, pharmacokinetic, and pharmacodynamic profiles; and much of the data needed for regulatory approval is already available.

There are some intellectual property benefits. While therapies can be repositioned after they are deprioritized or marketed, pursuit of multiple indications for therapies that are in active clinical development can preserve valuable patent life for successful indications [3]. Patents claiming compositions of matter provide stronger protection than a new use patent, because the composition can be applied not just for a new use. This could potentially be obviated with development of a new formulation of the therapy [11]. "Drug repurposing" is finding a new therapeutic indication (i.e., new disease) for an FDA approved drug or licensed biologic. Generally, "drug repositioning" is used in this chapter in reference to finding a new use for an experimental asset.

There is not a viable business plan in the private sector to recoup research and development (R&D) investment for the cost of clinical trials for drugs that do not have enforceable patent life remaining. While there is a possibility to obtain a new formulation of the therapy or a new use patent, with new uses, it is difficult to prevent "off-label" prescriptions for available generic drugs. There has not been a readily accessible data trail for the number of prescriptions written for old drugs that are being used for a new purpose. Basically, the new use patent holder does not have a way to monitor the indications prescriptions are written for, thereby making the patent difficult to enforce [12]. And even if the new use patent holder becomes aware of physicians and/or pharmacists who are prescribing and dispensing drugs for "off-label" use, suing them for contributing to or directing patent infringement is not practical or possible in some jurisdictions.

14.2.2 Drug Repositioning Challenges

In April 2011, NIH convened an NIH-Industry Roundtable that included a group of senior leaders and experts from the pharmaceutical industry, government, academia, and the non-profit sector. They discussed opportunities to facilitate drug repositioning partnerships. Participants agreed that more can and should be done to increase engagement and partnerships in drug repositioning and to enhance the success of these efforts.

14.2.2.1 Resources

Some of the challenges to repositioning include resource implications. Limitations for pharmaceutical companies include: the time and resources to maintain, update, and organize their compound libraries for drug repositioning. An investigator who wishes to access data from prior trials may find it difficult to obtain access to

available drugs and data about the drugs. The drug master file (DMF) is a document prepared for a regulatory agency, like the Food and Drug Administration (FDA). It has details about facilities, processes, or articles to manufacture, process, package, or store one or more human drugs. The data in a DMF submission to the FDA may be referenced in subsequent regulatory filings, but the actual data may not be available to the party that is filing for regulatory approval for a new use. Details about the manufacturing of a drug product active pharmaceutical ingredient (API) and quality control data, chemistry, purity, stability, and packaging information could shave years of testing off a new indication. However, the data is confidential and has proprietary information that helps a company protect intellectual property, while complying with regulatory requirements. It is submitted to the FDA with trade secret/confidential protections in place along with a New Drug Application (NDA) user fee. The production of the data may have cost millions of dollars, and often economic reasons have halted further development. So, in the absence of a monetary incentive for the data release, it may only be referenced in subsequent regulatory filings, but the actual data may not be available to the party that is filing for regulatory approval for a new use [8].

14.2.2.2 Intellectual Property and Exclusivity

Ninety percent of FDA-approved drugs are off patent, and there's no good way to commercialize them. There is little market incentive for companies to develop secondary uses of products after they are generic, so it is very difficult to find funding for a phase III trial on a new use of generic drugs. Drugs that are covered by patents that are close to expiring also may not be attractive to industry because the financial return and market incentives for the product are limited. Generally, the original use of the drug is covered under both a composition of matter patent and a use patent for the original intended use. Secondary uses could be covered under a use patent [4]. Patent term is measured from the filing date, and is determined to be 20 years from the earliest U.S. or international (PCT) patent filing (35 U.S. Code §154). Generally, the use patents offer 12.5 years of preventing competitor products, while biologics have a much longer period where competitors are staved off.

14.2.2.3 Public Availability of Experimental Assets

A limiting factor is the number of viable compounds that are accessible to the scientific community and which cannot be sold for profit. Often companies have a number of assets (experimental drugs or biologics) that could be used for repositioning, but they cannot be offered for public private partnerships, because the assets may be in the process of being out licensed. There could also be competition for resources with other projects (financial and technical expertise capacity) and a risk-averse perspective on legal matters, in the event that the therapy has new liabilities in a new patient population that impact an existing market [8]. In general, the

manufacturer of the active pharmaceutical ingredient is liable for any adverse events in a new patient population. If the manufacturing is transferred to a contract research organization (CRO), then typically the CRO assumes liability for any adverse events in the patient population.

14.2.2.4 Technical Expertise

From an academic perspective, the technical expertise for repositioning may not be readily available. Potential issues include lack of training in clinical research and regulatory aspects, as well as intellectual property and privacy concerns. Additionally, many academic investigators are measured by the impact of their publications as well as the grant funding that they receive. Not only may there be insufficient incentives for these types of academic-corporate collaborations, but there could also be conflicts of interest that arise in such arrangements. Moreover, these collaborations may be less sought out by university technology transfer offices, which serve as the commercialization arms of many universities. These offices are typically designed to out-license the intellectual property that their researchers and staff have generated, rather than improve upon the assets of third parties. While repositioning may fit the mission of academic research organizations, it could be difficult for academics to pursue alone, in light of aforementioned barriers.

14.2.2.5 Establishing Public-Private Partnerships

Generally speaking, there is a transactional hurdle in establishing public private partnerships between companies and academia. Much time and understanding of motivations and incentives is needed to bridge points of contention, and negotiate legal agreements that address the needs of all parties. Typically, clauses surrounding intellectual property rights and liability generate the most discussion.

14.2.2.6 Challenges with Rare and Neglected Disease

Drug companies may not always choose to develop a drug for an orphan disease, if there isn't a sufficient population to recoup their research and development costs in the marketplace. The Orphan Drug Act of 1983, when signed as Public Law 97-414 in the USA, was developed as an incentive for companies to develop therapies for rare diseases. It provides 7 years of marketing exclusivity and additional financial incentives [5].

14.3 Drug Development Partnerships Initiative

NCATS established a 3-way partnership between industry, academia, and government to test process improvements for drug repositioning. The goal of the program is to identify new therapeutic uses of proprietary assets (experimental drugs/biologics) across a broad range of human diseases in areas of unmet medical need. The short-term goal is to establish efficient drug repurposing partnerships through the use of template agreements, and to enable matchmaking of the best ideas from academics with experimental assets offered by pharmaceutical companies. It is expected that long term the community will adopt the strategy more widely, if projects have demonstrated success in the clinic (Fig. 14.2).

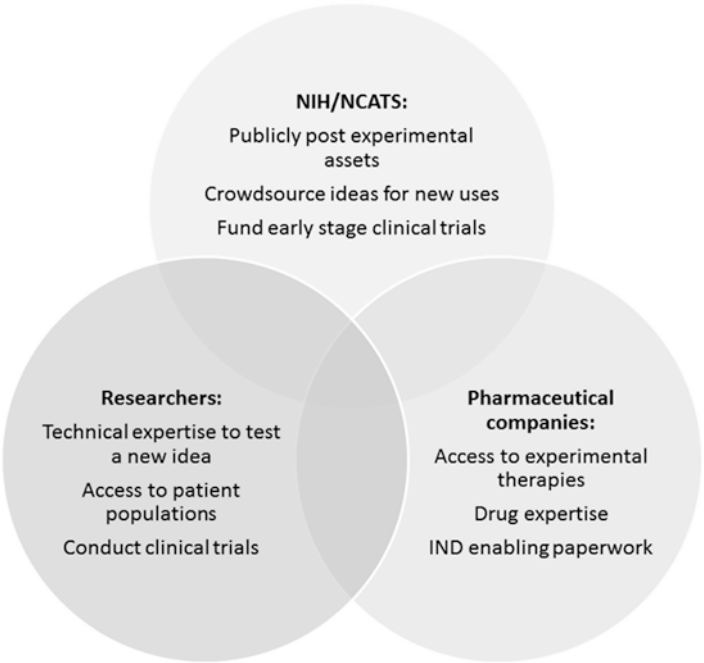

Fig. 14.2 New therapeutic uses public private 3-way partnerships (The figure depicts the roles each of the partners in NCATS new therapeutic uses partnership program with industry play, along with the areas of intersection)

14.3.1 NIH/NCATS

14.3.1.1 Template Agreements

The role of NIH/NCATS in the partnership program is to establish 3-way collaborative partnerships between the pharmaceutical industry, biomedical research community, and government through the use of template agreements. Template agreements are publicly posted to NCATS' website to streamline complex legal and administrative processes between academic technology transfer (or research administration) offices and pharmaceutical partners' legal teams. The template agreements that NIH/NCATS has developed save the academic and pharmaceutical partners considerable time and effort, as they provide a roadmap for handling intellectual property used in or developed through the program. The templates have demonstrated that they shorten the time required to establish public-private collaborations to about 3–4 months instead of the more typical 9 months to 1 year. Many participating pharmaceutical partners now use NCATS template agreements routinely when they establish new collaborations with academic collaborators.

NCATS executed a Memorandum of Understanding (MOU) with each of the pharmaceutical company partners to provide a framework under which specific proprietary assets will be provided to grant recipients, who collaborate with these partners. Template confidential disclosure agreements (CDAs) are executed between the grant applicant's institution and the pharmaceutical company that is providing an asset of interest. The CDA is to be executed before each party exchanges data. Terms of potential research collaborations are specified in template collaborative research agreements (CRAs).

14.3.1.2 Crowdsourcing

In order to facilitate drug repurposing, NIH/NCATS serves as a matchmaker between the best ideas from academics and experimental assets owned by pharmaceutical companies. In order to do this, limited confidential information about experimental assets is publicly posted, and ideas for new uses of the assets are collected from the collective intelligence of scientists who apply for funding. The basic type of information posted about the drug includes the type of information in the example below.

- Drug name: AZD0530
- Mechanism of action: Src Tyrosine kinase inhibitor
- Original indication: cancer
- Route of administration: oral
- Additional information:
  - Suitable for/exclusions
  - Safety/tolerability

- Additional characteristics
- Publications.

14.3.1.3 Team Science

NCATS and collaborating NIH institutes and centers provide peer review of ideas from academic investigators, funding for any necessary pre-clinical work, clinical trial planning, and Phase I and Phase II clinical studies. The 21st Century Cures Act was signed into law in December 2016. As a result, NCATS may also support phase III efficacy trials for rare disease, if special requirements are met. For all supported clinical trial phases, NIH negotiates milestones and provides project management/oversight of funded projects. Technical assistance is provided during the project period. There is periodic review of medical monitoring documents and study protocol(s), and the project team ensures the study milestones are being met and provides feedback for ways to address challenges. Projects that don't meet pre-clinical milestones don't graduate to clinical testing. Each project has an NIH project scientist with expertise on the disease population or drug that is being tested, and a medical monitor.

14.3.1.4 De-Risk and Hand Off

Generally federal funds are somewhat limited in capacity beyond Phase II clinical trials. For projects that are successful, the template agreements give pharmaceutical partners the first right of refusal to pursue Phase III clinical trials and commercialize a new therapy. If a pharmaceutical partner decides not to pursue the project further, the academic medical center may find a third party to work with.

14.3.2 Pharmaceutical Partners

Participating companies cover the costs for manufacturing pre-clinical and clinical supplies of drugs and placebos to funded investigators. They also can provide suitable documentation so funded investigators can file an Investigational New Drug application with the Food and Drug Administration, and they provide technical expertise on the drug that they developed. Criteria to participate in the program include the following:

- At least three assets will be contributed for the solicitation. This is done because the number of ideas received is directly proportional to the number of assets provided, and it takes a fair amount of time for both parties to negotiate template agreements.
- Mechanism of action for each compound must be known.
- Pharmacokinetics are suitable to explore the mechanism in a new indication.

- Phase I clinical trial has been completed; safety profile is understood.
- Company will provide pre-clinical and clinical supply for studies (both drug and placebo).
- Company must provide the appropriate regulatory documents (i.e., cross reference letter or study reports) to enable a funded investigator to file an Investigational New Drug application in the U.S. within one (1) month of NIH funding for projects that go directly into a clinical trial without pre-clinical work.
- Assets currently in clinical development can be included.

14.3.3 Academia

Academic investigators provide new therapeutic use ideas and technical expertise to conduct pre-clinical feasibility testing, Phase I and Phase II clinical trials, Phase III efficacy studies (for rare disease only), and access to patient populations. They determine the experimental research approaches, design clinical trial protocols, draft milestones and go/no go decision points, and submit investigator-sponsored INDs to FDA.

14.4 Drug Partnerships: Success and Lessons Learned

Some of the successes for the drug development partnerships were expected, and others were unanticipated.

- The template agreements shortened the time to establish new collaborations to 3–4 months, instead of the typical 9 months to 1 year or more. Some participating pharmaceutical companies have indicated that they use the template agreements as a starting point for academic collaborations outside the program. After several iterations of the program the agreements are no longer being edited as frequently or extensively. Fewer changes are needed and are typically restricted to institution, project, or drug-specific changes.
- Crowdsourcing was an effective way to launch collaborations. Even without NCATS support some projects have gone forward with either foundation or company support.
- Pharmaceutical partners like the peer review process and reviewer feedback before a decision is made about going forward with a project.
- At least one company has asked that the program include assets that are in active development. There are multiple open investigator INDs at the same time. This shaves off time and preserves patent life for additional indications.

Some of the success stories represent individual project success. While many of the studies are still in blinded Phase II clinical studies, some interim success has been identified.

- One applicant had never done a clinical study prior to the drug development partnerships program, and this jumpstarted drug development at their institution. It has changed the way they think about research going forward and was a tremendous professional growth opportunity.
- One project achieved attrition of only 3% in a schizophrenia population because their staff is very engaged in patient outreach. The typical attrition for this population is 20–40%.
- A project for an indication that hasn't seen a new therapy since 1999 improved an imaging method for monitoring disease progression that generated a lot of commercial interest and represents an improvement for monitoring disease progression in future clinical trials.
- One investigator tested a drug that failed fast for the proposed indication, but the collaboration that started in the program jumpstarted a much larger collaboration with a participating pharmaceutical company. The investigator accessed thousands of company compounds to test for efficacy against a neglected tropical disease parasite.

14.4.1 Pinch Points for Asset Availability

A variety of lessons have been learned, and there are still problems in need of creative solutions. In particular, there are many more available experimental assets than are provided for inclusion in the drug partnerships program. Pinch points for asset inclusion include the following:

14.4.1.1 Timelines for Support

It is difficult for companies to commit to timelines that last 3–5 years or more. Academics want more time for pre-clinical and clinical work. NIH enforces strict timelines because expanded timelines mean fewer assets would be available in the first place.

- Solution: There is not much room for solving this particular problem.

14.4.1.2 Manufacturing Expense

Right now, participating pharmaceutical companies are required to cover the costs to manufacture drug and placebo. They often have financial resources tied up in other priorities. The cost estimated to manufacture drug/placebo for the program is estimated at $350,000–$1 million. This depends on API availability and drug specific manufacturing costs. The packaging and shipping is a lower expense

($30–50,000), depending on the number of clinical study sites, as well as the size and duration of the study.

NIH cannot cover the costs of manufacturing without looking like they are lining the pockets of the biopharmaceutical industry. One possible solution is to identify third parties that can partially cover the costs of manufacturing for some return on investment like partial royalties. A model would have to be developed that sets realistic expectations for all parties and does not add additional time to the peer review process.

14.4.1.3 Liability

The manufacturer of the active pharmaceutical ingredient assumes liability for any adverse events in the new patient population. If a Contract Research Organization (CRO) manufactures, the liability typically transfers to it from the pharmaceutical company. One idea to address liability and manufacturing involves having a contract/subcontract mechanism in place. Pharma is accustomed to working with CROs. Some challenges are not insurmountable, however. For example, it is unlikely that academic institutions would be comfortable with companies assuming zero liability for the use of their drug. Academics would want to ensure that they are fully indemnified, and that there is no liability transferred to the academic institution.

14.4.1.4 Pharmacovigilance

Some companies are concerned about how pharmacovigilance will be handled in the program. This is more of an issue when there is more than one open Investigational New Drug (IND). For studies on a deprioritized asset, with only one study going on, the academic principal investigator is solely responsible for reporting safety updates to the FDA. When there are multiple open INDs for the same asset, the pharmaceutical company is the only party that sees emerging safety data from human studies. So, they are the only party that can be responsible for safety updates to the FDA. The U.S. government does not indemnify. However, it may be possible to address some of the pharmacovigilance concerns with more clarity and standardized expectations across projects through the use of best practices, clear policies and guidance, clinical trial toolkits with templates for clinical trial documents, and procedures/contacts for reporting unanticipated events and adverse events.

14.4.1.5 Three Asset Threshold

Currently the company participation criteria require inclusion of three assets in the program. The number of assets provided is directly proportional to the number of ideas received from academic partners. It takes a fair amount of time to negotiate

template legal agreements. For the effort taken by both parties, it is best that a sufficient number of assets be included so that a project using an asset is more likely.

Another factor is risk management for federal investment. Right now, there is not a good mechanism in place to ensure continued provision of an asset during the funding period for smaller, more volatile companies. We also have not received that much interest from small companies to repurpose ideas in a disease agnostic fashion. They are more likely to seek support for their own ideas.

Even with larger companies, it can sometimes be difficult for them to identify three assets that meet the criteria, have sufficient patent life for the investment, and the assets are not under consideration for out licensing deals or otherwise able to be sold for profit.

14.5 Repurposing/Repositioning Methods

14.5.1 Crowdsourcing

One of the limiting factors for widespread proposals of ideas for new uses of existing molecules, is that the existing experimental assets owned by pharmaceutical companies aren't publicly accessible. So, academic investigators (and other companies) aren't able to systematically know what exists. While it doesn't represent the full spectrum of available assets for repositioning existing molecules, there are several government funding programs that have tried to address the problem of access to information.

Partnerships to harness the strength of various stakeholders are a means to do drug repositioning in a systematic way. In the United Kingdom, a Mechanisms of Human Disease Initiative (MRC) was established that provides access to pre-clinical pharmaceutical compounds to UK investigators. MRC provides funding, and participating pharmaceutical partners provide scientific input, drug supply, and documents needed for regulatory and ethics paperwork.

In the United States, a similar program was created when the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) was formed. NCATS launched the Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program in January 2012. This program enables academic investigators to apply for funds to test new therapeutic uses for existing proprietary investigational drugs and biologics that have been through at least Phase I clinical trials. When funding opportunities are published, limited confidential information about investigational assets [new molecular entities (NMEs) and biologics)] from pharmaceutical companies is made publicly available. Publicly posted information includes: mechanism of action, safety/tolerability, route of administration, original indication, and exclusions for new use that the company is not interested in pursuing.

This approach of publicly posting investigational therapeutics for investigators to propose ideas for new therapeutic uses is referred to as crowdsourcing. Generally, crowdsourcing is an approach used for investigational therapeutics, not therapeutics that already have received regulatory approval, since approved drugs already are known to the public. Generally, any website that lists experimental pharmaceutical assets that could be repurposed for another use would be a crowdsourcing website.

An example of crowdsourcing is how NCATS matches researchers with a selection of pharmaceutical industry assets (https://ncats.nih.gov/ntu/assets/current) to test ideas for new therapeutic uses, with the ultimate goal of identifying promising new treatments for patients. Academic investigators submit ideas for new therapeutic use to NCATS for peer review. Applicants with the most meritorious ideas are put in contact with participating pharmaceutical company contacts. Together, the applicants and companies decide which ideas make sense to pursue, after additional data is exchanged. In some instances, partnerships have been initiated between academic medical centers and pharmaceutic partners outside of New Therapeutic Uses financial support, simply because investigators were able to find the publicly posted assets and connect with appropriate company contacts (Box 14.1).

Another example of a crowdsourcing approach is AstraZeneca's Open Innovation program (http://openinnovation.astrazeneca.com/what-we-offer/clinical-compound-bank/) reviewed in Frail et al. [7].

14.5.2 Computational and Informatics Strategies

In the era of big data science, there are over 1000 databases with information that could be used to predict a new therapeutic/indication for an existing drug. Commercially and publicly available computational strategies and algorithms can be used in combination with experimental validation in the lab to identify new drug targets. Common methods and sources of data include genetic association, gene or

Box 14.1: By serving as a matchmaker between academic experts and pharmaceutical partners, an Alzheimer's disease project team at Yale University found that a compound originally developed as a cancer therapy could be used to treat Alzheimer's disease. The Yale scientists tested the drug in a mouse model of Alzheimer's disease. After 4 to 6 weeks, the mice showed reversal of Alzheimer's symptoms such as spatial learning impairments and memory loss. The drug already was tested for safety in humans and passed key steps in the development process. By repurposing an existing drug, investigators began testing the drug in humans within 3 months; it would typically take a decade from the discovery of a promising compound to its readiness for clinical trials.

protein expression, phenotypic data, cellular network pathway analysis, structural and molecular modeling, and drug centric methods (drug response signatures, sensitivity signatures, or target expression). While all the methods can't be comprehensively covered here, generally the challenge is not the identification of new therapeutic/indication pairs. Rather, the challenge is identifying the most effective strategy to identify therapeutic/indication pairs that can be experimentally validated. Investigators often use multiple strategies and pair down the list of targets by finding out which new therapeutic/indication pairs are repeatedly identified with multiple methods. Rational decision making about what targets to pursue involves experts on the drug pharmacology, biology, and indication. Numerous factors play into the feasibility for later stage development, if a positive efficacy signal is found *in vitro* and *in vivo*. Such strategies are more comprehensively covered by Li, et al. [9].

14.5.3 Mining Clinical Data

Patient medical records, insurance records, pharmacy data, and other clinical data can also be mined for associations that show a signal for a new therapeutic/indication.

14.5.4 Phenotypic Screening

Phenotypic screening is a method used to identify drugs that alter cellular phenotypes. Human disease-relevant assays are conducted to help scientists explore the effects of small molecules on disease-related molecular processes. Drugs that change cellular function are further explored as possible lead candidates for drug discovery. Phenotypic screening and computational strategies are often used in tandem, for one method to validate the other.

14.6 Summary and Conclusion

Drug repurposing/repositioning funding opportunities for academic investigators are somewhat limited. They may apply to standard funding opportunities. However, if reviewers value the novelty of new chemical entities more highly than a therapeutic that has potential to get to the clinic faster, the applications may not score as well during peer review.

Progress has been made in recent years to address some of the gaps for public private partnerships, but more can be done. Many more pharmaceutical assets are available in individual companies than what is publicly available. Information about

assets is known to the FDA, but it is proprietary. Unless there is a way to monetize access to information in the drug master file, it can only be referenced.

Pharmaceutical companies are interested in pursuing new indications for existing assets, but there are barriers to working with academics, including concerns about liability, pharmacovigilance, and the manufacturing costs/timelines for academic projects.

A successfully repositioned drug from a public private partnership could tip the scale in favor of more assets offered for crowdsourcing new ideas from the collective intelligence of the academic community.

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Chapter 15
Patient Empowerment and Involvement in Research

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Abstract Patients with rare diseases often face difficulties in clinical care due to the low prevalence of their diseases and the resulting healthcare professionals' lack of expertise. Valid and standardized guidelines for clinical management are also lacking due to the scarcity of research and the variability of the clinical expressivity within each disease. In addition, in cases of rare diseases, the patient and health professional relationship may not fit with the traditional assumptions of medical care. Although the communication process between patients and healthcare professionals shares most of the general features of the standard patient-health professional interaction, rare diseases may be burdened with additional issues.

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In this sense, clinical decision-making in an uncertainty context should take advantage of involving patients in deeper informational process to promote valid shared decision-making between patients/caregivers and healthcare professionals. This process of patient/caregiver empowerment is a priority in the context of rare diseases, as it encourages acquisition of information that will help improving patient-healthcare professional's interaction, and building a collaborative relationship. It is also a chance for healthcare professionals to learn about rare diseases from the perspective of patients.

Engagement of patients and other stakeholders in clinical research may help to ensure that research efforts in rare diseases address relevant clinical questions and patient-centered health outcomes. However, the effectiveness of patient-engagement approaches, particularly for the study of rare diseases, has not been well studied.

Keywords Patient-centered care • Patient empowerment • Patient Involvement • Patient participation • Rare diseases • Research • Shared decision-making

15.1 Introduction

The increasingly more central role of the citizen in modern healthcare systems has led to the onset of a new patient-focused healthcare model. This fact, backed by current ethics statements that promote a clinical relationship based on joint deliberation and participation of the different actors of the National Health System (NHS) have been the basis for carrying out new healthcare strategies [18].

The term "patient-focused medicine" was introduced by Michael Balint [3], giving special prominence to the patient as a "person". This model arose in contrast to the "doctor-focused" or "disease-focused" model, where the symptom and professional's opinion are central axes and where the patient's life experience is not a preferential option [17].

The care model focused on the person or patient (or patient empowerment) uses her/him knowledge and experience to guide the clinical encounter. Treatment options that are more effective and in line with their desires, needs and preferences are considered [34]. This biopsychosocial perspective evaluates the patient as having personal experience, and that enables sharing decisions and responsibilities in a more cooperative way and assuming the intersubjective character of the relationship between healthcare professional and patient [37].

Therefore, this model enables patients to express their emotions and concerns, favors that their beliefs/expectations about the disease are explained, provides information to them and makes them equal partners in drawing up a plan for intervention. Therefore, a more comprehensive response is given to the individual problem and generation of the therapeutic alliance is sought.

Promoting the participation of people in their healthcare is considered an ethical imperative and it is thus set out in the Declaration of Salzburg [47]; one of the first public

consensuses that claimed the implementation of shared decisions between healthcare professionals and patients, as joint health producers. This ethics-related component implies that professionals recognize and facilitate the patient's self-determination, respect their autonomy but accompany them with their health decisions.

A result of the changing paradigm that makes the citizen the target of clinical actions is the opening-up of a new situation in which healthcare units or departments should build a new relationship with patients where it is necessary to develop new communication skills and invite participation in healthcare teams. Moreover, it is important to consider that failures in effective communication between health professionals and patients can lead to increased medical costs arising from overuse or misuse of medical services [4, 19, 36].

Therefore, from the point of view of clinical management, the patient-focused healthcare model provides the healthcare system with certain aspects of responsibility. In this sense, the undertaking to share information on healthcare and offer all the support required by patients to make choices against a backdrop of responsible clinical decision-making is assumed.

15.2 Patient Empowerment and Rare Diseases

Patients with rare diseases (RD) often face difficulties in clinical care due to the low prevalence of their diseases and the resulting healthcare professionals' lack of expertise. Valid and standardized guidelines for clinical management are also lacking due to the scarcity of research and the variability of the clinical expressivity within each disease. In addition, in cases of RD, the patient and health professional relationship may not fit with the traditional assumptions of medical care. Although the communication process between patients and healthcare professionals shares most of the general features of the standard patient-health professional interaction, RD may be burdened with additional issues (e.g., lack of information or knowledge about the disease, lack of expertise among the healthcare professionals, challenges related with the diagnosis and prognosis of an incurable disease and greater geographical distances between patients and health care services).

In this sense, clinical decision-making in an uncertainty context should take advantage of involving patients in deeper informational process to promote valid shared decision-making between patients/caregivers and healthcare professionals. This process of patient/caregiver empowerment is a priority in the context of RD, as it encourages acquisition of information that will help improving patient-healthcare professional's interaction, and building a collaborative relationship. It is also a chance for healthcare professionals to learn about RD from the perspective of patients.

It is important to note that patients with RD have limited access to useful information to guide treatment decisions. Beyond shared clinical decision-making, engagement of patients in clinical research may help to ensure that research efforts in RD address relevant clinical questions and patient-centered health outcomes. RD organizations may provide an effective means to facilitate patient engagement in research.

This change in the model of decision-making, in addition to being promoted by the NHS is a result of the demand generated by the users themselves as established by EURODIS, the European Organisation for RD (www.eurordis.org). The more active patient profile in the RD case has gone from undergoing important asymmetry of knowledge and decision capacity to enforcing their rights for autonomy.

15.3 Patient Involvement in Rare Disease Research

Although health research is conducted to produce knowledge that may ultimately lead to better treatments for patients, patients themselves do not always have a large influence on priority setting, design selection, collaboration in implementation, interpretation or dissemination of findings. Patients claim that researchers should think in advance about the usefulness of their study and do more practically oriented research. Patients also argue that research studies should be useful for them within a relatively short time frame [6].

Beyond the spread of democracy in all activities of public services, patient participation in health research is thought to contribute to the improvement of the quality and relevance of health research [7] as well as the acceptance of its findings [61]. Patients contribute through their specific knowledge based on personal experience with the disease, symptoms, therapy and the health care system. However, many clinicians and researchers have historically denied the validity of this experiential knowledge of patients because of its lack of objectivity, verifiability, universality or rationality. Nevertheless, in the literature two distinct kinds of arguments are given in favor of patient involvement in research: normative or ethical arguments that consider health research as a democratic political process where patients have a moral right to participate, and substantive arguments concerning the positive impact on health research in terms of quality and relevance that patient participation produces [11, 55, 59].

Gooberman-Hill et al., in 2013 [26], emphasized the ethical imperative of promoting a growing involvement of population and patients (IPP) in designing and conducting research activities and, later on, in the dissemination of research results, both as an expression of research democratization and as an strategy to extend the value of research and make their results more patient oriented. Serrano-Aguilar et al. (2009) [50] and Gagnon et al. (2014) [24, 25], suggested IPP as an effective approach to enlarge the identification of research objectives and to fit research opportunities and efforts to the more relevant societal concerns; making more efficient the use of available research funding and more prone to satisfy the views and needs of researchers and society (patients), without limiting rigor and internal validity of research results.

The term “involvement” was used in this context to explain a stronger relationship or active collaboration between society representatives and the scientific community along the research process. Increasing research involvement by society or

patients denote a patients' movement from a passive role in research under the main activity of data provision, to a more active and expanding role as co-researchers [15]. According to Springett, et al. (2011) [52] this expanding role includes from a simple consultation process where society or patients are surveyed by researchers along the research design to identify their research needs and priorities to make health research more patient oriented, to different forms of research collaboration. The more recent experiences of research collaboration by patients could affect to different research activities such as research needs identification, research agenda prioritization, patient recruitment, data gathering, adaptation of patient interventions, helping to make research results understandable for all and contributing to their dissemination; among others potential actions.

Beyond the progressive pathway from patient consultation in research design to a superior role of patient collaboration in several research activities, the research controlled by patients occurs when patients control either the funds and/or the research objectives. Good examples of this trajectories have been developed by INVOLVE in the United Kingdom (http://www.invo.org.uk/international-collaboration-on-participatory-health-research/); the Patient-Centered Outcomes Research Institute-PCORI (http://www.pcori.org) in the U.S.A. and the Participatory Canadá Research at McGill-PRAM (http://pram.mcgill.ca/pubs.php) in Canada [20, 24, 25, 30, 54]. IPP is also increasingly observed into the field of Health Technology Assessment (HTA) and Health Services Research, both of considerable value for the Health Care Systems. As direct beneficiaries, patients perceive the comprehensive health effects and social impacts of new diagnostic, therapeutic and/or rehabilitative health technologies on their specific health condition as well as on their quality of life [25].

In the case of RD, empirical data about the involvement of patients in research is still limited. Forsythe et al. (2014) [23] performed a systematic review and found 35 studies in which patients, caregivers, or other stakeholders participated in planning or conducting biomedical or health services research related to RD. All studies were observational, and 71% of them focused on a specific RD (e.g., achalasia, neuromuscular disorders, pulmonary arterial hypertension, cystic fibrosis, Paget disease, lupus), whereas the remaining recruited patients with different diseases. Nineteen studies reported on engagement of patients, 18 on engaging patient organizations, 13 reported engaging parents or other caregivers, and five reported engaging clinicians. Contents included narrative reports of involvement experiences, descriptions of specific initiatives reported on websites, or the use of qualitative or survey methods to obtain inputs from patients.

The authors classified the description of the engagement activities as "minimal" or "sufficient" to enable their replication by others researchers, and they found that only seven studies (20%) were classified as sufficiently descriptive.

15.4 Impact Assessment of IPP in Health Research

Very few experiences have been documented to inform on the potential impact of IPP in health research [38, 39, 53]. However, some studies show that organized patients are able to identify relevant research needs and to highlight variations in values and access to different types of services/treatments among regions or countries. Through literature review and more than 60 interviews with biomedical researchers, patients, representatives from patients' organizations and health care professionals in the Netherlands and the UK, Caron-Flinterman et al. (2005) looked for concrete examples of individual biomedical research processes that in some way have been changed by the inclusion of patient contribution. From a total of 21 cases of patient participation in biomedical research identified, concrete use of patients' experiential knowledge could be traced for nine of these cases. These studies show that patient's experiential knowledge is able to influence biomedical research at different stages of the research process. Patients' demands for research led to the formulation of additional research priorities within research projects or new research topics or questions to be investigated and, thus, to the launching of new research projects. Patients' ideas on etiological or therapeutic aspects were translated into new biomedical hypotheses or research questions [11]. From these findings we could assume that the real value of patient involvement on the research process is beginning to be reliably assessed and valued.

Commissioned by the NHS, Oliver et al. (2006) provided relevant information on the potential influence of IPP as well as its magnitude and costs, by means of their publication on the "Evaluation of public influence on the NHS Health Technology Assessment Programme" [39]. This report inform us that 28 (15%) of all commissioned projects related to HTA funded by the NHS in England and Wales were refereed by a lay people. The marginal costs for public involvement were approximately £30,000 a year, accounting for the 2.3% of the program management costs or the 0.3% of the total HTA budget. The total costs of the commissioned research influenced by public involvement were about £2 m, or 21.6% of the commissioned research. Therefore, the marginal costs of public involvement in identifying and prioritizing research is far outweighed by the influence on research subsequently funded.

The PIRICOM review emphasizes the importance of context and process consideration in the interpretation of IPP impact [8]. Context refers to the conditions required for IPP to have an impact. For example, the appropriate support and training, the appropriate funding, positive attitudes toward IPP, and appropriate time allocation might be important in a particular situation. Process refers to the methods used to undertake the involvement such as level of involvement and the stages of the research process where involvement occurs. While some studies did describe context and process information, it was rarely linked to any interpretation of impact; possibly because studies use to be focused on assessing the effectiveness of interventions.

While other research areas, such as patient experiences or patient-reported outcome measures have developed instruments that, with varying degrees of success, measure the concept of interest, IPP does not have a pool of robust, well developed instruments to measure IPP impact. Robust measurement of the extent of IPP impact could provide additional information that could enable a greater understanding of what works, for whom and in what circumstances. When exploring the impacts of IPP, it is important to consider also the economic impacts, particularly if forming a judgment about whether a particular involvement activity is cost-effective. However, only a very small number of papers mention costs of particular IPP activities. It is important that, in future theorizing of involvement, economic impacts are considered alongside forms of impact as part of a broader development of the patient and public involvement evidence-base.

In RD, the existing literature shows that patients and other stakeholders have been involved in the distinct phases of research. In the *preparatory stage*, they have been consulted to identify research topics, agendas or outcome measures not attended by current research, as well as to discuss about research funding. For instance, Edwards et al. (2011) [16] interviewed parents of children with cerebral palsy to identify priorities and needs about the design of a randomized controlled trial of osteopathy. Parents preferred a waitlist design that allowed all children eventually to receive the treatment; regarding outcomes, they suggested a range of factors relevant to their child's quality of life instead of focusing on isolated outcomes. They expressed a clear preference for the costs of treatment to be funded by the trial.

Involvement of patients and stakeholders in the *execution stage* of research has focused mainly in the improvement of patients' recruitment procedures. This is an important aspect in RD research due to the low number of patients suffering these diseases. For instance, DeWard et al. (2014) [13] discuss their experience in the field of phenylketonuria, and how partnership among clinicians, patients, study coordinators, genetic counselors, dietitians, industry, patient support groups, and families can help overcome the challenges of recruiting and retaining patients in clinical trials. Carroll et al. (2012) [12], recruited patients with pulmonary arterial hypertension and identified four thematic areas which resume factors that influence patients' decisions about enrollment in randomized controlled trials: (1) personal medical benefits, (2) personal medical risks/harms, (3) nonmedical benefits, and (4) nonmedical burdens. One third of the patients stated that they would defer the decisions enrollment to their treating clinicians. In other initiatives, patients have also participated collecting data by means of interviews [12]. Finally, several studies have focused on the *stage of research translation,* mainly in the dissemination of results.

However, despite these promising initiatives in the field of RD, there is not a standardized method of assessment of the impact of patient involvement in research, and current published studies have not formally assessed outcomes related to engagement.

15.5 The Public and Patients' Perspective

As Brett et al. reported in 2014 [8], from the *public and patient perspective*, the impact of IPP is valued more as a personal journey, with reports of users feeling empowered, valued, listened to and generally more positive about their experiences. Users also increased their knowledge of their condition and developed life skills. Many of these impacts reflect the wider societal benefits that demonstrate the potential for research to act as a positive force in society, engaging a broader range of individuals, involving them in meaningful ways to contribute to the generation of research that has potentially broader utility and relevance for the wider public. This positive experience motivated service users during and after the interaction to continue being involved in research. However, if negative impacts are reported, such as experiencing researchers' negative attitudes and perceptions, not feeling valued by the researchers, not receiving feedback from researchers, or feeling overloaded or emotionally overburdened, they can lead to reduced motivation of service users to be involved in research, and therefore have negative impacts on the research [32, 58].

15.6 The Researchers' Perspective

For researchers, the positive impacts reported were about gaining new insights into their work and gaining a greater understanding of the health condition under study. Researchers found possibilities for working in new ways and developed trust and advocates of their research within the community under research. This can lead to the development of more patient focused protocols, improvement in recruitment and the quality and relevance of data collected, more patient related themes being identified in the analysis, and wider dissemination of the results [5, 58]. One of the most challenging impacts on researchers is the lack of funding and time to conduct the IPP activity following the right processes and in the right context in order for the IPP activity to have a valid impact. There is a general feeling that IPP is still not taken seriously enough by some researchers, who do not see the need to include the perspective of patients in their research and the same happens with the funders, who see it as a low priority and therefore do not provide enough funding for it, although some funders such as NIHR in the UK now provide important support for IPP. Furthermore, IPP involvement needs additional time, and this needs to be accounted for in research proposals.

A lack of commitment and a tokenistic attitude towards IPP by researchers can have challenging impacts on the service users, who feel undervalued, unimportant in the process, and unable to contribute, which may lead to a reduced impact or no impact of user involvement on the research.

15.7 The Community Perspective

For the community, beneficial impacts reported included greater awareness of the condition and a better understanding of research. However, the increased expectations on the community can be time consuming and costly for community members, often with little money to compensate for this. A common theme identified in this review is the potential for challenging impacts which can result from colliding worlds, where the values and assumptions researchers have meet with the needs and aspirations of users and the community as a whole, and do not necessarily mesh well. This may negatively impact parties involved in IPP, and subsequently impact the success of IPP. Researchers report the challenging impact of having to compromise their working practices, and express concern that the impact of IPP may affect the integrity of the research, while service users report the issues of not being taken seriously, not being given a clear role, and not being given the knowledge or training needed to be able to contribute, leading to the loss of any hopes and aspirations for future involvement. This can create frustration and conflict between parties.

15.8 Some Experiences of IPP in Rare Disease Research

15.8.1 Patient Involvement in Research Recruitment Activities

Literature addressing strategies to improve patient recruitment has focused on clinical trials for common chronic conditions with very few references on recruitment for RD research [12, 13, 29, 33]. To overcome recruitment barriers in RD research, multi-institutional collaboration at international level is promoted [62, 63]. Although these efforts are contributing to advances in basic and clinical knowledge, socioeconomic research on RD is still neglected but required by health policy makers and Patients Organizations (POs). Although barriers to participation in clinical trials for cancer treatment have been reported, including fear of trials, competing clinical trials, information overload, distrust of trials and time burdens [10, 22, 57], information is limited regarding the assessment of barriers and outcomes of recruitment strategies among patients with RD. Unfortunately, no information is available on these issues for other study designs beyond the scope of clinical trials. A potential barrier to recruit patients with RD could be the high rates of delayed and erroneous initial diagnosis [21]. The high frequency of affected children in some RD might also reduce participation [33].

A few of international experiences exist, where patients taking up full control of this critical part of the research process. Our own experience along the BURQOL-RD project to develop a disease-based model capable of quantifying the socio-economic burden and health-related quality of life of patients with ten different RD and their caregivers in Europe [35], required recruitment strategies managed in every country by the corresponding national federation of RD, such as ACHSE in Germany,

Uniamo in Italy, the Alliance Maladies Rares in France, Rare Disease UK—GIC in the UK, RD Sweden, HUFERDIS in Hungary, NAPRD in Bulgaria and FEDER in Spain. All of them are non-profit organizations including >100 POs in their corresponding countries. These national federations contacted and invited the specific POs related to selected RDs. After agreement, all participant POs were instructed to send personalized e-mails to their associated patients, stating the project objectives and providing a link to a web-based questionnaire. POs were also asked to send two reminders to all patients 2 and 4 weeks after launching the initial e-mail round. There was no possibility of selective reminders, given that no personal identification was requested in the questionnaires. Once patients and/or their carers accessed the questionnaire, they were asked to consent by checking a box after being informed about the project objectives and procedures. Completed questionnaires were automatically saved in a central database built in MySQL. Links to all questionnaires in their adult and child (aged under 18) versions were also put up on the project's website (www.burqol-rd.eu). All the organizations involved in the project were requested to support recruitment by publishing the BURQOL-RD website link on their respective websites, social media (Facebook, etc.), newsletters, and so on. Paper questionnaires were distributed by postal mail for those RDs and countries with lower than expected responses (Prader—Willi Syndrome, Epidermolysis Bullosa and Scleroderma) or when patients were unavailable by e-mail. The entire recruitment process was completed in 4 months.

15.8.2 Patient Participation in HTA and Clinical Practice Guidelines Development

Several specific activities related to HTA and Clinical Practice Guidelines (CPG) development are prone of receiving added value by means of IPP, such as identifying and setting priorities among possible topics for HTA; recruiting patients locally for consultations to put in context potential previous findings from the existing literature and revising the initial HTA objectives according to local patient needs; including patient preferences and values in setting recommendations for CPG; helping in the writing to ensure patients understanding of HTA reports and CPG; and along the dissemination and implementation of results.

The CPG Program supported by the Spanish Ministry of Health (http://portal.guiasalud.es/web/guest/informacion-pacientes) promotes patient involvement in the CPG development process as a preliminary step for patient empowerment and informed decision making [14, 28]. Earlier, this participative and instrumental approach had been adopted by countries such as Australia, the United Kingdom, and the Netherlands among other countries [27, 31, 44, 48, 60].

Explicitly when undertaking the development of a CPG, three different but complementary activities are recommended to involve patients and include their views [50]. First, a systematic review of the international literature focused on the main

health problems and self-perceived health care needs related with the selected condition. Second, in order to receive feedback from people living with the specific disease, a consultative and consensus process is suggested at local (regional/national) level. Third, patient representatives are recruited for the guideline development group from the beginning to the end of the CPG development process.

Our research group has developed experience in IPP in HTA and CPG development focused on consulting patients to warrant that the objectives and final contents of HTA reports and CPG are patient centered and gives answers to the main patients´ concerns and needs. We used the Delphi method, rarely used for consulting patients, to support IPP in the context of HTA for different diseases such as degenerative ataxias (DA), Systemic Lupus Erithematosus (SLE) and Retinal Distrophies (RDis).

The Delphi method was selected to make possible the participation of scarce, scattered and disabled patients affected by RD allowing us to identify health needs and to clarify priorities through a well-structured and iterative process [1]. This procedure improved its efficiency by the use of electronic mail. Patients were not selected by probabilistic sampling procedures, but rather by the leaders of POs enrolling all participants via e-mail. Patients were formally invited to the consultation and informed consent was requested once informed on study aims and methodology [49, 50]. The three rounds of the Delphi consultation were distributed by e-mail and the principal investigator was responsible of the information exchange with patients to warrant protection of information confidentiality. The first round used an open questionnaire to explore three different issues: the most relevant self-perceived health problems associated with their disease, the main unmet needs, and the treatments commonly used. The second Delphi round was targeted at setting priorities among previously received answers to each question identified in the first round. Each participant assessed the importance of each of the topics previously identified on a scale of 1–10, assigning the highest scores to the most important and the lowest scores to the least relevant. Answers were ranked according to the degree of importance using the median value, given its robustness to treat extreme values and because data were not normally distributed. To establish order differences among factors having the same median value, we used the 10th–90th percentile range (10–90 PR), since factors having a lower 10–90 PR express a greater consensus among the study participants. The third Delphi round had the purpose of reaching a final consensus. To do so the overall results obtained in the second round, after ranked, were returned to all participants with additional indications of each individual's previous assessment. Finally, participants revised their earlier answers in light of this information [49, 50]. Majority voting was adopted to analyze final responses, given its value to offer reliable findings and to demonstrate controversial issues in this quite large panel [1].

Though some authors claim that IPP can make research activities more expensive and longer than expected [7, 61] we have learnt that, despite the low frequency of RD, our approach succeeded in recruiting a significant number of patients rapidly and inexpensively through the use of communication technologies. Although the use of e-mail to conduct a data collection using Delphi method has shown to be effective and efficient, the uneven availability of computers and potential technical

problems of communication should be considered as potential sources of bias. Among identified barriers to patient involvement in research it is the fact that most patients have difficulties with holding their own when facing a team of professionals; becoming easily overruled by professionals causing the collaboration to degenerate into tokenism [2, 40]. In our approach no face-to-face interactions between researchers and patients take place, overcoming this barrier and also preventing contamination effects among patients. Participants were therefore protected from the influences of the group and the prestige or power of certain participants, suggesting that their opinions and proposals might be more realistic [49, 50].

Overall, our results reinforce the value of IPP when undertaking a systematic review or CPG development [9, 42, 46, 49–51, 56]. We support that active patient participation in the process of CPG development helps to make guidelines more patient-oriented, contributing to enhance the quality of the guidelines. Though some authors have found no empirical evidence to support patient involvement [45], we found that patient engagement at earlier stages of CPG development helps to identify, prioritize, and include several topics relevant for patients, as questions to be answered in the CPG, that otherwise would be missed by clinical experts and researchers [49, 50]. Besides, we found that some of the health problems and outcome measures suggested by patients (changes in quality of life, ability to perform ADL or psychological aspects such as self-esteem or acceptance of the disease) were not considered in any of the studies assessed for the systematic review, providing an input to inform research agendas [42, 50].

15.9 PyDeSalud.Com: An Integrated Informational Tool to Empower Patients

PyDeSalud.com is an informational web-based platform published in 2012 for patients, caregivers and carers focused on the management of chronic diseases, aimed to improve patients decision making based on scientific knowledge obtained and analyzed by means of a combination of qualitative and quantitative research methods (mixed methods research) [43].

PyDeSalud.com has three main informative channels addressed to Spanish-speaker chronic patients to empower them in their own disease management: (1) patient experiences, (2) shared decision making and (3) informational and research needs from the patients´ perspective. These three channels are developed for chronic diseases such as diabetes mellitus, breast cancer, and depression. New contents for diseases such as colo-rectal cancer or SLE, are under development.

To guide the development of contents for every disease, an advisory board is set, formed by experts from different fields, researchers and patient representatives from POs. Advisory board members has also a certain degree of territorial representativeness along the 17th Spanish Autonomous Communities. This strategic issue is aimed to improve acceptability and adoption of the web page as well as in patient recruitment activities.

The third channel mentioned above was developed to identify and prioritize informational and research needs form the patient perspective. These needs are identified and prioritized by means of the Delphi method distributed by POs to registered patients with the aid of electronic mail. To identify research gaps, the information needs provided and prioritized by patients is contrasted with the findings from the literature review. Identified research gaps of interest for patients are communicated to dedicated research groups and research authorities to feed health policy research agendas. PyDeSalud.com offer information on patient research needs for breast cancer, depression, degenerative ataxias and lupus.

15.10 Challenges to the Extension of the IPP in Health Research

Barriers might happen in every element of the broad strategies to extend IPP from conventional participation as passive research subjects. According to Oliver et al. (2015), failure to start involvement may come from researchers' lack of motivation or their inability to identify appropriate people to involve. Barriers may come from skepticism or lack of interest amongst the people approached. The involvement methods chosen may be inappropriate, or not reach agreed standards, possibly through lack of resources. With insufficient time, training or skilled facilitators, researchers may be unable to explain the task clearly or prompt individual or collective deliberation. Once brought together, participants may be reluctant to express their views or be poor listeners. Research tasks themselves may not be open to influence by outsiders and the researchers and those they work with may be resistant to change. In addition, further work is needed on inequalities in involvement and how existing structures aimed at facilitating equal opportunities might in fact continue the exclusion of groups who are already alienated by organizational structures and procedures [41].

Lay people can offer public perspectives at all stages of the HTA/research programs. However, public input and influence is restricted by organizational and procedural boundaries. Another common concern and an overarching worry of researchers and patients was that patient engagement may become tokenistic (a false appearance of inclusiveness), resulting in a devaluated patients' input. An additional potential challenge described was "scope creep"; a theoretical concern that engaging patients in the research may include irrelevant community concerns and issues, which would make the research unfeasible. These boundaries represents barriers to mutual understanding, matching of interests, priorities, roles, time scales for effective working; and capacity in terms of funding, workforce, and research and interpersonal skills. Boundaries within the research or HTA programs constitute barriers to iterative and timely communication, face to face communication, and reflective practice.

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Part V
Cost-Effectiveness and Cost-of-Illness

Chapter 16
Cost-Effectiveness Methods and Newborn Screening Assessment

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Abstract Nowadays, health funding decisions must be supported by sound arguments in terms of both effectiveness and economic criteria. After more than half a century of newborn screening for rare diseases, the appropriate economic evaluation framework for these interventions is still challenging. The validity of standard methods for economic evaluation heavily relies on the availability of robust evidence, but collection of such evidence is precluded by the rareness of the conditions that may benefit from screening. Furthermore, there are a series of conceptual and methodological limitations that warrant further careful consideration when assessing the cost-effectiveness of newborn screening programs. In this chapter we provide a general overview of current economic evaluation methods and the challenges for their application to newborn screening programs.

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16.1 Introduction

16.1.1 Newborn Screening: A Brief History and Description

Newborn screening (NBS) for rare diseases first revealed its potential in 1958 in Cardiff, a few years after Bickel et al. shown the effectiveness of dietary control for phenylketonuria, and concluded that treatment achieved best results when started earlier [4].

The introduction of the Guthrie test [16] marked the development of modern NBS programs which, later, were able to incorporate additional disorders, such as congenital hypothyroidism. The original Guthrie test (which remains the most popular method to take samples for newborn screening) is an inexpensive method that use filter paper cards to take blood from a heel-prick. Cards are dried and led to the screening laboratory, where the dried blood is used for assay. Although earlier detection is generally related to better outcomes, the optimum timing for sampling heavily depends on the technology used and the disorders intended to be detected, since many of them require sufficient dietary intake to be unequivocally identified [10].

A number of laboratorial techniques can detect abnormal results on dried blood samples. Nonetheless, the introduction of tandem-mass spectrometry (MS/MS) notoriously boosted NBS for rare diseases due to its capability to rapidly detect an increasing number of inherited metabolic disorders from a single blood spot [25].

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16.1.2 Is Newborn Screening for Rare Diseases an Efficient Technology?

Wilson and Jungner proposed the main criteria that should be used to evaluate screening programs [40]. These criteria included not only the assessment of the effectiveness of the screening test and posterior treatments, but a careful consideration of the cost of case-finding. A latter review of this screening criteria has further emphasized the need to assess economic consequences alongside other factors when deciding on how to allocate scare resources [1].

Despite the wide international consensus on the efficiency, in terms of cost and effectiveness, of NBS for phenylketonuria [39], this consensus is challenged as new disorders are proposed to be included in a NBS program [34].

NBS programs might be relatively inexpensive, even when the confirmatory diagnostic tests for both the true and false positives and the follow-up and treatment costs of affected children are included. However, the high heterogeneity of the disorders potentially detected by screening, and the lack of robust and long-term scientific evidence on the effectiveness of the treatments and the natural history of the disorders, pose a number of methodological difficulties that limit the applicability of standard economic evaluation methods.

16.2 Cost-Effectiveness Methods: A General Overview

16.2.1 Economic Evaluation

Due to the widespread context of rising health care costs and stringent budget constraints, health care systems are increasingly incorporating health economic evaluations as a tool to inform funding decisions regarding whether or not to adopt new interventions. The critical issue is the widespread situation where patients' demands for health services exceed the system's ability to provide care, particularly concerning increasingly costly medical innovations. Therefore, an explicit criterion is required in order to decide which interventions ought to be publicly provided, under the aim of achieving the greatest health benefits to the population given available funds. A central concept in this matter is the so-called *opportunity cost*, defined as the health benefits that would be derived from using a resource in its best alternative use [12]. This concept emphasizes the need to make choices when allocating a health care budget, and the inevitable trade-offs faced by decision makers.

In order to incorporate these principles into funding decisions, economic evaluation provides a framework to compare competing health care alternatives, e.g. screening versus clinical detection, in terms of both their health outcomes and costs. The primary objective of these analyses is to enhance efficiency in the use of health care resources and to maximize total health gains in a population given a fixed budget. Strictly speaking, an economic evaluation consists of "the comparative analysis

Fig. 16.1 Incremental costs and outcomes of competing interventions

		OUTCOMES	
		WORSE	BETTER
COSTS	HIGHER	Reject new intervention	Trade-off
	LOWER	Trade-off	Adopt new intervention

of alternative courses of action in terms of both their costs and their consequences" [12]. Therefore, an economic evaluation requires a comparison of two or more treatment alternatives, and the examination of both costs and health outcomes.

When comparing a new intervention with an alternative option, such as the standard of care, costs may be higher or lower with the new intervention, and outcomes may be better or worse; Fig. 16.1 shows the combinations of these differences. If the intervention has lower costs and better outcomes than the alternative (falling into the bottom right hand quadrant of Fig. 16.1), then the recommendation will be to adopt the new intervention that will be regarded as a *dominating* alternative. If the new intervention incurs higher costs and worse outcomes than the alternative (top left hand quadrant of Fig. 16.1) then the recommendation will be for the new intervention to be rejected, as the intervention is then *dominated*. In the most common scenario, where a new intervention is more effective than the alternative but only at a higher cost (top right hand quadrant of Fig. 16.1), then the decision requires the consideration of the trade-offs derived from the extra costs and the improved health outcomes obtained with the new intervention. Similarly, there is a trade-off when the costs of a new treatment are lower but at the expense of a worse health outcome (bottom left hand quadrant of Fig. 16.1).

These trade-offs are quantified and summarized by the *incremental cost-effectiveness ratio* (ICER), defined as the incremental cost divided by the incremental effectiveness of two competing alternatives Eq. 16.1.

$$\text{ICER} = \frac{\text{Cost}_{\text{new}} - \text{Cost}_{\text{standard}}}{\text{Effectivenss}_{\text{new}} - \text{Effectiveness}_{\text{standard}}} \tag{16.1}$$

The ICER represents the additional cost required to achieve one additional unit of effectiveness. However, information of the cost per outcome gained is not enough to ultimately make adoption or otherwise recommendations on the basis of *cost-effectiveness*. In the case where an intervention exhibits higher costs and better outcomes, the ICER needs to be compared with a value that indicates the maximum amount considered acceptable to be paid for health gains in the health system. This value is known as the *cost-effectiveness threshold*. If the ICER of the technology lies below (above) the cost-effectiveness threshold, then the intervention will (not) be considered *cost-effective*.

Table 16.1 Types of economic evaluations

Analysis	Costs	Outcomes
Cost-minimization	Monetary valuation	Same across alternatives; external evidence of equivalence
Cost-effectiveness	Monetary valuation	Single indicator of physiology, morbidity, or mortality
Cost-consequences	Monetary valuation	Array or profile of different measures
Cost-benefit	Monetary valuation	Monetary valuation
Cost-utility	Monetary valuation	Combined index of morbidity and mortality (QALYs)

16.2.2 Types of Economic Evaluations

Economic evaluation can be categorized depending on the unit of measurement of the health benefits under evaluation. Table 16.1 provides an overview of the different types of analyses according to the outcome measure. Under each type of evaluation, costs are measured in monetary terms using the currency of interest. Health benefits can be measured using different approaches defining the following types of studies:

1. Cost-minimization analysis (CMA): When there is strong evidence of equivalence in terms of effectiveness across the interventions being compared, an economic evaluation could focus exclusively on measuring costs differences. Note that this is not the same as ignoring differences on effectiveness; a CMA requires explicit evidence that the interventions achieve the same clinical outcome.
2. Cost-effectiveness analysis (CEA)[1]: These analyses measure effectiveness by means of a clinical indicator, normally a disease-specific measure related to the condition under study, e.g. cholesterol level, cases detected, etc. A particular relevant indicator is Life Years (LYs), used to quantify the impact on mortality of the alternatives being compared.
3. Cost-benefit analysis (CBA): This sort of analysis involves the quantification in monetary terms of the health benefits of the interventions under evaluation. The methods used to translate health outcomes into monetary units include: (i) the human capital approach based on the measurement of productivity gains/losses, (ii) willingness to pay questionnaires to elicit individuals monetary valuations of health gains, and (iii) revealed preferences methods based on the observation of individual choices. Although commonly used in the field of transport and environmental economics, the application of this general approach to health economics is more limited.
4. Cost-consequence analysis (CCA): Some evaluations do not combine the information on costs and effectiveness into a single index to derive an ICER value, but instead provide a summary based on an array or profile of different health

[1] It is worth noting that the term cost-effectiveness analysis is used extensively in the literature as a synonymous to *economic evaluation*, independently of the outcome measure used in the analysis.

measures. This is particularly the case when there is information on a series of primary and secondary clinical outcomes that are not combined into a composite health index.
5. Cost-utility analysis (CUA): The most widely used and recommended effectiveness measure in economic evaluations in most countries are Quality-Adjusted Life Years (QALYs). The next section provides further details as to how this measure is developed.

16.2.3 Quality-Adjusted Life Years (QALYs)

QALYs are a composite index that combines information on the two main components of people's health: life expectancy and health-related quality of life (HRQoL). This generic measure of health status is applicable to a wide range of health conditions and treatments, which allows for a comparison across different disease areas and types of treatments. QALYs are computed following three steps.

1. First, health states are described based on generic questionnaires, such as the EQ-5D [13]. The EQ-5D provides a descriptive profile that is reducible to a single index value for health status. The EQ-5D descriptive system consists of five dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored at one of three levels, depending on whether the respondent has no problems (score = 1), some problems (=2) or serious problems (=3) with each dimension. This descriptive system defines 243 EQ-5D health states. A new version of the EQ-5D have been developed that includes 5 levels per dimensions, yielding a total of 3125 health states.
2. The second step consists of attaching HRQoL weights to each of the health states described by the generic questionnaire. Those weights represent the preferences of the population for these health states, and are known in economic terms as *utilities*. The values range from 1 (perfect health) to 0 (death), with potential negative values denoting states considered worse than death. The methods used to elicit population preferences for health states includes the Visual Analogue Scale (VAS), Standard Gamble (SG) and Time Trade-Off (TTO) techniques. For more information, see [12].
3. Finally, in order to calculate QALYs, the HRQoL values are combined with the time that individuals spend in each health state. For instance, if an individual spends 10 years in a health state with a utility value of 0.8, the number of QALYs is computed as 10*0.8 = 8 QALYs.

16.3 An Example: Economic Evaluation of Newborn Screening for Biotinidase Deficiency

To illustrate the concepts explained in the previous section, we will pose an example based on the economic evaluation of the newborn screening for biotinidase deficiency (BD), published elsewhere [36]. Other interesting examples are Castilla et al. [8], Cipriano et al. [9], Carroll & Downs [7], Autti-Rämö et al. [3], and Pandor et al. [27].

BD is an autosomal recessive inherited disorder in which the biotinidase enzyme is defective, hence precluding the recycling of the biotin vitamin. If untreated, BD causes neurologic and cutaneous symptoms with varying severity. Treatment of BD consists of lifelong supplementation with oral biotin.

A cost-utility analysis was undertaken to compare the lifetime costs and health outcomes of a Spanish birth cohort with and without an NBS program for BD. The analysis took the perspective of the National Health Service (NHS) and effectiveness was measured in terms of QALYs. Costs were expressed in US$2013.

The cost-utility analysis was based on a decision analytical model, illustrated in Fig. 16.2. The main data source was a regional register that had collected results during 25 years, and a systematic review of international literature. Costs were estimated from the resource use of BD assays, equipment, and staff costs for both screening and diagnostic confirmation, and lifelong treatment and follow-up of affected cases. QALY calculations were based on values related to BD complications that were taken from the literature and identified by a previous review [15].

The results of the analysis showed that BD screening is associated with a mean incremental cost of $1.24 and a mean QALY gain of 0.00005 per neonate. The ICER was thus estimated in $24,677 per QALY, a result that is considered cost-effective at standard threshold values in Spain and other countries.

16.4 Limitations of the Economic Evaluation Applied to Newborn Screening

Having reviewed the basis on economic evaluation, a number of limitations arise when applied to the assessment of NBS programs, including paucity of data availability, heterogeneity, uncertainty on key parameters, and methodological difficulties to apply classical techniques from the economic evaluation field.

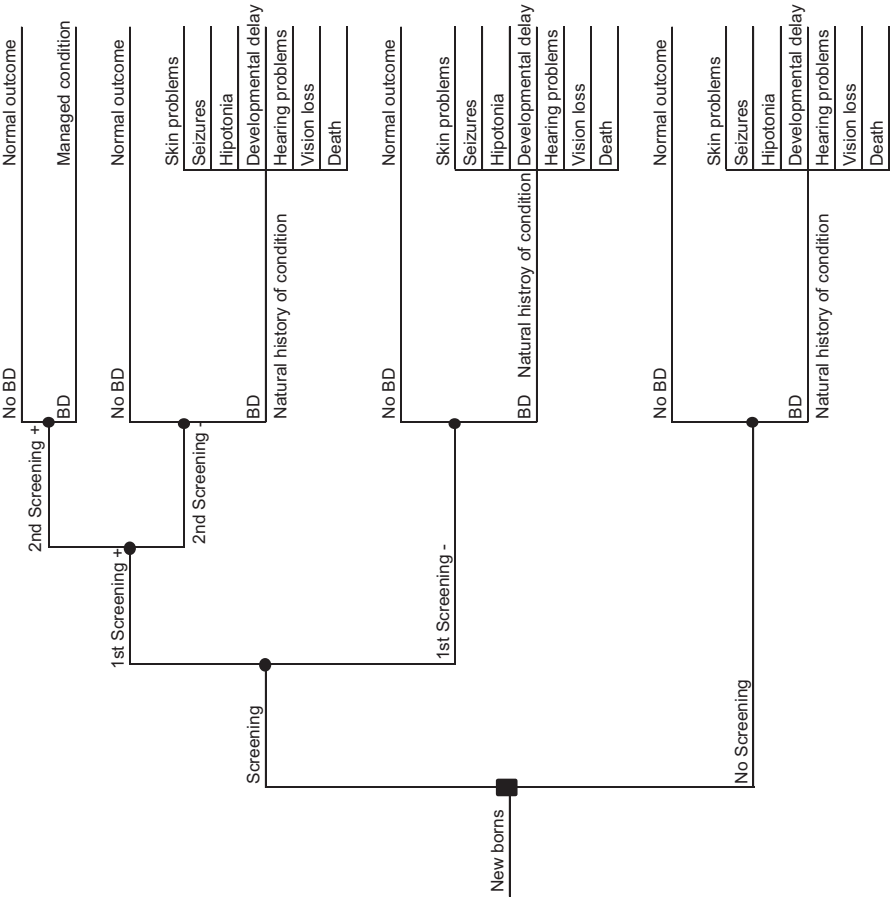

Fig. 16.2 Decision tree to assess NBS for biotinidase deficiency (Source: [36])

16.4.1 Lack of Direct Comparison Evidence

Data availability limits the strength and robustness of these analyses. Randomized Control Trials (RCTs) are considered the most powerful research design for establishing whether an intervention is effective, since they most successfully eliminate bias as compared to other research design. However, there is an absence of RCTs on NBS due to obvious ethical and logistic considerations. The only available data source to assess the effectiveness of NBS are commonly observational studies alone with no direct comparison among screened and not screened children.

16.4.2 Evidence Based on Limited Number of Cases

Furthermore, due to the rareness of these diseases, only case series with a very limited number of patients are normally available to collect evidence of the natural history of the disease or the effectiveness of treatments. Case series are the lowest quality source of data and constitute weak evidence regarding the natural history of a disorder. In the context of NBS, they are subject to three types of biases: spectrum bias, since individuals without symptoms may escape clinical detection; survival bias, since affected individuals may die prior to a diagnosis, and referral bias, since more severely affected individuals may be overrepresented in published case series based on referrals to academic medical centers. Focusing on publications reporting series of all consecutive cases over a period partly addresses these biases, while the use of well-structured cross-national registries seems the most promising tool to improve data availability about these disorders.

16.4.3 Evidence Synthesis of Different Data Sources

In most cases, the use of elicited expert opinion about parameters of interest is unavoidable in the absence of (or limited) data. Since prior beliefs and observational data may well be affected by bias, the techniques that are used to combine expert opinion, observational evidence and/or registry information should take into account the different nature of data sources. Meta-analyses that simply pool data from all sources together are not likely to be appropriate since they fail to recognize the different types of evidence being synthesized. A number of methods can be used to overcome this problem, including Bayesian techniques that provide ways of combining the evidence from a variety of disparate sources. Furthermore, the very low number of cases included in the available studies and/or registers often means that some corrections are needed in order to deal with “no-event” findings. This in turn might introduce some bias especially when applied to small studies [24].

16.4.4 Heterogeneity in Clinical Practice

There is a high heterogeneity in the disorders included in the screening panels; and in the diagnostic, treatment and follow-up protocols among countries and even regions [6, 20]. This scenario is mainly a product of the lack of robust evidence but also results from the disparate pace in adopting new technologies and treatments. As a consequence of this heterogeneity, a direct comparison of results obtained from different economic assessments becomes unachievable due to the variance in techniques, devices and timing used at every stage of the clinical pathway. There have been certain efforts to harmonize NBS programs [22, 32], to synthetize the existing evidence to create clinical guidelines [2, 17], and to promote transnational registries such as E-IMD[2] and E-HOD.[3] Unfortunately, the treatment and follow-up for most of these disorders is still based on the clinician experience solely.

16.4.5 Incidence Versus Prevalence Data

Another consequence of the lack of data sources for robust evidence is the high uncertainty surrounding key parameters of the economic evaluation, such as the number of cases affected by a birth defect. Among the methods generally used to estimate this number, birth prevalence is generally recommended over incidence [23].

Incidence (Eq. 16.2) can be defined as the probability of a medical condition in a population at risk for that medical condition over a specific period. Although it could be considered as the logical form of expressing the occurrence of new cases, it is not a practical measure of the proportion of birth defects. The main difficulty relies on how to apply the concept of population "at risk". Strictly speaking, the "risk" of a birth defect appears at some time during the prenatal period, which is a fuzzy definition. Moreover, not all pregnancies result in a birth, hence making impossible to reach an accurate estimate.

$$\mathrm{I} = \frac{\text{Number of new cases over the specified period}}{\text{Size of pulation at risk over the specified period}} \times 10^{\mathrm{n}} \qquad (16.2)$$

Birth prevalence (Eq. 16.3) can be defined as the number of cases of a birth defect among the total number of live births. This ratio includes in the numerator the identified cases among spontaneous fetal deaths and induced terminations. The fact that birth prevalence is a ratio and not a proportion makes difficult the interpretation of this value, though it is considered a more accurate prediction of the actual incidence.

[2] www.e-imd.org

[3] www.e-hod.org

$$\mathrm{BP} = \frac{\text{Number of cases}}{\text{Total number of live births}} \times 10^{n} \tag{16.3}$$

16.4.6 Bias Affecting Prevalence Data

Spectrum, survival and referral biases are especially relevant to birth prevalence, and favor regions implementing NBS over those regions where new cases are identified solely by clinical signs and symptoms [38]. Survival bias is very frequent in disorders such as fatty acid deficiencies [5], whereas spectrum and referral biases appear in disorders with late or mild onsets [21].

16.4.7 Accounting for Unintended Findings

Unintended findings of potentially asymptomatic or oligosymptomatic cases (either carriers or mild forms of the disorder) are possible with NBS, even when international agreements recommend using screening methodologies that avoid them [11]. From a pure economic perspective, these findings may increase the costs of screening when compared to the clinical detection, without a remarkable improvement on health condition. The risk of overmedication and the impact of the side effects of the (possibly unnecessary) treatments must be taken into account. The detection of these cases might not improve the health condition of the affected children but could be used for reproductive choice of the parents. However, capturing the impact of reproductive choice politics requires analyzing the evolution of the incidence of the disorders which, at the same time, would require a multi-cohort analysis. Most economic evaluations are single-cohort based, that is, they follow a group of patients from the moment they are intervened to a predefined time horizon, long enough as to represent all the relevant consequences of the intervention. Adapting these evaluations to a multi-cohort scenario is not straightforward and requires a careful synthesis of the results [26].

False positives are a different kind of unintended findings. From a payer perspective, the impact of a false positive may be captured by including the costs related to the additional diagnostic tests and follow-up. From a societal perspective, other effects appear that should be incorporated to the analysis. For example, some studies have shown an increment in parental stress [37] and other psychosocial consequences [31] due to a false-positive result. However, the fact is that neither the additional costs that may derive from the potential overprotection of children nor the health-related quality of life impact on the parents are typically included in economic evaluations of NBS. Additional costs might be included straightforward, but there is no clear link between the mentioned psychosocial consequences and early health care utilization [19]. Although costs do not pose any significant

methodological complication, there are no standard guidelines about how to incorporate health-related quality of life effects from persons other than those directly affected by the intervention. In any case, the inclusion of any of these effects should be carefully considered due to the published evidence on the high tolerance of parents for false positive NBS results [29].

Parents and siblings of affected children may be also detected as a result of performing the screening test [30] but, again, no clear methodological guidelines on how to incorporate these results in the economic assessment are available.

16.4.8 Limitations of Measuring QALYs in Pediatric Population

As previously mentioned, QALYs are the preferred effectiveness measure in economic evaluation. However, QALY measurement in newborn populations poses serious methodological challenges [18, 35]. In order to estimate QALYs associated to particular conditions, researchers need to elicit the description of such health states from the relevant patient and/or proxies as well as the relevant preferences for such health states, which becomes very complex when applied to newborns and children. First, children may lack the cognitive skills to respond to tools designed and validated for adults. Besides, there are dimensions of the questionnaires, such as autonomy, that may not discriminate among a pathological condition and the physiological development of children [33]. "Proxies" solve most of these difficulties but validity of information is controversial in these situations [14]. Specific QoL questionnaires for children, such as PedsQL™, effectively discriminate among different diseases, and between healthy and ill children. Nevertheless, they have not shown the same effectiveness to distinguish among severity degrees or progression of the disease, as it happens with sickle cell disease [28].

16.5 Conclusions and Future Research

We have reviewed the fundamentals on economic evaluation and its limitations when applied to the assessment of NBS. Despite these limitations, NBS for rare diseases is a dynamic field, where new treatments are being developed for previously unmanageable disorders, and new techniques and the lower cost of sequencing technologies are improving the prompt identification of affected children. The consequences of these new findings would be to reconsider the decisions previously taken. Thus, further research is required to create a robust methodological framework that allows health economists to properly and timely assess the cost-effectiveness of screening for a specific disorder or set of disorders. This framework should go further in the establishment of recommendations and guidelines on a

number of issues, such as the identification and proper use of the (scarcely) available information; and the selection and usage of adequate effectiveness measures.

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Chapter 17
Cost-of-Illness in Rare Diseases

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Abstract Cost-of-illness (COI) studies quantify the economic burden of a disease, including direct healthcare and non-healthcare costs and productivity losses. Different approaches can be adopted to evaluate the resources associated to a disease and to calculate the total costs. Prevalence-based studies estimate the total costs of a disease during a given period, while incidence-based studies measure lifetime costs from onset until death. Data can be collected from individuals, using a bottom-up approach, or from population statistics, using a top-down approach. Different perspectives are possible, but the broadest and also mostly used is the societal one. Appropriate discounting should be applied for future costs and a sensitivity analyses of main parameters should be performed. The main limitation of COI studies is that they don't account the outcomes or benefits of possible treatments.

There is a lack of COI studies in the field of rare diseases. A multinational COI study (BURQOL-RD) evaluated recently the burden of 10 rare diseases in Europe, using a prevalence-based method with a bottom-up approach to quantify resources from a societal perspective, which is the mostly used methodology for COI studies in rare diseases; however, several other studies illustrate different approaches to conduct COI analysis in this field, such as incidence-based methods or narrower perspectives.

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COI studies are useful to inform policy-makers about the magnitude of a disease. To support correctly the decision-making process, it is necessary to identify the cost-drivers through COI studies with robust design and standardized methodology.

Keywords Cost-of-illness • Burden • Direct costs • Productivity losses • Incidence-based • Prevalence-based • Top-down • Bottom-up

17.1 Introduction

Existence of any disease creates a burden for the society derived from utilization or loss of resources. Cost-of-illness (COI) studies measure the economic burden of a disease estimating the maximum amount that could potentially be saved or gained if a disease were to be eradicated [33]. This estimation consists in identification, quantification and evaluation of all economic resources associated to a disease.

The value of COI studies can be seen in their frequent use by policy makers. Knowledge of the costs of an illness and its final impact on public budgets can help policy makers to decide which diseases need to be addressed first by health care and prevention policy; for a pharmaceutical corporation, they can demonstrate which diseases are highly costly to manage and thus directing where a possible next R&D investment should be made. Additionally, they can provide important information for other types of economic evaluations, such as cost-effectiveness or cost-utility analyses. Although they represent only one part of cost analysis, COI studies can provide a framework for the cost estimation in these analyses [33]. In addition to their use by government organizations, COI studies are often cited in disease studies that attempt to highlight the importance of studying a particular disease [15]. As Clabaugh et al. pointed out, "analyzing cost of illness presents useful opportunities for communicating with the public and policy makers on the relative importance of specific diseases and injuries" [7].

Although an increasing number of COI studies have been conducted over the past three decades, only a small part of them is dedicated to rare diseases (RDs) [2].

17.2 Methodology of Cost-of-Illness Studies

A complete COI study has to include both direct and indirect costs. Direct costs can be medical or non-medical and direct payments are made for them, based on market prices; indirect costs are also called productivity losses and represent lost resources due to disability, morbidity and mortality. Another cost category, which is rather optional for COI studies, are costs related to quality of life impairments; these intangible and psychological costs can include grief, pain, emotional problems or anxiety due to

economic dependence and social isolation. It is very difficult to quantify this type of costs in monetary terms, because they are not directly measurable by lost output.

17.2.1 Direct Costs

There are two main categories of direct costs: (a) medical costs and (b) non-medical costs. Medical costs, also called healthcare costs, include all type of healthcare costs directly related to the studied disease from diagnosis and treatment to continuing care, rehabilitation or terminal care. Total healthcare costs include all the costs associated with the resources used, while net direct costs take into account future medical costs avoided due to the patient's death. A typical example of healthcare costs used in most of COI studies would include drugs, hospitalizations and emergency visits, medical outpatients, health professional's care, rehabilitation care and home health care [22].

Non-medical or non-healthcare costs are not linked directly to the medical care, but normally represent a large part of total costs; they include costs of transportation for healthcare provision, rehabilitation or comfort items, such as vision aids, speech devices, humidifiers, etc., and all types of social services; however, the largest part of non-healthcare costs is normally formed by the informal care, i.e. care provided by nonprofessional caregivers, often patient's relatives that are not paid for provided care. A possible method to value this caring time is the proxy good method, which values the care provided by the informal caregivers, considering that if they don't provide these services, they would have to be substituted by another person [21, 37].

17.3 Productivity Losses

Productivity losses, also called indirect costs, quantify the output lost due to cessation or reduction of patient's or family members' productivity, as a consequence of morbidity, mortality and disability caused by the disease under investigation. Also lost time from leisure and other activities, as well as unwanted job changes or loss of opportunities for promotion or education, can be quantified. There are several calculation methods, including human capital method, friction cost method and willingness-to-pay method [15]. In any case, the estimation of these costs is a complicated process and it should be made carefully in order to obtain the most accurate and meaningful estimate.

The human capital method is one of the first formal methods of valuing life and it estimates the hours of work lost by the person due to the disease and then multiplies them by the hourly wage. The cost is therefore seen from patient's perspective and they can be calculated up to the patient's retirement age [24, 29]. The limitations of this method lay in underestimating costs in cases of children or

elderly, and in overestimating costs in cases of long-term absence, disability or premature death [8].

The friction cost method is used for the employer's perspective and it takes into account only hours lost by the person until he/she is replaced by another employee. This period until a new employee is hired in the place of the patient, is called friction period and it is a function of the availability of labour. The limit of this method is that it can underestimate the costs of productivity loss.

The willingness-to-pay method suggests that the avoidance of a disease can be estimated from the amount people would be willing to pay to reduce the probability of morbidity or mortality due to this disease. This method can be useful in quantifying the intangible costs, such as pain or suffering, which are not possible to asses in terms of monetary value [30].

17.4 Perspective

Different perspectives can be adopted to carry out a COI study; the decision depends on the purpose of the study and it implies to include different types of costs mentioned above. Mostly used perspectives are those of society, government, healthcare system, insurer (third party payer), employers and families. The most comprehensive perspective is the societal and it is also the most frequently used in COI studies, because it comprises costs occurred for the whole society [14], but logically it also requires the most data, which can be a problem especially in less prevalent diseases such as RDs [15]. In these situations, data from a third-party payer could be more reliable [14].

17.5 Cost Estimates

A COI study can use prevalence-based or incidence-based estimation to quantify total costs; prevalence is the total number of cases in a limited period of time, while incidence is the number of new cases arising in a period of time. The decision about the type of cost estimate to be used depends on the objectives of the study: to quantify reduction in costs resulting from a decrease in the incidence of a disease, the incidence-based estimate is needed, while to quantify the economic burden of a disease in a given period, the prevalence-based estimate is appropriate.

Most of COI studies use the prevalence-based approach. It estimates the current annual economic burden based on the prevalence of a disease during a year, measuring the total costs of the disease during that year [33]. This approach is considered most suitable for assessing the total economic burden of a disease, especially in chronic conditions whose cost remain relatively stable over time, or for short-term, acute diseases [18], but it is necessary to keep in mind also the objectives of the study; according to Jo [14], the prevalence-based approach can be particularly

useful when the main purpose is: (a) to draw an attention from the decision-makers for diseases whose burden has been probably underestimated, which could be the case of RD; (b) to design cost containment policies, because this approach provides decision makers with a picture of the global burden and the major cost components.

The incidence-based approach measures lifetime costs from onset until cure or death. This approach can show how costs vary with disease duration, which may be useful in planning interventions targeted at specific stages. This method is suitable for cost-effectiveness studies of preventive and therapeutic interventions, where decrease of incidence results in reduction of costs. Taking into account the objectives of the study, the incidence-based approach is particularly useful when the study aims at: (a) considering preventive measures, where potential savings can be calculated; (b) analyzing the illness management during the entire period [14]. However, many parameters are needed to make a reliable estimation, including the incidence and progression of the disease and probabilities of cure and survival at each stage [15].

The COI study can be carried out either in prospective or retrospective way, depending on the study kick-off and the data collection. The prevalence- and incidence-based COI studies can be both performed either in prospective or retrospective way [14]. The retrospective approach has a clear advantage being less costly and time consuming than the prospective approach, but for diseases with a long duration, sufficient observational datasets are needed. The advantage of the prospective way is that the investigators can decide what data are collected.

17.6 Methods of Resource Quantification

There are two different approaches to quantify resources and calculate costs: (a) top-down approach and (b) bottom-up approach. The choice of the approach depends on the disease under investigation, as well as the study question; healthcare costs can be calculated using either approach, while productivity losses are normally calculated with bottom-up methods, because population data are usually not available [18]. A third type of approach can be adopted is the econometric approach, which tries to estimate the incremental difference in costs between a cohort with the disease and another cohort without the disease [14].

The top-down method, or population-based method, uses aggregated data normally collected at national level or from a smaller population sample; it operates with data on mortality, morbidity, hospitalizations, outpatient visits or pharmaceutical costs among others [15]. This approach is inherently limited in its capacity to capture all related costs, especially in cases of complex diseases such as RDs, because it relies on the availability and quality of epidemiological evidence. Therefore, this approach can be more suitable for highly prevalent diseases, where it better reflects the overall magnitude of the disease than the bottom-up approach, which by extrapolating per-person costs could magnify any biases [18].

On the other hand, the bottom up approach, also called person-based method, collects resource use from individuals with the disease of interest, either using detailed questionnaires or evidence from other sources, and multiplies them with unit costs of each resource [18]. For example, average cost of treatment would be calculated as the average unit costs multiplied with the average utilization. Average costs per patient are then extrapolated to the whole population using population prevalence or incidence data. For complex diseases, the bottom-up approach is likely to be more comprehensive than the top-down method, because it doesn't rely on epidemiologic data or a priori assumptions regarding comorbidities and it can better capture variability related to differences in important demographic characteristics between patients, which makes this approach less prone to bias due to averaging than the top-down method [18, 35].

The econometric approach is not very frequently adopted by COI studies. It requires matching between two cohorts, one with the disease and another without the disease, usually through a series of regression analyses by demographic factors and other chronic conditions. Because this approach measures the incremental difference between affected and not affected persons, it often requires only one dataset, which could be seen as an advantage of this method [14, 33].

17.7 Discounting and Sensitivity Analysis

Discounting allows us to calculate the present value of income or cost that occur in the future. Future monetary costs are discounted to enable meaningful comparisons between costs incurred in different time periods [12]. Discounting is relevant for direct costs and productivity losses that occur after the first year. The discount rates range from 0 to 10% [14, 15] and many studies use a baseline choice of 5%, which is the preferred rate for economic evaluations in health care since 1970s, although more recently a 3–3,5% rate is increasingly preferred, as proposed by the US Public Health Service Panel and the NICE [26].

There is always some uncertainty involved in COI studies mostly due to the chosen approach and range of sources and assumptions made. Sensitivity analysis is understood as a technique to determine how different values of explanatory variables affect the explained variable [14]. A one-way sensitivity analysis examines the impact of varying one variable while keeping the rest constant; probabilistic sensitivity analysis permits changing more than one variable at once and it is understood as a useful technique in quantifying the level of confidence that a decision-maker has in the conclusions of the COI study [14, 15]. A sensitivity analysis on the discount rate, prevalence/incidence rates and other parameters should accompany COI studies.

17.8 Limitations

COI studies have their limitations, mainly due to their focus on costs without taking into account the benefits or outcomes [3]. Therefore, they can demonstrate the magnitude of the need by identifying and measuring all the costs of a disease, but they don't provide information to suggest inefficiency or waste, as they tell very little, if anything, regarding the benefits of a possible intervention or treatment [3]. Beyond that, they do not provide an insight in the extent of amenability of the various diseases. As in some cases low cost diseases could be fully amenable at low cost, by focusing on the magnitude of expenditures COI studies could actually divert attention away from areas where important health gains can occur at low cost [3]. For optimal decisions regarding the allocation of healthcare resources, COI studies must be used in combination with full economic evaluations such as cost-benefit, cost-effectiveness, or cost-utility analyses, which assess both costs and outcomes [31].

17.9 Review of COI Studies

17.9.1 BURQOL-RD Project

"Social economic burden and health related quality of life in patients with RDs in Europe" (BURQOL-RD Project) was a project financed by the European Commission between 2010 and 2013 and up to date it was the largest COI study in the field of RDs at European level. Its main aim was to quantify the economic burden and health-related quality of life (HRQOL) of patients with 10 RDs and their caregivers. The study adopted a prevalence-based method with a bottom-up approach to quantify all resources associated to one of 10 RDs: Cystic Fibrosis, Prader-Willi Syndrome, Haemophilia, Duchenne Muscular Dystrophy, Epidermolysis Bullosa, Fragile X Syndrome, Scleroderma, Mucopolysaccharidosis, Juvenile Idiopathic Arthritis and Histiocytosis. These diseases were targeted in the following countries: Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK [20].

The data on resource use were collected via on-line questionnaires for each patient and included medical resources related to the disease (e.g. hospitalization, consultations, drugs), non-medical resources (e.g. walking sticks, wheelchairs, modifications to house and car), services (e.g. home care, transportation), informal care and productivity losses. The lists of resources for each disease were adapted with the help of national experts (healthcare professionals and patients), taking into consideration the socio-cultural and economic characteristics of each country. The questionnaire asked for information covering the 6 month period prior to the study (12 months for hospital admissions) and data for the preceding 6 months were extrapolated to the entire year, allowing the mean annual costs to be estimated from a societal perspective.

The distribution of the questionnaire in each country was coordinated by national RD federations and patients' organizations [34]. The survey was totally anonymous, as the patients were contacted by their organization or registry, and their responses weren't associated with any identifying data (name, ID, address, e-mail), being sent directly to the researchers.

A total of 3232 complete responses were analyzed. Mean annual costs were calculated and divided into 4 categories: direct health care costs (drugs, medical visits, exams, material); direct non-health care formal costs (professional carers, social services); direct non-health care informal costs (unpaid carers); and indirect costs (patient's and carer's productivity loss). In all countries and for almost all diseases, a large part of the total costs was associated with informal care, i.e. the time of non-paid carers, usually members of the patient's family. Informal care is usually an "invisible cost", as it is not associated to a budget. However, from a social perspective, carers' time is a valuable resource that must be identified, measured and valued [22].

The mean annual costs per patient in € 2012 can be seen in Table 17.1. There are several factors that affect the amount of total cost per patient; firstly, the unit costs vary among countries significantly (prices, wages); secondly, some extremely expensive treatments (e.g. biological treatments) were available only in certain countries, which influenced direct healthcare costs; thirdly, for some diseases the recruited sample may not be representative and comparable with other countries, since the recruitment depended fully on patients' organizations.

It is important to have an insight into the distribution of the total costs. As an example of a more detailed result, the Table 17.2 shows a breakdown of costs of scleroderma in Spain, where all cost categories included in this COI study can be observed [21, 23]. There were large direct healthcare costs, especially due to medication, but the productivity losses (indirect costs) play an important role, too, especially due to early retirements. The informal care, although not unimportant, did not add up to the total costs as much as in other diseases, where patients' dependency on informal caregiver is higher (e.g. Prader-Willi syndrome or Duchenne muscular dystrophy).

Table 17.1 Average total annual costs per patient (€ 2012)

	Bulgaria	France	Germany	Hungary	Italy	Spain	Sweden	UK
CF	22,295	28,433	53,256	21,144	29,870	32,911	46,694	48,603
PWS	3937	38,960	67,484	11,979	29,586	41,877	59,007	49,200
HEMO	6660	21,046	194,491	15,248	99,877	62,955	8228	–
DMD	9166	–	55,270	7657	41,547	34,603	43,860	34,658
EB	17,671	14,931	46,116	9809	49,233	43,137	9509	19,758
FXS	–	35,737	–	4951	21,586	31,008	58,862	–
MPS	79,323	25,993	209,420	24,520	84,921	94,385	165,945	–
JIA	–	–	27,634	–	28,645	–	36,396	31,546
HISTIO	6832	33,283	26,442	–	11,883	31,622	–	–
SCL	–	21,557	30,797	4607	12,560	21,640	12,728	26,542

CF cystic fibrosis, *PWS* Prader-Willi syndrome, *HEMO* haemophilia, *DMD* Duchenne muscular dystrophy, *EB* epidermolysis, *FXS* fragile-X syndrome, *MPS* mucopolysaccharidosis, *JIA* juvenile idiopathic arthritis, *HISTIO* histiocytosis, *SCL* scleroderma

Table 17.2 Average annual costs per patient with scleroderma in Spain

	Spain	
Scleroderma	Mean	SD
Drugs	4258	6796
Medical tests	534	421
Medical visits	1610	2341
Hospitalizations	1509	3844
Health material	517	1520
Healthcare transport	6	65
Direct healthcare costs	**8433**	**9804**
Professional carer	911	2840
Non-healthcare transport	36	439
Social services	99	192
Direct non-healthcare formal costs	**1046**	**2868**
Main informal carer	4150	12,834
Other informal carers	533	3983
Direct non-healthcare informal costs	**4684**	**14,986**
DIRECT COSTS	**14,162**	**19,587**
Sick leave	1445	5129
Early retirement	6033	9466
LABOR PRODUCTIVITY LOSSES	**7478**	**9917**
TOTAL COSTS	**21,640**	**24,657**

The information on the burden and loss of quality of life as a consequence of RDs in different European countries should help policy makers, at country and European level, evaluate the current situation of families affected by RDs, and using the same instruments in the future, monitor the impact of new policies, interventions, treatments and diagnostic techniques. Patients' organizations and RD federations should use this information and the BURQOL-meter to give more weight to their requirements when addressing health policy makers. For the scientific community, the results that emerge from this project should stimulate future research in the field of RDs and allow them to be compared with other diseases.

17.9.2 Other COI Analyses in RDs

Researches from the BURQOL-RD project conducted in 2011 a systematic review of cost studies of the 10 diseases they selected [2, 15]. They concluded that the cost evidence on RDs appeared to be very scarce. The most studied diseases were cystic fibrosis and haemophilia while they did not find any study for Prader-Willy Syndrome.

To illustrate the broad range of methods used to estimate the COI in RDs, we conducted a rapid search of literature in Pubmed in June 2016 to identify two types

of papers: (a) papers on COI analyses of any of the RDs included in the BURQOL-RD project and published after 2011, and (b) reviews on COI of RDs published in the last 10 years which will be useful to discuss this topic. We used the MESH "cost-of-illness" to gain specificity and only selected papers published in English.

The first large group of recently published COI studies are the results of BURQOL-RD Project (see previous section); ten multinational COI studies were published in the European Journal of Health Economics in 2016 [22] and another eight country-specific COI studies of fragile-X syndrome in France [4], cystic fibrosis in the UK [1], France [5], Bulgaria [13] and Hungary [27], haemophilia in Italy [17] and scleroderma in Spain [21] and in France [6]. As commented above, these were prevalence-based studies using the bottom-up approach and societal perspective.

Apart from BURQOL-RD results, we identified 6 new original analyses on COI of cystic fibrosis [38], haemophilia [11, 28, 39], and Duchenne dystrophy [19, 32]. These studies can be helpful to illustrate other ways of conducting COI analysis in RDs. Two studies adopted a perspective different from the societal [28, 38]. Van Gool et al. adopted the very common perspective of the health care system to estimate the cost of cystic fibrosis in Australia. This perspective was chosen by the authors because it is advocated by Australian guidelines on health economic evaluation [38]. Price et al., on the other hand, adopted a limited perspective to estimate the cost of haemophilia A or B in Canada from the perspective of patients and families. Their aim was to highlight the burden for families with children with this condition. They included transportation, accommodation, meals, cost of medical supplies and other out-of-pocket costs, and indirect costs defined as time off work for haemophilia-related care [28].

Among the studies that adopted the societal perspective, Henrard et al. estimated the cost of haemophilia in Belgium including medical costs (treatments, visits, hospital admissions, cost of transport and indirect costs) [11]. The cost of absence from work due to invalidity or premature death was assessed for adults by means of the friction cost method. Given the lack of precise data in Belgium the authors used a uniform distribution ranging from 2 to 6 months to model the friction period [11].

Two studies adopted an incidence-based approach. Both van Gool et al. and Henrard et al. consisted of mathematical models to estimate, explicitly, the lifetime cost of the disease [11, 38]. Van Gool et al. used individual data from 3 years from the Australian Cystic Fibrosis Data Registry to estimate transitional probabilities to model the progression of cystic fibrosis and to estimate the health care resource use; the unit costs were obtained from several sources. They chose 47 years as horizon time based on the age of the oldest patient in the registry. This horizon was tested in the sensitivity analysis. Following recommendations they discounted the future costs using several rates, 0%, 3.5%, and 5% [38]. Henrard et al. modelled the lifetime costs for new cases born in 2011 in Belgium and applied 0% and 3.5% as discount rates for costs [11].

There are several options to reach the patients and collect data. Apart from getting collaboration from patients' associations to distribute on-line questionnaires, like in the BURQOL-RD project [34], researchers find patients in claims databases

[11, 19], registries of patients [32, 38], or specialized centres [28, 39]. Schreiber-Katz et al. conducted a COI analysis of Duchenne and Becker muscular dystrophies in Germany. The way to access the patients was through the German dystrophinopathy patient registry, a registry established within a network of excellence funded by the European Union [32]. This is obviously an easy way of identifying patients and accessing data. Most of studies adopted a bottom-up approach, i.e. collecting data from patients by means of questionnaires or extracting individual data from already existent databases.

In both cases the collection of data is usually retrospective with potential bias. For example, Zhou et al. estimated the costs of haemophilia A in USA in the context of a prospective cohort study, according to the authors definition [39]. The patients were recruited in specific treatment centres for patients with this condition and the authors only collected medical data from these centres; consequently the sample included a high proportion of severe cases and cost could be underestimated, as the authors admitted. On the other hand, the questionnaires were administered by phone or online each month in the first year and semi-annually in the second year; this unusual measure probably lessened the risk of recall bias [39]. Larkindale et al. also used several sources of data: commercial and MEDICARE claims data to estimate direct medical costs and a survey to estimate the nonmedical costs and indirect family income loss of Duchenne muscular dystrophy in the USA [19]. Henrard et al. adopted a mixed approach using both individual data from administrative databases (National Alliance of Christian Mutualities database, largest sickness fund in Belgium) and aggregated data from statistics and literature [11].

Most of the studies estimated the cost per person per year that is the usual method in this type of study. Four studies estimated the national costs of the diseases for their respective countries, two of them assumed an approximate prevalence [32, 38]. Larkindale et al. explained how they estimated the national cost of the diseases (not only Duchenne dystrophy, but also amyotrophic lateral sclerosis and myotonic dystrophy) in the USA. The total national costs were calculated by multiplying the total per-patient cost by the prevalence of each disease according to the prevalence rate reported in ORPHANET and adjusted by studies on the prevalence in the USA population [19]. Henrard et al. also reported national estimates. In its probabilistic model they included a range from 1/5500 to 1/4500 newborn males for the incidence of haemophilia based on literature and other data from the Belgian Haemophilia Association for the proportions of severe, moderate and mild cases [11].

Apart from the systematic review by the BURQOL-RD project [2, 15], we identified three systematic reviews on the costs of RDs, when we define RD as that one with 5 or less cases per 10,000: systemic vasculitis [36], psoriatic arthritis [16] and juvenile idiopathic arthritis [10]. If we define RD with a broader criterion (6–9 per 10,000), we could include another three systematic reviews: two on costs of systemic lupus erythematosus [25, 40] and one on the costs of Crohn's disease [9]. Of these four reviews, the reviews by Gidman for juvenile idiopathic arthritis and Zhu for lupus are the most focused in COI studies and the analysis of their characteristics [10, 40].

17.10 Discussion

The COI studies measure the economic burden of a disease for a specific period in a specific area, usually a country [33]. This methodology have been used for the estimation of the economic burden of some RDs. However, the evidence seems to be scarce [2]. The fact of being non-prevalent and the associated lack of available data could be the main limitation for the estimation of the economic burden of RDs. Nevertheless, it is possible to conduct COI studies of these diseases following the methods described in literature [18].

Although the most usual approach is the prevalence-based estimation [33] and authors like Zhu et al. did not find any study following incidence-based approach for lupus [40], we were able to find, in the context of our limited review, two incidence-based studies for two different diseases and by two different research teams [11, 38]. This means that, despite the requirement of an important amount of data and the lack of available data for most of RDs, it is still possible to conduct this type of exercise in at least some contexts and for some RDs. For similar reasons the case–control design to estimate real incremental costs should be possible in COI analysis of RDs [40].

Overall the health economists are advocates of the societal perspective [14]. Gidman et al. found that the treatment costs of juvenile idiopathic arthritis exceeded the indirect costs, but also that the latter were likely underestimated as the scope of the costs considered was limited. Gidman highlighted that the cost of the future productivity loss by children was not considered in any study and argued that the societal perspective should be reported given the fact that the advantages of costly biologic medication are the hypothetical future productivity gains of children [10]. Other medical and non-medical costs incurred by patients and carers should be included in the estimation of the cost of those diseases where there are no treatments or where the out-of-pocket expenses are important as it happens in several RDs such as lupus [40].

Most of the studies use a bottom-up approach collecting data retrospectively from patients and/or reviewing clinical charts [10]. We have tried to find an example of COI analyses with a top-down approach but didn't succeed. This could be a sign of the scarce of data in RDs. When there is no available data related to a specific disease, the only way is gathering data from primary sources such as patients or clinical charts.

Zhu et al. found that those studies executed in clinics and specialized centres could recruit easily homogenous samples, but there may be a risk of overrepresentation of patients with severe status [40]. Nevertheless, as in other more prevalent diseases, sometimes the researchers prefer selected samples for practical reasons [10], and these reasons could be even more justified for RDs when it is known that there are specific health care reference centres.

The researchers have an interest in calculating the national cost estimates but it is difficult to estimate a precise figure when the prevalence rates are not reliable. Although the annual per patient cost cannot show the true dimension of the economic

burden for the whole population, it is useful to know the cost drivers and inform the decision making [35]. Interestingly, Angelis et al. observed that, among the diseases included in the BURQOL-RD project, there was more data availability for those diseases with pharmaceutical treatment and that indirect costs formed a significant proportion of total costs [2]. Other authors have found that the biological therapies, new and expensive treatments, are associated with the increase on the health care costs in diseases like juvenile idiopathic arthritis or lupus [10, 40]. This shows the importance of studying the COI in diseases, rare or not, their cost drivers and the evolution of the COI.

Finally, although there are some methodology texts describing how to conduct a COI study [18], some authors demand guidelines and international standards for conducting and reporting more transparent COI studies. COI studies are descriptive studies which can be executed in different ways, useful to inform policymakers and support the decision-making process [35]. To achieve this, robust designs capable of measuring the true costs of the disease and identifying the cost-drivers are needed [18, 40]. Healthcare policies could be monitored based on high-quality data from COI studies over time. There is consensus on the need of more epidemiological studies of RDs. Similarly, the COI analyses of RDs should be in the agenda of researchers and authorities to comprehend the magnitude of the burden of these conditions for the society.

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Part VI
Rare Diseases Prevention

Chapter 18
Primary Prevention of Congenital Anomalies: Special Focus on Environmental Chemicals and other Toxicants, Maternal Health and Health Services and Infectious Diseases

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Abstract Congenital anomalies (CA) represent an important fraction of rare diseases, due to the critical role of non-genetic factors in their pathogenesis. CA are the main group of rare diseases in which primary prevention measures will have a beneficial impact. Indeed, since 2013 the European Union has endorsed a body of evidence-based recommendations for CA primary prevention; the recommendations aim at facilitating the inclusion of primary prevention actions the National Rare Disease Plans of EU Member States and encompass different public health fields, from environment through to maternal diseases and lifestyles.

The chapter overviews and discusses the assessment of main risk factors for CA, such as environmental toxicants, maternal health and lifestyles and infections, with a special attention to issues that are emerging or need more knowledge.

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Overall, the availability of CA registries is important for estimating the health burden of CA, identifying possible hotspots, assessing the impact of interventions and addressing further, fit-to-purpose research.

The integration of relevant public health actions that are already in place (e.g., control of noxious chemicals, vaccination programmes, public health services addressing chronic maternal conditions) can increase the affordability and sustainability of CA primary prevention. In developing countries with less primary prevention in place and limited overall resources, a first recognition phase may be pivotal in order to identify priority targets. In the meanwhile, policy makers should be made aware that primary prevention of RD supports publicly endorsed societal values like the knowledge-based promotion of health, empowerment, equity and social inclusiveness.

Keywords Primary prevention • Congenital anomalies • Environmental chemicals • Maternal health • Health services • Infectious diseases

18.1 Introduction

Congenital anomalies (CA) are a global health issue affecting around 1 in 33 infants and producing an estimated burden of approximately 3.2 million cases of disability and 270,000 deaths during the first 28 days of life every year [108]; moreover, a number of risk factors associated with CA (e.g., alcohol drinking, tobacco smoking) also increase the risk of other adverse birth outcomes, such as preterm birth and developmental delays, with an additional burden for community health [91, 92]. Most CA are considered multifactorial diseases, where genetic predisposition interacts with exogenous factors and agents. It is noteworthy that the risk of CA is enhanced in resource-constrained communities, where mothers may have increased and concurrent exposure to imbalanced nutrition, poor environment and lifestyle as well as infections [106]. Therefore, CA are a public health issue calling for science-supported primary prevention policies [91, 92]. Since 2013 the European Union has endorsed a body of evidence-based recommendations for CA primary prevention; the recommendations aim at facilitating the inclusion of primary prevention actions the National Rare Disease Plans of EU Member States [91]. The recommendations deal with drugs, food, lifestyles, maternal health and health services and environmental risk factors (including biological and chemical hazards), thus encompassing different public health fields. The targets can be either specific, high-risk groups (e.g., women with chronic illness needing drug treatment during pregnancy) and/or the whole community (e.g., policies to reduce active/passive smoking). Implementing each recommendation can reduce the incidence of one or several main groups of CA; well-established examples include improved folate status and the risk neural tube defects [89], as well as avoidance of tobacco smoke and the risk of orofacial clefts and congenital heart disease [39]. In the case of drugs and chemicals, the pre-marketing toxicity tests required by regulations in industrialized countries aim at minimizing the chance of human exposure to teratogenic substances; nevertheless, epidemiological surveillance is still necessary to identify any unrecognized risk (for

a discussion concerning pesticides see Clementi et al. 2007 and references therein) [13]. Overall, CA primary prevention, calling for integrated actions encompassing diverse groups of risk factors, appears a major field for implementing translation of research into public health practice [78].

The following sub-chapters discuss specific aspects of the topic (drugs; food; maternal health and health services; infections; environmental chemicals) giving attention to recent developments.

18.2 Environmental Chemicals and Other Toxicans

In industrialized Countries chemicals used in industry, consumers products or food production are tested for their safety, including possible effects on the developing organism. Even though risk management may be quite different among different Countries as well as among substances with different usages, the potential for developmental toxicity and in particular for teratogenicity usually triggers a very high level of concern. Accordingly, international testing protocols to assess developmental toxicity, including teratogenicity, in laboratory animals are in place and periodically updated [4]. A number of environmental substances are identified as teratogens in laboratory animals, eliciting malformations through mechanisms that are independent from and more sensitive than any indirect impact on the embryo exerted by maternal toxicity. Such mechanisms may span from histone deacetylase inhibition, as for boron compounds [34], interference with retinoic acid metabolism as for triazole fungicides [81], and impaired hormone signalling as for genital malformations induced by antiandrogenic chemicals [80].

The identification of environmental scenarios that increase the risk of congenital anomalies is often more difficult and tricky, due to the intrinsic uncertainties of epidemiological studies, such as the characterization of exposure and the presence of confounding factors. In environmental scenarios exposures are often combined (to different chemicals) as well as aggregated (through different pathways, such as air, drinking water, foods). The use of biomarkers gives a more accurate estimate of the *internal* exposure (the actual dose within the body); however, risk managers may be interested to know also the environmental compart(s) more important as exposure vehicles. Therefore, an accurate risk assessment would require information on both internal and external exposure (for a discussion on biomonitoring concerning heavy metals, see Frazzoli et al. 2015) [31]. Another aspect is the presence of multiple pollutants in the same area: again, epidemiological tools may easily point out than in a given environmental setting there is a problem, but risk managers may want know what are the priority pollutants in order to prevent human health effects. Indeed, the most well-kmown environmental teratogens are methylmercury [41] and polychlorinated dioxin-like compounds [96], following episodes of peak pollution occurring in Eastern Asia in the 1960s: such episodes make up a significant part of the historical background of modern teratology, but represent instances different from the long-term, combined exposures generally associated with

environmental pollution. As for the so-called confounders, it is, indeed, relevant to understand how and what extent, diet, lifestyles and socio-economic determinants do *interact* with environmental toxicants. For instance, substances naturally present in the diet may interact in different ways with environmental endocrine disrupters, exerting protective but also additive effects [1]; however, more evidence is needed in order to draw robust conclusions. Other important uncertainties in epidemiological studies have an impact on the accuracy of meta-analyses, such as varying methodologies and the rarity of many specific malformations [12]; indeed, meta-analyses seem more effective in finding associations with more frequent adverse pregnancy outcomes, such as pre-term birth and low birth weight [70].

Taking into account the above mentioned problems, a number of recent epidemiological studies strove to characterize the potential link between non-occupational environmental factors and malformations. Examples concerning air pollution, indoor environment and pesticides are presented in the ensuing paragraphs.

18.2.1 Air Pollution

Air pollution is emerging as relevant risk factor for congenital anomalies. According to Nieuwenhuijsen et al. [70] the available meta-analyses found significant associations with environmental tobacco smoke and outdoor air pollution. On the contrary, Chen et al. [12] when considering seventeen articles in the systematic review and thirteen studies in the meta-analysis, found a moderate association between increasing NO2 concentrations and coarctation of the aorta (OR = 1.20 per 10 ppb, 95% CI 1.02–1.41) as the only significant effect; these authors strongly recommend that future studies should make avail of improved exposure assessment methods, in particular more accurate spatial measurements or modeling.

A population-based case–control study in Northern Italy (228 cases of birth defects and 228 referent newborns) investigated if maternal exposure to PM10 and benzene from vehicular traffic during early pregnancy was associated with excess teratogenic risk; exposure to each pollutant was estimated through a dispersion model, with adjustment for exposure to the other pollutant. The study did not identify any excess risk associated with benzene; conversely, higher exposure to PM10 was associated with increased risk of birth defects overall. Anomaly categories showing the strongest dose–response relation with PM10 exposure were musculoskeletal and chromosomal abnormalities, Down syndrome showing a strong association; these results may hint that PM10 exerts a genotoxic action on germ cells as well as a teratogenic action [101].

18.2.2 Indoor Environment

The majority of the general population spents the greatest part of lifetime in indoor environments. The indoor environment make up most of indoor air pollution. Occupational exposure to organic solvents during the 1st trimester of pregnancy has been associated with congenital anomalies; therefore, it is reasonable to investigate the possible teratogenic risk from exposure to organic solvents used in paint products of home environments. Hjortebjerg et al. [46] in 2012 using data from the Danish National Birth Cohort, interviewed more than 20,000 women in their 30th week of gestation about the use of paint in their residence during pregnancy: 7% had been exposed to paint fumes during the 1st trimester of pregnancy. After adjustment for usual confounders and occupational use of solvents, exposure to paint fumes was positively associated with congenital anomalies of the renal system (OR 2.16, 95% CI 1.02–4.58); a potential association, albeit below the formal statistical significance threshold, was also observed for anomalies of the nervous system (OR 2.19, 95% CI 0.76–6.32), ear, face and neck (OR 2.15, 95% CI 0.84–5.55). A Chinese study focused on congenital heart diseases (CHD) as the main group of anomalies potentially associated with maternal occupational exposure to organic solvents [60]. A multi-hospital case–control study (346 cases and 408 controls) was performed: maternal exposure to housing renovations was identified through a questionnaire given to women during pregnancy. The overall risk for CHD was significantly increased (OR: 1.89, 95% CI 1.29–2.77); the risk was slighly higher when considering the sunbgroup of CHD with other malformations (OR 2.65). Although results were not completely consistent and the exposure assessment was only performed by questionnaire, the data indicate that certain solvents or other components present in house paints, in conditions enhancing exposure (e.g., renovation), may increase the birth defect rate.

The toxic heavy metal *lead* can be a significant component of indoor dust, especially in non-European Countries. Another case–control study by Liu et al. [61] on pregnant women making antenatal examinations explored in 2015 the association between maternal lead exposure and CHD risk. The study included 316 cases and 348 controls; exposure was assessed by the maternal hair lead levels, a practical biomarker of long-term intake (see, e.g., Peña-Fernández et al. 2014) [75]. The median level of lead in maternal hair of case (0.670 ng/mg) was significantly higher (OR 3.07, 95% CI 2.00–4.72) than that of the control (0.461 ng/mg). Consistent with Lu et al. 2015 [61], the OR was somewhat higher (3.55) for CHD cases with other malformations. This more recent study assesses internal exposure in an accurate way; in the meanwhile lead is a widespread contaminant and aggregate exposure usually occur. In Europe, diet is the main route of exposure [23]; however, in Countries like China indoor dust as well as drinking water and outdoor emissions from industrial and mining activities may make up most of the environmental lead burden [105].

18.2.3 Pesticides

Pesticides are a large and diverse ensemble of chemicals including many toxic compounds. In Europe pesticides are strictly regulated, and compounds identified as developmental toxicants should be restricted or banned; nevertheless some compounds may be inadequately regulated or regulations may be insufficiently applied. Non-occupational exposure to pesticides may occur through the living environment of agricultural areas [25] or through residues in foods. Since many different substances are likely to be used in different crops grown in one area, it is complex to assess non-occupational exposure in field situations. Under this respect it may be useful to discuss some studies performed in Italy, a country with many areas devoted to intensive, specialized farming, such as vineyards and fruits. Clementi et al. (2007) performed a 6-year study in an agricultural area of northeastern Italy, where a good control of pesticide use is in place [13]. Data on congenital malformations were obtained from the northeast Italy Congenital malformation Registry, using several sources of ascertainment, while detailed data on pesticide use were obtained through interviews with users and sellers; municipalities of three contiguous provinces were divided into those with a high, low or intermediate use of pesticides. In the study period there was a total of 146,239 consecutive pregnancies terminating in birth or induced abortion because of congenital malformation. No significant differences in the prevalence of congenital malformations were observed among the three different areas. The results indicated that a control of the use of pesticides can prevent a teratogenic risk in the general population.

Other studies investigated the potential link between pesticides with putative endocrine activities and the risk of hypospadia and cryptorchidism, two birth defects associated with the intrauterine exposure to antiandrogenic or estrogenic agents. The investigations were carried out in the province of Ragusa (Sicily), another area with intensive agricultural activities but with social, climatic and environmental characteristics quite different from the North-Eastern region. A preliminary analysis was based on data from the local pediatric services and a ranking of municipalities according to the degree of pesticide intensity of agricultural activities. A significant positive trend was observed between increasing pesticide impact and the prevalence of hypospadias ($P = 0.003$) as well as with the combined prevalence of the two birth defects (trend test, $P = 0.001$) [8]. Further more detailed analyses identified only slight, non-significant increases of risk for direct or indirect (transport, retail) occupational exposures [9]. On the other hand, diet resulted a potential risk factor: in a population-based case-control study (90 cases and 202 controls) data on dietary habits of the mothers were collected through interviews. Increased ORs were observed for mothers of children with hypospadias who, during pregnancy, frequently consumed fish (2.33, 95% CI 1.03–5.31) and market-purchased fruit (5.10, 95% CI 1.31–19.82): these data suggest a possible role for bioaccumulating contaminanys (e.g., dioxins, polychlorinated biphenyls) and pesticides used either in the field or post-harvest. For cryptorchidism, increased risk was observed in mothers consuming liver (5.21, 95% CI 1.26–21.50), which again suggest a role for

bioaccumulating contaminants, and smoked products (2.46, 95% CI 1.15–5.29), which are associated with intake of toxic by-products such as policyclic aromatic hydrocarbons. In addition for the two malformations pooled together, increased risk was associated with frequent consumption of wine (1.98, 95% CI 1.01–3.86). Thus, rather than the environmental presence of pesticides, the results suggest more attention to the high intake of endocrine-disrupting chemicals in some foods liable to contamination [36]. Further research on pesticides and birth defects would definitely require focussing on specific groups of relevant compounds, identified on the basis of toxicological properties. Modelling of exposure can be refined: the North Carolina U.S. Cohort used a metric that estimates total chemical exposure (as pounds of active ingredient) based on crops within 500 m of maternal residence, specific dates of pregnancy, and chemical application dates based on the planting/harvesting dates of each crop [77]. This model has identified a set of elevated ORs for some birth defects, especially CHD (e.g., atrial septal defects: OR 1.70, 5% CI 1.34–2.14); however, it seems to give limited attention to the toxicological aspects supporting biological plausibility, which is a critical aspect of valid epidemiological information. Exposure assessment by appropriate biomarkers would be desirable [65]. Since most currently used pesticides are not bioaccumulating, any level assessed in biological fluids at or after birth, when the congenital anomaly is diagnosed, may not reflect the exposure during the vulnerable period of embryogenesis. This deserves attention especially for pesticides, where exposure may not be continuous as for environmental pollutants, rather it occurs by pulses during the year according to the agricultural usage patterns. It is therefore envisaged the exploitation of mother-child bio-banks, such as the recently established AGORA biobank in the Netherlands [98].

18.2.4 Food Contaminants

An adequate diet with a balanced intake of specific nutrients (e.g., zinc, vitamin A) is critical for prevention of congenital anomalies [87, 91]. In particular, folate and folic acid are effective beyond any doubt in reducing the prevalence of neural tube defects [89]; in the meanwhile, the vitamins B12 status is also important, since this vitamin is needed for proper folate metabolism, and vegan subjects not taking supplements are at risk of vitamin B12 [91]. Moreover, furthere research is needed on the risk factors (e.g., immune factors, inositol metabolism) for the fraction (30–50%) of neural tube defects that are resistant to folic acid supplementation [17, 37].

Besides nutrition, the role of toxicants that may be present in foods as risk factors for human birth defects is definitely more elusive. There is no doubt that a number of undesirable substances in foods damage the embryo-development in animal studies at dose levels lower than those eliciting animal toxicity: examples include the mycotoxin zearalenone, which mimics an estrogenic action, [24], or acrylamide, an industrial chemical which is also formed when certain foods (especially starchy foods) are prepared at high temperatures [27]. The presence of these compounds in

foods must be held in check giving due consideration to the prevention of developmental hazards. In the meanwhile, it is still difficult to assess the role of specific toxicants in human birth defects, also because the available studies suffer from shortcomings in the measurement of actual exposure. For instance, a case-control study found no significant association between congenital anomalies and maternal dietary intake of nitrates, nitrites and nitrosamines; the study was apparently well controlled, but the intake was estimated by a food frequency questionnaire and no attempt was made to assess a possible combined effect of the chemicals [48]. A growing attention toward the effects on the next generation is leading to more conservative approaches. For instance, the concern for the specific developmental neurotoxicity of methylmercury, a major environmental pollutant of fish food, has stimulated both lower tolerable limits in seafood and approaches to reduce the contamination of farmed fish of toxicants in food [66]. It is noteworthy that the current high rank of methylmercury as a developmental hazard is related to its potential for inducing long-term functional deficits, rather than congenital anomalies. The same consideration holds true for *endocrine disrupting chemicals* (EDC), a heterogenous ensemble of chemicals that can damage human health by altering the hormone balance. EDC, which represent a top-level issue for toxicologists worldwide, can contaminate human foods by two main pathways: as persistent, bioaccumulating pollutants (dioxins, polychlorinated, polybrominated or perfluorinate substances) or as plasticizers present in food contact materials (bisphenol A, phthalates) [64]. EDC feature prominently among developmental toxicants, as they may induce subtle, but persistent impairments of reproductive and neurobehavioural functions [57]; recent and increasing evidence point out their role as obesogens [45]. EDC with estrogenic and/or antiandrogenic activities do impair directly male reproductive development and are considered as risk factors for the etiology of hypospadia as cryptorchidism [86]: it may be worth mentioning that a recent study in New Zealand observed markedly different ethnic patterns between these two anomalies, leading the Authors to hypothesize the involvement of differethe risk factors in hypospadia and in cryptorchidism [38]. Although, the available evidence do not allow to pinpoint any specific chemical as main agent, the cumulative exposure to EDC in foods and environment is a likely candidate as additional human teratogen in regard to congenital anomalies of the male reproductive organs.

18.3 Maternal Health and Health Services

Maternal health both immediately prior to and during pregnancy is an important risk factor for congenital anomalies as well as infant death, chronic illness, and disability which in turn has a significant impact on individuals, families, health-care systems and societies [108]. The maternal health risk factors associated with CA often increase the risk of other adverse birth outcomes, such as preterm birth, low birth weight and neurodevelopmental outcomes, resulting in an increased health burden for health services [104].

Maternal health factors along with several environmental and exogenous factors are strongly suspected or proven to damage or cause abnormal development of the fetus [35]. As most CA are multifactorial there is an interaction between risk factors and genetics. Maternal health is often poorer among resource-constrained families and in countries where mothers may have increased and concurrent exposure to a number of risk factors, such as imbalanced nutrition, poor environment and lifestyles as well as infections [106].

Scientific evidence shows that by improving maternal health and reducing recognized maternal risk factors it is possible to lower the incidence of CA. Two European projects, EUROCAT (European Surveillance of CA – http://www.eurocat-network.eu/) and EUROPLAN (European Project for Rare Diseases National Plans Development – http://www.europlanproject.eu/), have recently issued a body of evidence-based recommendations for CA primary prevention, that was endorsed by European Union Committee of Experts on Rare Diseases in 2013 [91]. Amongst these Recommendations are primary prevention strategies to be developed for improving maternal health (e.g. counselling of fertile women with chronic illness on the risks and benefits of medication choices) and broader public health targets relevant to prenatal development (e.g. community policies promoting healthier dietary patterns or reducing active/passive smoking). Each Recommendation can improve maternal health with respect to a CA or a group of CA. For example improved maternal diet and folate status can reduce the risk of neural tube defects [89]. Maternal health can also be improved by lifestyle such as avoidance of tobacco smoke and alcohol intake. Timely modification of maternal diet and lifestyles can reduce respectively the risk of orofacial clefts, CHD [39, 47] and fetal alcohol syndrome [97].

A plan of action aimed at improving general maternal health may achieve an added value higher than the sum of individual isolated interventions. Public health services aimed at improving pre pregnancy maternal health are limited by resource restrictions by policy makers despite the fact evidence-based maternal care can provide primary prevention of CA. More investment in maternal health services and the integration of actions that are already in place in most industrialized countries and in some rapidly developing countries would be a cost-effective policy and may indeed lead to better use of health services. In developing countries health services should direct efforts to a first phase of identifying the priority targets – for example maternal nutrition or infection – on which to devote the limited resources available.

We already discussed environmental teratogens from the standpoint of risk assessment. In the meanwhile, policies to minimize the exposures to teratogenic chemicals may also have an important impact on maternal health and empowerment, and such policies would be better implemented at trans-national level. The European Union has built two important systems based on risk assessment for foods and chemicals that pivot on the European Food Safety Authority (EFSA – http://www.efsa.europa.eu) and the European Chemical Agency (ECHA – http://www.echa.europa.eu/). Information provided through the internet on maternal health and risk factors should be seen as a potential resource in the empowerment of women in

improving their health prior to and during pregnancy. How to achieve such empowerment is an issue that health services should address as a small investment in making information readily available could have an important impact.

Maternal health services should include genetic counselling services alongside genetic testing. This is important for couples with a family history of known conditions, syndromes or Rare Diseases (RD) [28, 90]. Most CA meet the criteria for being considered as RD [22] and represent an important fraction of the total RD burden; due to the critical role of non-genetic factors in their pathogenesis they are a group of RD in which primary prevention measures directed at maternal health may have a beneficial impact. Significant progress has been made in identifying many modifiable maternal health risks or preventive factors for birth defects [78]. Available scientific evidence indicates that acting through maternal health services on identified risk and protective factors a reduction of CA incidence can be achieved. This has implications not only on maternal and child health but also on the health service and social burden [91]. Until recently, however, translation of scientific and epidemiologic findings into successful strategies for maternal health and birth defects prevention in the population has not been achieved. More work is required in studying maternal health risk factors and successful public health service action and scientific evidence is needed from public health research to create an evidence base for complex interventions and behavior change strategies.

CA registries are a method of monitoring maternal health factors and prenatal services, the implementation of strategies and their efficacy. As advances in knowledge regarding maternal health lead to changes and development of clinical evidence, mechanisms should be envisaged for consistent and timely translation of scientific knowledge into evidence-based actions by health services, as well as for identifying relevant knowledge gaps. For this purpose maximizing maternal health surveillance and related research mechanisms to monitor preconception health is needed. Community health data are already used systematically in several European states to conduct public health surveillance and to evaluate and improve maternal health, health programs, and health policies [49]. Several public health agencies in Europe conduct and maintain data collection and surveillance systems in the field of maternal and child health benefits. It is important to apply public health surveillance strategies to monitor selected preconception health indicators (e.g. folic acid supplementation, smoking cessation, alcohol misuse, drug use, obesity, vaccinations etc.) and to develop or modify existing measures to monitor evidence-based interventions used in maternal preconception health services [51].

Maternal health issues related to multifactorial endocrine-related disorders, food and nutrition provide examples of knowledge requirements and gaps for updating primary prevention policies.

Rather than focusing solely on teratogenic risk recent scientific studies try to deal with risk-benefit analysis of interventions for chronic health conditions that can affect a significant fraction of fertile women. Chronic diseases such as thyroid diseases [19, 79] or diabetes [62, 93, 94, 102] may pose a risk to the fetus. The challenge in maternal health services is to prepare women for pregnancy and design treatments during pregnancy that are effective without added or different risk to the

fetus compared to the disease itself. An example is the treatment of hyperthyroidism, which has been reported in 3% of pregnant women [7]. Balanced therapy indicates propylthiouracil (less damaging to the embryo but inducing long-term liver toxicity) in first trimester, followed by the use of methimazole (which has a higher teratogenic potential but lower maternal toxicity) in the rest of the pregnancy [19]. An adequate dietary intake of iodine in food such as fish and eggs, and the use of iodized salt, is a basic requirement for proper thyroid function, critical for intrauterine growth and development. A high intake of isoflavones, thiocyanates and nitrates from vegetables or subclinical deficiencies of some nutrients such as selenium may compound the effect of low iodine, especially due to the higher needs during pregnancy [26]. An adequate intake of selenium has been proposed to prevent autoimmune hypothyroidism, frequent in fertile women, but this hypothesis requires further evidence [99].

Pregnant women with either type 1 or type 2 (T2D) show a similar risk of CA, as maternal hyperglycaemia is the key teratogenic factor [54]. T2D represents a high maternal health concern as its incidence is rapidly rising in both high and middle income countries calling for maternal health strategies based on increasing women's awareness to bring about lifestyle modifications [85]. T2D has a complex pathogenesis and genetic predisposition, the risk of T2D may be reduced by the diffusion of healthier nutritional choices and increased physical activity, adjusted to reflect local food availability and individual's needs [55]. Basic primary prevention is paramount to build up the health of the community as well as of the next generations, thus it should start with education and empowerment from early childhood. Against this background, preconceptional care of the many women currently affected by T2D will increase their potential for healthy motherhood. The available guidelines pivot on the preconception control of blood glucose and metabolism as a priority action [62, 93]. Other recommendations include high-dose folate supplementation (5 mg/day) as well as empowering the woman, by encouraging regular exercise, management of weight and a diet with high levels of complex carbohydrates, soluble fibre and vitamins and reduced levels of saturated fats [62]. Striving to reduce blood glucose may increase the risk of maternal hypoglycemia in the first trimester [102] so the preconceptional strategy should aim at supporting the woman to maintain her health. Interconception care is an opportunity as yet under exploited that may protect maternal and infant health in women with a history of gestational diabetes [94]. Obesity is a related metabolic condition which shares many features with T2D. The global rise in obesity involves high,low- and middle-income countries [76, 85]. Obesity is a complex pathogenesis involving lifestyles, (high calorie diet with low physical activity), genetic predisposition, and other factors [52]. Maternal obesity increases the risk of pregnancy complications and CA, including neural tube defects [48]. Primary prevention of obesity-related birth outcomes should integrate community actions and targeted preconceptional care for individual obese women [72]. Both levels need to empower women to healthier diets and reasonable physical activity [94]. The primary prevention of T2D and obesity share many features and should be integrated in a concerted and cost-effective public

health plan for the population as a whole, but with special reference to maternal health and pregnancy [85].

The CA risk associated with endocrine-metabolic disorders also point out the central role of nutrition in maternal health. A recent U.S. study reported that instead of supplements, an improved dietary pattern may reduce the risk of neural tube and congenital heart defects [87]. The scientific literature supports that within an adequate diet, a well-balanced intake of specific nutrients such is critical for prevention of congenital anomalies. A folate rich diet and periconceptional supplementation with folic acid are effective beyond doubt in reducing the prevalence of neural tube defects but vitamins B12 and B6 are also needed for proper folate metabolism [91]. Inadequate or unbalanced intake of micronutrients is a global problem where multiple-micronutrient supplementation could be an effective action in improving maternal health and preventing congenital anomalies. However care is required in the selection of supplemental doses, as excessive intakes may be harmful or, as in the case of many trace elements, may impair the bioavailability of other nutrients [40]. Additional scientific research could also refine and improve the use of folic acid supplementation to improve maternal health including effects on CA other than neural tube defects [15, 18], 5-methyl-tetrahydrofolate as an alternative to folic acid [71] and the mechanisms in maternal health such as immune factors and inositol metabolism that cause resistance to folic acid [17, 37]. Folic acid is an issue for public health research in [5] and a robust and consistent definition of recommended intake levels for folates [88]. Flour fortification with folic acid is an opportunity to create equity in maternal health though there is much public debate [30]. Although implemented in North America, some South American countries and Australia, it is yet to be implemented in Europe. Against the certain benefits in prevention of neural tube defects and probably other CA, particularly among women who are at high risk due to poor diet or lack of pregnancy planning, are the possible resistance of the public to universal additives, problems in trading flour-based products across European Union countries with different policies and diets, and uncertainties about cancer promotion or epigenetic effects [89]. Ultimately, it is matter of public preference how to weigh CA prevention against such uncertainties, and a consultation mechanism is needed.

The role of diet and nutrients in CA prevention is an evolving field. Interest is increasing in the effects of low vitamin D status; a possible risk factor for some adverse pregnancy events, including gestational diabetes which is a recognized CA risk factor. However the available evidence is not yet robust enough to design specific preventive actions [44, 103].

Food contaminants and toxic agents are another factor in maternal health and CA, with available studies suffering from shortcomings in the measurement of actual exposure. A recent case-control study found no significant association between CA and maternal dietary intake of nitrates, nitrites and nitrosamines but the study was limited to livebirths and intake was estimated by a food frequency questionnaire [48]. The problem of exposure assessment is highly relevant to environmental risk factors which has been previously discussed elsewhere in this chapter.

It is important that in all policies for maternal health and health services targeting only pregnant women is only a part of the answer, since organogenesis occurs early in pregnancy before many women know they are pregnant and many pregnancies are unplanned.

At a national level actions for maternal health will be based both on international recommendations and on country priorities [91]. Primary prevention of CA through improved maternal health and health services is feasible because many risk factors are recognized and can be targeted by well-identified community actions, such as counselling of fertile women with chronic disease regarding medication choices, evidence based vaccination policies and regulations on occupational exposures of either pregnant women and women of childbearing age in the workplace, as well as through individual information and empowerment: taking periconceptional folic acid supplements at the right time and in the right dose, avoiding over- or underweight, promoting alcohol avoidance in women who are pregnant or could become pregnant. The results of scientific research, identifying new maternal health risk factors and/or new aspects of recognized risk factors can develop and strengthen these actions.

Maternal health services however must address this issue in order to maximise maternal health and minimize CA and other adverse pregnancy outcomes. Improving maternal health requires a multidisciplinary approach to integrate patient-oriented periconceptional action with actions at community level involving food, lifestyles and healthcare.

18.4 Infectious Diseases

Viral and bacterial infections in pregnancy are causes of congenital disorders that can vary in their clinical manifestation depending on the agent and gestational age at exposure [63]. Moreover, women have an increased risk of acquiring certain transmissible diseases during pregnancy due to transient immunosuppression [69].

Infections responsible of congenital malformations are known with the acronym TORCH (Toxoplasma, others, rubella, cytomegalovirus, herpes). The “others” category has expanded to include several viruses and bacteria known to cause neonatal disease. The infections of concern during pregnancy are those caused by rubella virus, syphilis, cytomegalovirus (CMV), and herpes simplex virus (HSV). Moreover, potential infectious diseases now known to cause congenital infections with potential associated malformations include parvovirus B19 (B19V), varicella-zoster virus (VZV), West Nile virus, measles virus, enteroviruses, adenovirus, and human immunodeficiency virus (HIV). Recently, Zika virus (ZIKV) has been identified as responsible for congenital disorders [3, 21, 63, 69]. Such infections during pregnancy, particularly during the first 9 weeks, can cause serious congenital abnormalities (e.g. maternal infections such as cytomegalovirus, VZS or rubella) [63]. In this chapter we will focus on pathogens that are responsible of considerable public

health impact, such as CMV, rubella, VZV, and ZIKV, including two vaccine preventable diseases (rubella and VZV).

CMV is very common and can infect anyone, is transmitted by direct contact with infectious body fluids, such as urine or saliva, other possible routes of transmission include sexual contact, organ transplantation, transplacental transmission, transmission via breast milk, and blood transfusion [6]. The prevalence of congenital CMV is different depending on the geographical areas, varying between 0.15% and 2% and it is higher in North America and lower in Europe [6]. According to data from the US CDC, in the United States 1 in 150 children is born with congenital CMV infection and 1 in 750 develops permanent damage due to the infection. The estimated number of US children who each year develop permanent damage because of congenital CMV is about 8000 [63]. In Italy congenital infection prevalence is among the lowest reported in the literature: varies from 0.15% in babies born to women over 24 years and 0.51% in women under this age, confirming that advanced age pregnancy can be considered a protective factor against congenital infection [2].

The infection contracted during pregnancy, in particular during the first trimester, and transmitted to the fetus can in fact be severe and cause congenital malformations: 30% of infants with severe CMV infection die; among survivors, more than half eventually develop neurological sequelae, including microcephaly, mental retardation, and/or sensorineural hearing loss. Seven percent of asymptomatic neonates develop sensorineural hearing loss or developmental delays during the first 2 years of life [2, 32, 59, 73, 94, 95]. Five percent eventually develop microcephaly and neuromuscular defects, and 2% develop chorioretinitis. Congenital hearing loss is the most common sequela of recurrent CMV infection [58].

CMV may be detected by viral culture or polymerase chain reaction (PCR) of infected blood, urine, saliva, cervical secretions, or breast milk. CMV infection is usually diagnosed using serologic testing. Serum samples collected one to 3 months apart can be used to diagnose primary infection. Seroconversion is clear evidence for recent primary infection. However, diagnosis of CMV infection between birth and 1 year can be complicated by the presence of maternal CMV IgG [3].

Rubella, is an RNA virus found to infect only humans, that is present throughout the world and in temperate countries occurs mainly in winter and early spring [67]. It is spread by airborne respiratory secretions and the virus travels from the upper respiratory tract to the cervical lymph nodes and is then disseminated throughout the body and, 20–50% of infected patients are asymptomatic. The incubation period is 2–3 weeks. Antibodies against rubella do not appear in the serum until after the rash has developed. Fetal infection results from transplacental vertical transmission. Rubella in fact, is one of the more teratogenic viruses: when the disease is contracted in the first trimester of pregnancy, the rate of foetal infection is nearly 50% of which as many as 80% develop the Congenital Rubella syndrome (CRS) [67]. Before the introduction of the rubella vaccine, in 1969, in the United States the disease showed recurrent epidemics that occurred every 6–9 years with an estimated of approximately 20,000 CRS-affected children born each year; n Europe outbreaks occurred every 3–5 years and struck mainly children aged between 5 and 9 years [16]. The incidence of congenital rubella syndrome has decreased dramatically in

the United States because of rubella vaccination; currently, fewer than 50 cases occur each year [33]. In 1996, it was estimated that, in developing countries, approximately 110,000 children were born annually with CRS [11]. Since the introduction of the vaccine in countries with high vaccination coverage, outbreaks have become very rare. However, sporadic cases are still present [109] and in 2015, the WHO European Region reported 7 cases of CRS; in Italy from January 2005 to August 2016 a total of 84 cases of CRS have been notified (76 confirmed and 8 probable), according to the EU case definition [29], through the National Surveillance System [50].

The European Region of the World Health Organization (WHO-EURO)includes among its objectives for CRS elimination the reduction of the incidence of congenital rubella to less than one case per 100,000 live births by 2015 [29].

Congenital rubella syndrome (CRS) is characterized by intrauterine growth restriction, intracranial calcifications, microcephaly, cataracts, cardiac defects (most commonly patent ductus arteriosus or pulmonary arterial hypoplasia), neurologic disease (with a broad range of presentations, from behavior disorders to meningoencephalitis), osteitis, and hepatosplenomegaly. Heart defects in these infants include ventricular septal defects, patent ductus arteriosus, pulmonary stenosis, and coarctation of the aorta. The presentation of rubella at birth varies greatly. Most of these complications develop in infants born to mothers who acquire rubella infection during the first 16 weeks of pregnancy. Ninety percent of infants present with some finding of congenital rubella if infection occurs within the first 12 weeks, and 20% present with congenital disease if the infection occurs between weeks 12 and 16 [16, 67]. Cataracts result when infection occurs between the third and eighth week of gestation, deafness between the 3rd and 18th week, and heart abnormalities between the 3rd and 10th week [16]. Safe vaccines against rubella, exist and are very efficient in preventing infection in the mother [11, 33]. It is clear that CRS can be eradicated by vaccination programmes, a goal that has already been reached in the Scandinavian countries and the United States [11]. However, the vaccine cannot be administered during pregnancy as it is a live attenuated vaccine. Immunization of unexposed child bearing age women and teenage girls prevent CRS.

VZV is a DNA herpes virus very common that carries risks for both the mother and fetus during pregnancy [42]. Morbidity and mortality rates associated with VZV infection are much higher in adults than in children. Following primary VZV infection that confers lifelong immunity, it can remain latent in the dorsal root ganglia. VZV is most often transmitted to the fetus transplacentally; however, ascending infection from lesions in the birth canal has been reported, even though the mechanism of in utero VZV infection is unknown [83]. The risk of a baby being affected by congenital infection and abnormalities is 1–2% if the mother is infected during second trimester. Congenital varicella syndrome (CVS) results in spontaneous abortion, chorioretinitis, cataracts, limb atrophy, cerebral cortical atrophy, and/or neurological disability. Spontaneous abortion has been reported in 3–8% of first-trimester VZV infections, and CVS has been reported in 12% [14, 20, 43, 68, 74, 83, 84]. VZV immunization in unexposed women or teenage girls helps prevent CVS, but varicella vaccine (live attenuated virus) is not administered during pregnancy.

Since 2007, Zika virus (ZIKV) was generally considered an arbovirus of limited importance, causing a mild self-limiting febrile illness in tropical Africa and Southeast Asia [56]. In 2015, ZIKV underwent trough its largest and fastest geographical expansion. The first autochthonous cases of ZIKV on continental America were confirmed in Brazil in May 2015 and, since then, it has been detected in 46 countries and territories [3]. The virus is mainly transmitted through Aedes mosquito bites, but sexual and post-transfusion transmissions have been reported [82, 100]. Different from other flavivirus infections, ZIKV has proven to be related to more serious complications. As evidence grew for a causal link between Zika infection and microcephaly and other serious congenital anomalies [10], the World Health Organization (WHO) declared the Latin American Zika epidemic a public health emergency of international concern in February 2016 [107]. These include Guillain-Barré syndrome and neonatal congenital malformations, such as microcephaly and neurologic damage to the developing fetus, particularly if the maternal infection occurs early in pregnancy [3]. However, to date, a more precise assessment of long-term risks requires key data gaps to be filled.

18.5 Conclusions

EU Member States are implementing national plans on RD) [90]. Indeed, CA represent an important fraction of RD [22] and, due to the critical role of non-genetic factors in their pathogenesis, are the main RD group in which primary prevention measures will have a beneficial impact.

The above subchapters have discussed in detail the assessment of main risk factors for CA, such as environmental toxicants, maternal health and lifestyles and infections. Overall, the availability of CA registries is important to estimate the health burden of CA, identifying possible hotspots and assessing the impact of interventions [53]. Extending such tools with up-to-date quality standards is required to plan and implement robust and sustainable primary prevention plans. Epidemiology can be, however, a double-edged weapon. In particular, epidemiological studies on potential teratogens in foods and environment provide indications of possible associations, but in the majority conclude that “further research is needed”. Whereas advancing knowledge is always warranted, for the purpose of primary prevention further research should fit for purpose, i.e., provide the missing data that serve to address the action by risk managers. When a predictable association between birth defects and a well-characterized developmental toxicant does exist, then, actions aimed at risk reduction should not be unnecessarily delayed, such as in hotspots of environmental pollution.

Whereas a number of potentially effective individual measures can be envisaged (e.g., promoting folic acid supplementation), concerted group actions aimed at protecting the conceptus are likely to achieve a higher added value. Public health actions currently have to face resource restrictions by policy makers; moreover many policy makers appear not to be highly sympathetic toward primary prevention,

because of political reasons (e.g., unwillingness to engage conflicts), limited awareness about the benefits of prevention as well as preference toward health measures that are believed to bring benefits, hence political support, at shorter term. Moreover, policies to minimize the exposures to chemicals of high concern, including teratogenic substances, are likely to impact on international trade; thus, such policies should be implemented at a transnational level These actual difficulties may be overcome by stressing the integration of actions that are already in place in most industrialized countries and in several industrializing countries (including control of noxious environmental emissions, vaccination programmes, public health toward chronic maternal conditions and lifestyle, etc.); thus, a primary prevention plan would be cost-effective and may indeed spare resources by optimizing their use. In developing countries with less primary prevention in place and limited overall resources, a first recognition phase may be pivotal in order to identify priority targets. On the other hand, in areas like Europe it should be stressed that primary prevention of RD supports publicly endorsed societal values like the knowledge-based promotion of health, empowerment, equity and social inclusiveness.

An integrated approach to primary prevention of RD would be effective, feasible and affordable: it will entrain the interplay among scientists (who provide knowledge), risk assessors (who analyse and make avail of scientific data), risk managers (who take decisions and select tools to enact them), policy makers (who elaborate on values and protection goals) and, last but not least, the multiple voices from society.

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Chapter 19
Newborn Screening: Beyond the Spot

Tiina K. Urv and Melissa A. Parisi

Abstract The newborn screening paradigm of testing all newborns in the United States for treatable conditions within the first few hours of birth has proven to be a remarkable success story in the realm of public health by reducing neonatal and childhood morbidity and mortality. The Newborn Screening Saves Lives Act of 2007 and its successor, the Reauthorization Act of 2014, legislated the establishment of a Department of Health and Human Services Advisory Committee to make recommendations around newborn screening and a methodology to establish and add new conditions to a Recommended Uniform Screening Panel (RUSP) which currently includes 34 core conditions. In spite of the *absence* of a federal mandate that requires each of the states in the U.S. to screen for the disorders on the RUSP, most state public health laboratories have adopted the conditions on this panel. Moreover, the evolution of the evidence-based review process for adding new conditions to the RUSP has led to improvements in incorporating the public health impact and feasibility and implementation considerations. The cooperation between the federal partners who support implementation and rollout of state-based screening programs, develop technical standards and proficiency materials for laboratories, review and approve new technology platforms, and promote research to develop new assays and treatments for screenable disorders, points to the success of the newborn screening enterprise nationwide. As new technologic advances are made in the realm of genomic sequencing, the potential for incorporating these technologies holds great promise for newborn screening, but the ethical ramifications must be carefully considered to avoid harming the existing trust in the program.

Keywords Early diagnosis • Newborn screening • Rare disease

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Abbreviations

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
ACMG	American College of Medical Genetics and Genomics
APHL	Association of Public Health Laboratories
CCHD	Critical Congenital Heart Disease
CDC	Centers for Disease Control and Prevention
CLIR	Collaborative Laboratory Integrated Reports
CRF	case report forms
ELSI	Ethical, Legal and Social Issues
HHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
IRB	Institutional Review Board
NBSTRN	Newborns Screening Translational Research Network
NHGRI	National Human Genomic Research Institute
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
PKU	Phenylketonuria
R4S	Region 4 Stork
RUSP	Recommended Uniform Screening Panel
SCID	Severe Combined Immunodeficiency;
TMS	Tandem Mass Spectrometry

19.1 Introduction

Shortly after birth, almost all babies born in the United States take part in one of the largest and most successful public health programs in the country, one that is considered among the ten most significant public health achievements in the United States between 2001–2010 by the Centers for Disease Control and Prevention (CDC) – Newborn Screening [9]. (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm). The purpose of newborn screening is to identify newborns with conditions that may cause disease, disability or death while the baby is asymptomatic and intervene with treatments that may prevent or lessen the severity of the disease. While newborn screening is often thought of as just a blood spot on a card, it is in actuality a complex system that involves research scientists, clinicians, families, laboratorians, policy makers, and public health programs [4].

As a public health program, newborn screening began in the early 1960's with the development of a screening test for phenylketonuria (PKU) by Robert Guthrie [7]. The "PKU test" was the first widespread newborn screening test that identified

and treated asymptomatic babies, thereby preventing thousands of cases of intellectual disability. During the course of the following 50 years, the number of conditions screened for expanded dramatically with the advent of tandem mass spectrometry (TMS), which allowed for testing new conditions and testing for multiple disorders simultaneously.

Newborn screening public health programs are managed by individual states. With the newfound ability to screen for a larger number of conditions, discrepancies across states became apparent with some screening for as few as four and others as many as 50 different conditions (https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/reportsrecommendations/reports/sachdnc2011report.pdf) [34]. To facilitate greater uniformity across state programs, actions were taken at the Federal level. The first was to establish the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (since renamed the Advisory Committee on Heritable Disorders in Newborns and Children, or ACHDNC) under the Public Health Service Act, Title XI, § 1109 (42 U.S.C. 300b-10). https://www.congress.gov/110/plaws/publ204/PLAW-110publ204.htm), also known as the Newborn Screening Saves Lives Act of 2007 (P.L. 110–204). This was later amended by the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113–240); https://www.congress.gov/bill/113th-congress/house-bill/1281/text). The mission of the ACHDNC is to reduce morbidity and mortality in newborns and children who have, or are at risk for, heritable disorders. The ACHDNC advises the Secretary, U.S. Department of Health and Human Services, on the most appropriate application of universal newborn screening tests, technologies, policies, guidelines, and standards.

A second step to help facilitate uniformity was the development of the Recommended Uniform Screening Panel (RUSP). The Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA), commissioned the American College of Medical Genetics and Genomics (ACMG) to develop guidelines for selecting and adding conditions to state newborn screening panels [40]. The selection of the disorders was based on an approach that included convening a broad array of relevant experts into a steering committee and several work groups, developing a set of principles to guide the analysis and rank of the conditions, and then utilizing criteria to evaluate the conditions chosen to review. Currently, the Committee recommends that every newborn screening program includes the 34 core disorders and 26 secondary disorders on the RUSP. Testing includes not only the use of dried blood spots for metabolic, endocrine, hematologic, and immunologic disorders but also hearing screening and the use of pulse oximetry for critical congenital heart disease. Although individually most of the conditions are rare, with the exception of hearing loss and critical congenital heart disease, collectively they impact a significant number of newborns. It is estimated that state newborn screening programs identify ~12,000 newborns per year out of ~4.1 million total births in the United States whose lives are saved or improved because of early diagnosis and treatment [41]. Moreover, in the most populous state in the country, California, with ~500,000 births per year, the population prevalence of metabolic, endocrine, hemoglobin, and cystic fibrosis disorders was 1:500 births between 2005–2010 [12].

The most prevalent disorder among those screened was primary congenital hypothyroidism (1 in 1706 births).

19.2 The Recommended Uniform Screening Panel (RUSP)

In 2002, when the ACMG was commissioned by HRSA to develop list of conditions for nomination to the RUSP, the ACMG was also charged with recommending an implementation approach for it, model policies and procedures as well as minimum standards for state screening programs, develop a decision-matrix for the expansion of state screening programs, and propose a national process for quality assurance and oversight [29]. Although the Wilson and Jungner criteria for assessing the validity of a screening program for public health purposes were considered for this effort, the relative lack of an attached quantitative metric compelled the ACMG to develop its own framework for a scoring system [42]. With an understanding of the rather arbitrary nature of the conditions screened for by the different state programs, the ACMG sought to establish a rigorous process for selecting conditions for the RUSP. The expert group solicited the views of experts, including individuals and organizations with an interest in newborn screening as well as consumers, via a survey tool. Next, the scientific literature was reviewed to establish the evidence base for the inclusion of a condition. The 3 minimal criteria that guided the scoring of each condition were:

- It can be identified at a period of time (24–48 h after birth) at which it would not ordinarily be clinically detected.
- A test with appropriate sensitivity and specificity is available.
- There are demonstrated benefits of early detection, timely intervention, and efficacious treatment.

As a consequence of this process, the Uniform Panel Work Group developed the data collection instrument to use during the project's first phase to evaluate the features of conditions under consideration for inclusion in the RUSP. Using a weighted scoring system, each condition was scored and ranked quantitatively according to criteria in three main categories: 1. the clinical characteristics of the condition; 2. the analytical characteristics of the test; and 3. diagnosis, follow-up, treatment, and management of the condition. Within each of these categories, different component criteria were scored. Ultimately, the rank order of conditions was determined, and a (somewhat arbitrary) cutoff score of 1200 was established [40], with a recommendation to include most of the conditions that scored better than or equal to cystic fibrosis for inclusion on the RUSP; those that scored lower had, in general, natural history that was less well understood or lacked effective treatments. The resulting original panel of 29 conditions included 9 organic acidurias, 5 fatty acid oxidation disorders, 6 amino acidopathies, 3 hemoglobinopathies, and 6 others (including congenital hypothyroidism, biotinidase deficiency, congenital adrenal hyperplasia, galactosemia, hearing loss, and cystic fibrosis); see Table 19.1.

Table 19.1 The core conditions on the Recommended Uniform Screening Panel (RUSP)

Recommended uniform screening panel							
Core conditions							
(As of November 2016)							
		Metabolic disorder					
ACMG code	Core condition	Organic acid condition	Fatty acid oxidation disorder	Amino acid disorder	Endocrine disorder	Hemoglobin disorder	Other disorder
PROP	Propionic Acidemia	X					
MUT	Methylmalonic Acidemia (methylmalonyl-CoA mutase)	X					
Cbl A,B	Methylmalonic Acidemia (Cobalamin disorders)	X					
IVA	Isovaleric Acidemia	X					
3-MCC	3-Methylcrotonyl-CoA Carboxylase Deficiency	X					
HMG	3-Hydroxy-3-Methyglutaric Aciduria	X					
MCD	Holocarboxylase Synthase Deficiency	X					
ßKT	ß-Ketothiolase Deficiency	X					
GA1	Glutaric Acidemia Type I	X					
CUD	Carnitine Uptake Defect/Carnitine Transport Defect		X				
MCAD	Medium-chain Acyl-CoA Dehydrogenase Deficiency		X				
VLCAD	Very Long-chain Acyl-CoA Dehydrogenase Deficiency		X				

(continued)

Table 19.1 (continued)

Recommended uniform screening panel							
Core conditions							
(As of November 2016)							
		Metabolic disorder					
ACMG code	Core condition	Organic acid condition	Fatty acid oxidation disorder	Amino acid disorder	Endocrine disorder	Hemoglobin disorder	Other disorder
LCHAD	Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency		X				
TFP	Trifunctional Protein Deficiency		X				
ASA	Argininosuccinic Aciduria			X			
CIT	Citrullinemia, Type I			X			
MSUD	Maple Syrup Urine Disease			X			
HCY	Homocystinuria			X			
PKU	Classic Phenylketonuria			X			
TYR I	Tyrosinemia, Type I			X			
CH	Primary Congenital Hypothyroidism				X		
CAH	Congenital adrenal hyperplasia				X		
Hb SS	S,S Disease (Sickle Cell Anemia)					X	

Hb S/ßTh	S, ßeta-Thalassemia					X	
Hb S/C	S,C Disease					X	
BIOT	Biotinidase Deficiency						X
CCHD	Critical Congenital Heart Disease						X
CF	Cystic Fibrosis						X
GALT	Classic Galactosemia						X
GSD II	Glycogen Storage Disease Type II (Pompe)						X
HEAR	Hearing Loss						X
SCID	Severe Combined Immunodeficiencies						X
MPS I	Mucopolysaccharidosis Type 1						X
X-ALD	X-linked Adrenoleukodystrophy						X

"Recommended Uniform Screening Panel." Health Resources and Services Administration, H R S A. HRSA, 1 Nov. 2016. Web. 25 Apr. 2017

Table 19.2 The Secondary Conditions on the Recommended Uniform Screening Panel (RUSP)

Recommended uniform screening panel[a]						
Secondary[b] Conditions[c]						
(As of November 2016)						
		Metabolic disorder				
ACMG code	Secondary condition	Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders	Hemoglobin disorder	Other disorder
Cbl C,D	Methylmalonic acidemia with homocystinuria	X				
MAL	Malonic acidemia	X				
IB G	Isobutyrylglycinuria	X				
2MBG	2-MethylbutyryIglycinuria	X				
3MGA	3-Methylglutaconic aciduria	X				
2M3HBA	2-Methyl-3-hydroxybutyric aciduria	X				
SCAD	Short-chain acyl-CoA dehydrogenase deficiency		X			
M/S CHAD	Medium/short-chain L-3-h ydroxyacyl- CoA dehydrogenase deficiency		X			
GA2	Glutaric acidemia type II		X			
MCAT	Medium-chain ketoacyl-CoA thiolase deficiency		X			
DE RED	2,4 Dienoyl-CoA reductase deficiency		X			
CPT IA	Carnitine palmitoyltransferase type I deficiency		X			
CPT II	Carnitine palmitoyltransferase type II deficiency		X			
CACT	Carnitine acylcarnitine translocase deficiency		X			
ARG	Argininemia			X		
CIT II	Citrullinemia, type II			X		
MET	Hypermethioninemia			X		
H-PHE	Benign hyperphenylalaninemia			X		
BIOPT (BS)	Biopterin defect in cofactor biosynthesis			X		
BIOPT (REG)	Biopterin defect in cofactor regeneration			X		
TYR II	Tyrosinemia, type II			X		
TYR III	Tyrosinemia. type III			X		
Var Hb	Various other hemoglobinopathies				X	
GALE	Galactoe pimerase deficiency					X

(continued)

Table 19.2 (continued)

Recommended uniform screening panel[a]						
Secondary[b] Conditions[c]						
(As of November 2016)						
		Metabolic disorder				
ACMG code	Secondary condition	Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders	Hemoglobin disorder	Other disorder
GALK	Galactokinase deficiency					X
	T-cell related lymphocyte deficiencies					X

[a]Selection of conditions based upon "Newborn Screening: Towards a Uniform Screening Panel and System." *Genetic Med*. 2006; 8(5) Suppl S12–S252" as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA)

[b]Disorders that can be detected in differential diagnosis of a core disorder

[c]Nomenclature for Conditions based upon "Naming and Counting Disorders (Conditions) included Newborn Screening Panels." Pediatrics 2006: 117(5)3uppl: S308–S314

"Recommended Uniform Screening Panel." Health Resources and Services Administration, H R S A. HRSA, 1 Nov. 2016. Web. 25 Apr. 2017

An additional 26 conditions were included on a secondary target panel of conditions that may be identified when screening for the core 29 conditions on the RUSP as they are generally in the differential diagnosis for core conditions but for which natural history and/or treatments are lacking (Table 19.2) [40].

19.3 Challenges of Adding New Conditions to the RUSP

Since the adoption of the RUSP by the ACHDNC and the Secretary of HHS, criteria for consideration of a new condition and a process for evaluating nominations for addition to the RUSP have been developed, with modifications since the original RUSP was adopted [8, 31]. The current process is outlined in Fig. 19.1.

In short, anyone can nominate a condition for consideration by the ACHDNC, but typically nominations have the greatest chance of success when a multidisciplinary team is engaged and a population-based pilot study of the assay proposed has identified at least one true positive newborn through a newborn screening pilot study based on a population and methodology comparable to that in the United States [5]. Next, the Nomination and Prioritization Workgroup reviews the package and drafts a summary for consideration by the ACHDNC. The ACHDNC votes on whether there is sufficient evidence to move the condition to the external Condition Review Workgroup (CRW). The CRW completes a systematic evidence-based review and presents a report to the ACHDNC on the condition, which then votes; by the Newborn Screening Saves Lives Reauthorization Act of 2014, this process is required to be completed within 9 months of starting the CRW's evidence review.

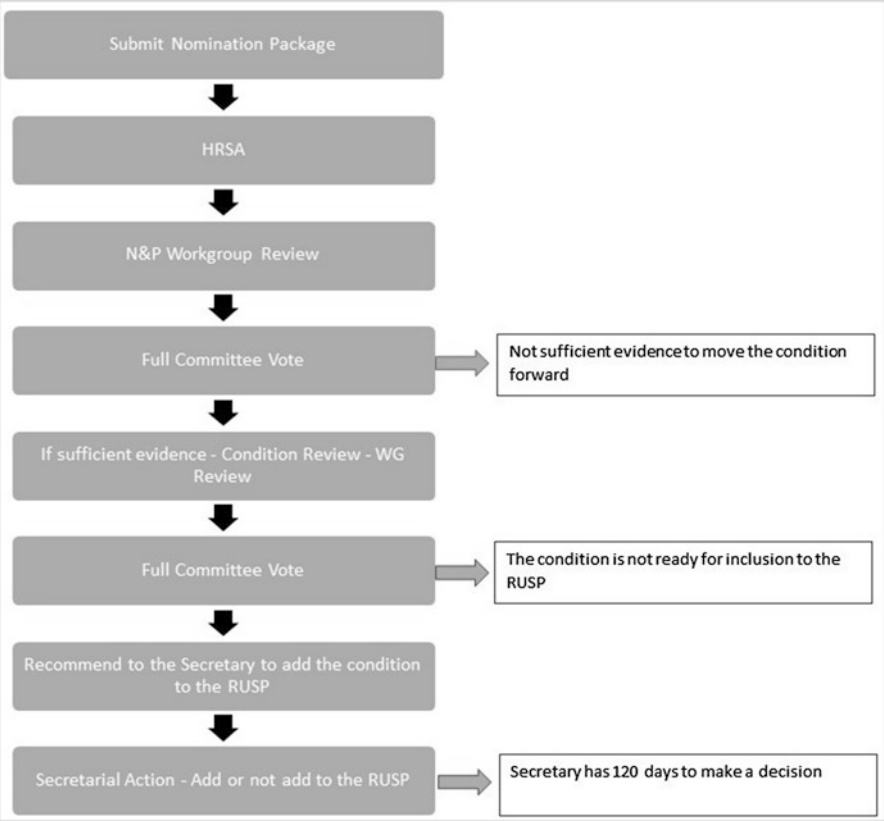

Fig. 19.1 Condition review process

The Decision Matrix for considering a condition is summarized in Fig. 19.2 and incorporates not only elements about the certainty of net benefit from screening, but also the readiness of public health departments to adopt the screen for the condition and the feasibility of implementing the screen, including economic considerations [13, 20, 32].

The public health impact is a relatively new addition to the evaluation process [20], and is based on evolving decision analytic modeling paradigms, with a recognition that there are limited data on the costs of screening, follow-up, treatment and long-term disability [32]. In fact, the cost-*effectiveness* of newborn screening programs has long been assumed, while the actual cost *savings* of incorporating screening has been questioned [15], especially in light of the lifetime costs of providing special medical foods or dietary interventions for those with the inborn errors of metabolism that represent many of the screened conditions [36]. The full committee votes whether to add the condition to the RUSP, and if so, a recommendation is made to the Secretary of HHS to this effect. The Secretary has 120 days to make a decision about the condition. It is important to note that the presence of a condition

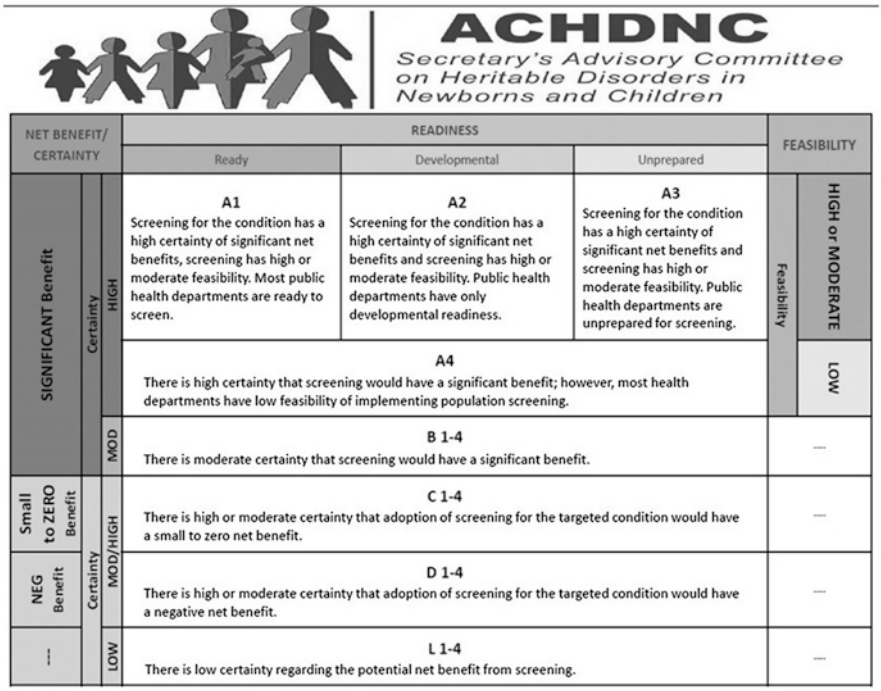

Fig. 19.2 Decision Matrix used by the ACHDNC to consider the addition of a condition to the RUSP. https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/decisionmatrix.pdf

on the RUSP does not, in most states, represent a mandate to screen for the condition; however, many states adopt these new conditions as resources permit, with some being early adopters and others later adopters.

The history of the review of conditions has demonstrated a variable course (Table 19.3). Since the original panel of 29 conditions was approved by the Secretary of HHS in May 2010 [6], 5 additional conditions have been added to the RUSP. The first was Severe Combined Immunodeficiency (SCID), for which the original nomination was rejected because no single case had been identified through the CDC-funded state pilot screening programs underway at the time, although non-SCID T-cell lymphopenias were also detected by the same assay [2, 11].

In response, a coordinated effort involving HRSA, CDC, and the National Institutes of Health (NIH), was launched (Fig. 19.3) to increase the number of newborns screened, and with the addition of California to the pilot studies, with its birth rate of approximately 500,000 births per year, cases of SCID were soon identified. SCID was approved by the ACHDNC in January 2010 and ultimately the Secretary of HHS.

Experiences among the different states varied considerably, with several states, particularly those with large Hispanic populations, demonstrating higher than

Table 19.3 Summary of nominated conditions to the RUSP as of Feb 2016

Condition	Submission to HRSA	N&P WG review	Committee vote to send to ERG	ERG preliminary report and/or update presentation	ERG final report presentation	Committee vote to add to the RUSP	Secretary approval to add to the RUSP
Adrenoleukodystrophy (ALD)	09/13	10/13	01/14	02/15; 05/15	08/15	Approved 8/15	02/16
Adrenoleukodystrophy (ALD)	02/12	8/12	NOT Approved 9/12	–	–	–	–
MPS I (alpha-L-iduronidase deficiency)	02/12	04/12	Approved 05/12	9/13; 01/14	02/15	Approved 02/15	02/16
Pompe Disease	02/12	04/12	Approved 05/12	09/12	05/16	Approved 05/13	03/15
2q11 Deletion Syndrome	01/11	12/11	NOT Approved 01/12	–	–	–	–
Critical Congenital Heart Disease (CCHD	10/09		Approved 01/10	05/10	09/10	Approved 09/10	09/11
Hyperbilirubinemia/Kernicterus	07/09		Approved 01/10	01/11	01/12	NOT Approved 01/12	–

Hemoglobin H Disease	04/09		Approved 09/09	01/10	05/10	NOT Approved 05/10	–
Spinal Muscular Atrophy	06/08		NOT Approved 11/08	–	–	–	–
Krabbe Disease	01/08		Approved 08/08	05/09	09/09	NOT Approved 09/09	–
Fabry Disease	12/07		NOT Approved 08/08	–	–	–	–
Niemann-Pick Disease	12/07		NOT Approved 10/08	–	–	–	–
Pompe Disease	10/07		Approved 01/08	08/08	10/08	NOT Approved 10/08	–
Severe Combined Immunodificiency (SCID)	09/07		Approved 01/08	11/08	02/09	Approved 01/10	02/10

"Nominated Conditions." Health Resources and Services Administration, H R S A. HRSA, 1 Nov. 2016. Web. 25 Apr. 2017

Fig. 19.3 Combined federal efforts to support pilot studies for screening for Severe Combined Immunodeficiency (SCID)

expected prevalence rates for SCID and T cell lymphopenias [23]. Another process of note was that undertaken for consideration of screening for Critical Congenital Heart Defects (CCHD), which was added to the RUSP in 2011 and represented only the second Point-of-Care condition added to the panel (in addition to hearing loss) [21]. Although there was limited information about the effectiveness of the proposed screening algorithm (based on differential pulse oximetry measurements in the limbs of neonates, suggestive of cyanosis) and barriers to appropriate follow-up (including neonatal echocardiogram), this condition was widely adopted by 46 states and the District of Columbia within 4 years. A partnership between the CDC and the American Academy of Pediatrics convened a multi-disciplinary expert panel to identify best practices in CCHD screening, identify and optimize the algorithm, and identify areas for improvement [30].

Challenges to the current system of screening have been brought to light [1]. Slow condition-by-condition review in an era of rapid discovery has become increasingly frustrating, especially for patient advocates. Commercial options for newborn screening are becoming available that could provide information about additional conditions that are not on the RUSP but may impact a child's health. Changes in the technology of screening, using digital microfluidics with even shorter processing and detection times and multiplexed panels of simultaneous assays for a group of lysosomal storage disorders, for example [17, 35], may potentially lead to a reconceptualization of newborn screening. In fact, on Feb 3, 2017, the FDA approved such a platform that allows screening of Mucopolysaccharidosis type I, Pompe disease, Gaucher disease, and Fabry Disease (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm539893.htm). Novel paradigms for expanding newborn screening in a responsible and time-sensitive manner are currently being explored. Recently, the ACHDNC addressed the issue of timeliness in processing and reporting newborn screening results, and its conclusions resulted in new recommendations for blood spot acquisition, transport, processing, and confirmation at the state public health program level which were approved at the April

2015 meeting [38]. The recommendations for timeliness in newborn screening are as follows:

1. Presumptive positive results for time-critical conditions should immediately be reported to the child's healthcare provider and no later than 5 days of life.
2. All presumptive positive results for time sensitive conditions should be reported to the healthcare provider as soon as possible but no later than 7 days of life.
3. All newborn screening results should be reported within 7 days of life (the "normal" screening results).
4. In order to achieve these goals (and reduce delays in newborn screening):
    - Initial newborn screening specimens should be collected in the appropriate time frame for the baby's condition but no later than 48 h after birth.
    - Newborn screening specimens should be received at the Laboratory as soon as possible; ideally within 24 h of collection.

19.4 Clinical Challenges of Newly Added Conditions

Once an infant has been identified as having a likely newborn screening condition on the basis of point-of-care testing (e.g., for hearing loss or CHD) or blood spot testing (all other conditions), the public health system enters a new phase: notification of the primary care physician or health care provider to arrange appropriate follow-up. In many cases, there may be a need for confirmatory laboratory testing or additional testing of the infant. For many health care providers in the primary care setting, this may be the first time that one of their patients has had a presumptive newborn screening condition, and the next steps may be daunting. Once notified of the result, the health care provider is expected to notify the parents of the infant's positive screen results, arrange confirmatory testing if required, and coordinate subspecialty referral. However, in one survey, over 50% of providers preferred that the laboratory provide the initial evaluation and didn't feel competent to help families navigate next steps [22]. To assist with this process, the ACMG has developed ACTion (ACT) sheets to provide management guidelines for each condition on the RUSP, including a short description of the disorder, the next actions to be taken, methods of confirmatory testing, clinical prognosis, and resources (which can be customized to include local resources) [28]. In addition, the Newborn Screening Clearinghouse is a user-friendly resource for parents and health professionals about newborn screening and living with the conditions as well as programs and policies in each state; this website is housed on BabysFirstTest, supported by a cooperative agreement from HRSA (http://babysfirsttest.org/).

The Newborn Screening Technical assistance and Evaluation Program (NewSTEPs), funded through a cooperative agreement to the Association of Public Health Laboratories (APHL) by the Genetic Services Branch of HRSA, provides quality improvement initiatives, a data repository, and technical resources for state newborn screening programs (https://www.newsteps.org/). The data repository

collects state profile information, which includes the disorders screened, the number of annual births, the program contact information and policies, and storage conditions and length of retention of dried blood spots for each state, as well as de-identified data on all positive cases identified. Case definitions for each condition on the RUSP are also a part of the resource, and quality indicators allow a state to compare how it is doing with regard to percent of dried blood spot specimens with complete information, percent of eligible newborns with valid newborn screening tests, and percent that are not lost to follow-up. Although the public can access the state profile information, the more detailed quality indicator data can only be accessed by the individual programs and used to develop state-specific reports that allow states to improve their programs by comparison with quality indicators that have been agreed upon by relevant stakeholders. Short term follow-up describes "the process of ensuring that all newborns are screened, that an appropriate follow-up caregiver is informed of results, that confirmatory testing has been completed, that the newborn has received a diagnosis and, if necessary, treatment" (https://www.newsteps.org/quality-practice-resources/short-term-follow). This resource is focusing on developing tools and best practices that allow states to follow-up invalid samples or out-of-range test results, or locate infants that are difficult to find.

19.5 Research Under the Auspices of the Hunter Kelly Newborn Screening Research Program

The Newborn Screening Saves Lives Act of 2007 included a number of provisions to expand newborn screening nationwide and one that specifically encouraged the expansion of newborn screening research. This legislation established the Hunter Kelly Research Program housed at the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD), within the NIH. The types of research that the legislation encouraged included:

1. The identification and development of new screening technologies in order to improve existing tests and expand the number of conditions for which screening tests are available.
2. Developing experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and or functional conditions that can be detected through newborn screening for which treatment is not yet available.

In the Newborn Screening Saves Lives Reauthorization Act of 2014, the types of research and responsibilities of the Hunter Kelly Research Program were expanded to include:

1. The provision of research findings and data for newborn conditions under review by the ACHDNC to be added to the RUSP.

2. Conducting pilot studies on condition recommended by the ACHDNC to ensure that screenings are ready for nationwide implementation.

In order to facilitate and provide infrastructure support for such a broad range of research that falls under the auspices of newborn screening research, the Newborn Screening Translational Research Network (NBSTRN) was established by NICHD through a contract awarded to the ACMG. The primary purposes of the NBSTRN is to provide an infrastructure for research that facilitates the development of new screening methods, clinical trials for new therapeutic interventions, and supports longitudinal research to study the long-term health of children identified through newborn screening (Fig. 19.4).

An example of a resource provided by the NBSTRN includes the Virtual Repository of Dried Blood Spots (VRDBS). The VRDBS is an open-source web-based tool that facilitates communication between researchers and state-based newborn screening programs. It permits investigators, with appropriate Institutional Review Board (IRB) permission and privacy protections, to access for research purposes the dried blood spots and other biological specimens that have been collected by state programs. Using the website tools, participating state program personnel can control and manage access to specimens for newborn screening related research. At this time, the system has data on over 3 million dried blood spots, while the spots themselves remain at their state of origin. (The VRDBS is compliant with regulations mandated by the Newborn Screening Saves Lives Reauthorization Act (H.R. 1281)).

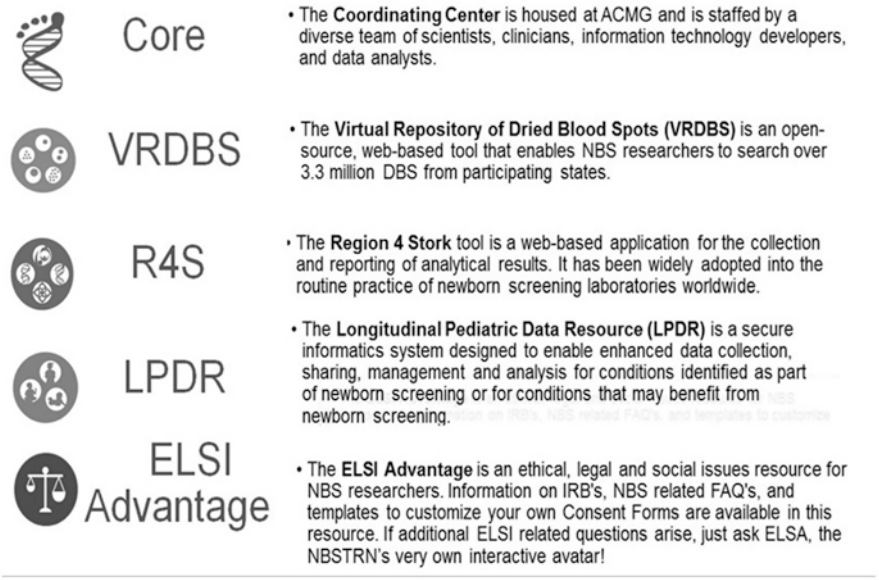

Fig. 19.4 Resources available through the NBSTRN
"Research Tools." Research Tools | Newborn Screening Translational Research Network (NBSTRN). NBSTRN/NICHD, 25 Apr. 2017. Web. 25 Apr. 2017

A second valuable resource within the NBSTRN is the R4S (Region 4 Stork, now CLIR, Collaborative Laboratory Integrated Reports). This resource began as a regional laboratory quality improvement project when newborn screening expanded to include tandem mass spectrometry (TMS) and has developed into an international resource with participants from 64 countries [16, 25]. It is important to emphasize that once a test is added to the RUSP, quality improvement is an ongoing process. As the number of babies screened for new or existing conditions increases and the results are compared, more accurate cutoff values can be established. By combining TMS data from 154 laboratories in 49 countries, including 767,464 results from 12,721 affected cases, R4S developed a multivariate pattern recognition software that that integrates multiple test results into a method to determine affected status that is much more robust than single analyte cutoff values; in Minnesota, R4S has allowed the state to reduce its false-positive rate below 0.1% and improve its positive predictive value to over 60% [24]. In another example, Hall and colleagues [16], in a retrospective evaluation, reviewed the outcomes of 176,186 newborn screening results in the state of California between Jan 1–June 30, 2012 and found that by using the R4S interpretive tools, second-tier tests, and other evidence-based interpretation rules, the false-positive results in the state could have been reduced by 90%, from 0.26% to 0.02%.

A third resource within the NBSTRN is the Longitudinal Pediatric Data Resource (LPDR). While there has been an emphasis on research to develop screening tools and treatments for disorders that can be identified by newborn screening, a comprehensive understanding of the natural history of specific disorders has rarely been available. This gap in knowledge weakens the ability to develop and measure the most effective treatments and interventions for infants and children identified via newborn screening, particularly as they age. The LPDR provides researchers with tools that enable longitudinal data collection of clinical and research information within a secure environment that provides permission-based access and data sharing.

The NBSTRN's LPDR has worked collaboratively with subject matter experts and the National Library of Medicine (NLM) in a national consensus-based process to identify standards-based, disease-specific datasets that would be useful in both clinical care and research efforts. The datasets are integrated into a set of data capture, data management, and data almanac tools that leverage the Research Electronic Data Capture (REDCap) system. The resource provides access to electronic case report forms (CRFs) and allows users to download updated paper CRFs. Through this flexible system, data can be collected as part of a standard clinic visit and entered into a centralized or institutionally-enabled REDCap instance for aggregation, management and analysis, with a future goal of electronic data entry at the time of the clinic visit. Both disease-specific electronic CRFs and disease-agnostic dataset are available. As of late 2016, the LPDR included 60 conditions with common data elements (CDEs), 48 conditions with subjects/cases, 292 users, and more than 1.1 million data points from 5548 individual subjects (165 with Krabbe disease, 3369 with sickle cell disease). The number of time points of data per case averages 4.6 and ranges from a minimum of 1 to a maximum of 32. Information

regarding the common data element sets available for individual conditions may be found at www.NBSTRN.org .

The fourth resource available through the NBSTRN is the ELSI Advantage. This tool provides researchers an aid to promote the inclusion of ethical, legal and social issues (ELSI) into the planning and implementation of their research. ELSI Advantage specifically helps investigators with issues related to IRB approval, informed consent, incidental findings, and the return of results to families. Consultations in planning projects, statistical supports, and provision of letters of support for research proposals are also available. Such supports have become increasingly valuable as newborn screening moves into an era of potential genomic testing.

19.6 Newborn Screening in the Genomic Era

Newborn screening, as it stands today, has limitations in the number of rare diseases that can be identified. There are currently over 7000 rare diseases that can be inherited, and newborn screening public health programs identify only a fraction of them. Genome sequencing technologies have advanced dramatically over the past decade, and the costs of collecting genome-level sequence data are falling below the costs of conducting some individual genetic tests or even panels of tests. Such innovations have led to the point where the prospect of conducting a comprehensive analysis of a person's entire genome rather than performing "one-off" tests of individual genes might soon be feasible and, perhaps, cost effective.

Noting these trends and recognizing that moving forward in this direction required careful and deliberate study, the National Human Genome Research Institute (NHGRI) and the NICHD partnered to establish a program to explore the feasibility of genomic screening in the newborn period. The two NIH institutes partnered to sponsor a workshop in 2010 attended by experts from academia, industry, and federal agencies in the fields of newborn screening and genomics to identify important factors to consider prior to implementing genomics in either the screening of newborns or newborn screening as part of public health programs:

- It is important to evaluate genomic data in newborns using newborn screening as a framework
- It is important to prioritize clinical validity and clinical utility, not just analytical validity
- It is important to address ethical, legal and social concerns

As a follow-up to the meeting, NICHD and NHGRI then funded the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program. The purpose of the research program has been to explore, in a limited but deliberate manner, the implications, challenges and opportunities associated with the possible use of genomic sequence information during the newborn period. The NSIGHT program consists of four teams: (1) Brigham and Women's Hospital/Boston Children's

Hospital/Baylor College of Medicine; (2) Children's Mercy Hospital, Kansas City/Rady Children's Hospital, San Diego; (3) University of California, San Francisco; and (4) University of North Carolina at Chapel Hill. The program has focused primarily on three areas:

1. Acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period;
2. Clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and
3. Research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns.

An overview of the NSIGHT program can be found in reference [3]. Each of the programs has a unique approach to the questions of sequencing newborns, with interests that range from sick newborns in the neonatal intensive care unit (NICU), to previously screen-positive newborns with a condition on the RUSP, and even healthy newborns. Advances derived from this research program include the rapid analysis of neonatal genomes. Sick infants in the NICU at Children's Mercy Hospital in Kansas City had whole genome sequencing and bioinformatics analysis leading to diagnosis within 50 h in some cases [33], allowing for a shortened differential diagnosis and a faster progression to genetic and prognostic counseling. This line of research has also stimulated a thoughtful and informed dialogue around the ELSI-related challenges of sequencing newborns in the newborn period. One group explored the psychosocial factors influencing parental interest in genomic sequencing of newborns and found that parents in the study expressed interest in the hypothetical possibility of genomic sequencing of their newborn (76.1%); however, the prior experience of the parents receiving worrisome health information and the level of parental stress were factors that ultimately diminished their enthusiasm [39]. The difficulties in return of results to families with healthy versus ill neonates pose interesting quandaries, as many of the potentially reportable variants have onset in adulthood, and the true likelihood that an asymptomatic infant will develop a given condition during his or her lifetime is often unknown [14, 26]. The program has also been successful in generating new resources to aid in newborn sequencing, and one of the groups has generated a curated list of genes for reporting results from genomic analysis in this unique population [10].

19.7 Prenatal and Carrier Screening

Although the focus of newborn screening has been on screening infants in the newborn period for potentially treatable conditions with otherwise devastating consequences, there has been interest in expansion of newborn screening programs into the prenatal period. However, the logistic challenges of coordinating such screening, which would need to be provided in a variety of health care settings, including obstetricians' offices, community health clinics, among others, coupled with the

technical requirements and cost of prenatal sampling of amniotic fluid (via amniocentesis) or placenta (via chorionic villus sampling) make this mechanism of prenatal screening untenable. However, the expanding availability of cell-free DNA analysis (also known as noninvasive prenatal screening or testing, NIPS or NIPT) from a maternal blood sample has been shown to dramatically improve the accuracy of prenatal screening for chromosomal aneuploidy conditions such as Down syndrome, especially in high-risk pregnant women [27]. However, the yield of screening for the monogenic disorders that underlie most newborn screening programs is likely to be much lower, and at this time, technically challenging [18].

Likewise, there is interest in but little agreement about offering widespread carrier testing to prospective parents or individuals of reproductive age. Consensus regarding which conditions should be the focus of carrier screening is also difficult to achieve, and in some cases may be predicated by the predominant socioeconomic and religious groups in a region or state, as the carrier rate for some conditions are likely to be higher in populations where they are known to be concentrated. Already, many newborn screening programs will identify carriers for conditions where the levels of the analyte being tested are lower than in the healthy non-carrier population but higher than in affected individuals who carry two aberrant copies of a recessive gene. Another disorder often reported is the carrier status for sickle cell disease, which is typically known as sickle cell "trait." Controversy erupted in 2010 when the National Collegiate Athletic Association (NCAA) mandated that all Division I student-athletes be tested for sickle cell trait so that training regimens could be tailored to avoid exercise- and/or heat-related acute illness or death due to excessive exertion and/or dehydration in those with this hemoglobin trait. The ACHDNC issued a briefing paper that recommended against routine testing in the college setting given the lack of scientific evidence that adequately showed causation (most cases are anecdotal) and the not-insignificant risk of stigma associated with identification of a genetic trait in those of predominantly African-American descent [19]. Other professional societies have agreed with the ACHDNC and have concurred with the recommendation that any testing and counseling regarding sickle cell trait carrier status be performed in a medical setting and that universal precautions to prevent dehydration and rhabdomyolysis in student athletes be adopted regardless of trait status and ethnicity [37].

19.8 Conclusion

As newborn screening programs have evolved over the past 5 decades, the original "PKU test" has now expanded to test for conditions that affect approximately 1 in 25 newborns, or 4% of the 4 million births in the U.S. each year. A coordinated system of newborn screening with remarkable uptake by the different state laboratories within the United States now exists. These public health programs are state-based, yet have been quite nimble in adopting the original federally-developed RUSP and newer conditions that it encompasses, which in turn helps reduce

disparities in access to timely diagnosis and ultimately, life-saving treatments across the different regions of the country. In spite of the absence of a federal mandate for specifying the tests required for each state to screen, policies of the ACHDNC have been developed, emphasizing a formal, evidence-based process for adding conditions to a *recommended* panel, which has proven to be remarkably effective. As additional treatments for rare and common conditions that impact infants become available, there may be improved health outcome studies that can promote care throughout the lifespan, and facilitate therapeutic interventions for conditions of childhood or adult onset. The rapid pace of research, especially within the genomics realm, may allow for an expansion of diagnosable conditions, extension of screening to earlier or later time points in childhood, and potentially effective prenatal and/or carrier screening. The interrelationships among these newborn screening resources can help facilitate progress in all of these domains. The next 50 years will surely see exciting developments in newborn screening, well beyond the bloodspot.

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Part VII
New Research Perspectives in RD

Chapter 20
A Global Approach to Rare Diseases Research and Orphan Products Development: The International Rare Diseases Research Consortium (IRDiRC)

Christine M. Cutillo, Christopher P. Austin, and Stephen C. Groft

Abstract Rare diseases present unique challenges to researchers due to the global distribution of patients, complexity and low prevalence of each disease, and limited availability of data. They are also overwhelming and costly for patients, their families, communities, and society. As such, global integration of rare diseases research is necessary to accelerate the understanding, diagnosis, and treatment of rare disorders. The International Rare Diseases Research Consortium (IRDiRC) was born out of that need for a coordinated international community. IRDiRC was launched in 2011 to facilitate cooperation and collaboration on a global scale among the many stakeholders active in rare diseases research to stimulate better coordination, and thereby maximize output of rare diseases research efforts around the world. Members include funders, academic researchers, companies, and patient advocacy organizations all of whom share the common goals and principles of IRDiRC. The overarching objectives of the Consortium are to contribute to the development of 200 new therapies and a means to diagnose most rare diseases, by 2020. As IRDiRC approaches the end of its fifth year, these initial objectives have been largely achieved and new partners from across the globe are joining. This presents the Consortium with the exciting opportunity to set new and even more ambitious goals for the next phase with the ultimate goal of improved health through faster and better diagnostic capabilities and novel therapies for people living with rare diseases and conditions throughout the world.

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20.1 Introduction

Rare diseases are widespread – there are an estimated 5000–8000 rare diseases (RD) that affect approximately 400 million people worldwide [6]. They are difficult to assess in aggregate because of the large number and diversity of rare disorders, the complexity of each disease, small patient populations, and the limited availability of data. Because of their rarity and phenotypic variability, many RDs are difficult to diagnose. They are often medically devastating and lack effective treatments, leading to lifelong complications and disabilities that require multi-specialist care from multiple institutions.

National government research organizations, individual research investigators and networks, and biopharmaceutical and medical device companies have been studying RDs for several decades with varying levels of coordination and collaboration among themselves and with the patient advocacy community. RD research has remained fragmented due to the large number of RDs, the extreme heterogeneity of expression, the global distribution of patients, and the lack of research resources adequate to the scope of the problem. There is not even an agreed-upon total number of RDs, despite numerous efforts.

These dynamics have led to the realization that collaboration of unprecedented depth and scale is needed to accelerate the understanding, diagnosis, and treatment of rare disorders. Complementing national and regional efforts, the International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 to foster global research collaboration and investment in the field of RD research. The purpose of IRDiRC is to facilitate cooperation and collaboration at the international level, to stimulate better coordination, and thereby maximize output of RD research efforts around the world. IRDiRC fosters collaboration between public and private sector organizations, and among constituencies and stakeholders, all of whom are active supporters of RD research. Each of the funding body members (comprised of government, non-profit organizations, and companies) spends at least $10 million US dollars over a 5-year period on RD research. Other funding organizations can also form a group of funders that together reach the $10 million threshold and join the collaborative efforts. Umbrella patient advocacy organizations – for example, EURORDIS,[1] the Genetic Alliance,[2] and the US National Organization for Rare Disorders (NORD)[3] – who represent groups of patient organizations, are also encouraged to join the Consortium. All members share the common goals and

[1] http://www.eurordis.org/

[2] http://www.geneticalliance.org/

[3] https://rarediseases.org/

principles of IRDiRC and have agreed to work in a coordinated and collaborative manner within the multinational Consortium, but they each support their own programs and projects through their current funding mechanisms of contracts, grants, or cooperative agreements. All of the funded research projects adhere to a common framework and set of principles. Current members are from Europe, North America, Asia, Australia, and the Middle East.

IRDiRC aims to facilitate the achievement of two overarching objectives by the year 2020: to contribute to the development of 200 new therapies and the means to diagnose most RDs. The key outcome of this work will be improved health through faster and better diagnostic capabilities and novel therapies for people living with RDs and conditions throughout the world.

20.2 History of IRDiRC

In October 2010, the Directorate General of Research for the European Commission (EC)[4] and the Director of the US National Institutes of Health (NIH)[5] announced their intention to focus on RD research. At the first preparatory workshop in Reykjavík, Iceland, the two institutions planned to coordinate their research funding on RD and to make major investments in the research field. Several challenges and needs were identified during this initial conference: (1) establish and provide access to harmonized clinical data and bio-specimen samples from numerous sources; (2) elucidate the molecular and clinical characterization of all RD; (3) expand the preclinical, clinical, and translational research efforts leading to more approved diagnostics and therapeutics for the prevention, diagnosis, and treatment of RDs and conditions; and (4) address and streamline the ethical and regulatory procedures and practices. During the course of the Reykjavík workshop, it became clear that the success of the initiative would be dependent on the integration of the activities of funding agencies, academic research investigators, biopharmaceutical, medical device and diagnostics companies, regulatory agencies, and patient advocacy groups. As such, membership of IRDiRC was expanded to include academic researchers, companies, and patient advocacy organizations [8] (Fig. 20.1).

IRDiRC was officially established and launched during a second workshop at the US NIH in Bethesda, U.S.A. in April 2011 [9]. The group of funding agency representatives agreed to form an Executive Committee of representative members (now named the Consortium Assembly). The group chose Dr. Ruxandra Draghia-Akli from the EC as the Consortium Chair. Seven breakout sessions were held to stimulate discussions on the various policy issues receiving consideration and working groups were formed around key areas: (1) understanding the pathophysiology of RDs – genomics analyses; (2) understanding the pathophysiology of RDs – animal models and *in vitro* systems; (3) development and use of ontologies; (4) development

[4] http://ec.europa.eu/research/index.cfm?pg=dg

[5] https://www.nih.gov/

Fig. 20.1 Participants from the first preparatory workshop on fostering transatlantic cooperation in research into rare diseases in Reykjavík, Iceland

and use of natural history studies; (5) development and use of validated biomarkers for clinical trials; (6) patient registries and bio-specimen repositories; (7) preclinical research and clinical trials; (7) communication of the consortium, intellectual property rights, and data sharing policies; and (8) developing and disseminating information on RDs. The working groups were tasked with developing the policies and drafting up the policy documents around each area that would guide IRDiRC in its activities.

A third IRDiRC workshop held in Montréal, Canada in October 2011 gathered over 100 participants representing public and private funding organizations, scientists, regulators, industry, and patient groups. It focused on continuous efforts to develop common scientific and policy frameworks to guide the activities of the participating IRDiRC members. In the following months, the Scientific Committees were formed around overarching scientific areas: (1) Diagnostics; (2) Interdisciplinary; and (3) Therapies. These committees were formed to: (1) advise the Consortium Assembly on research priorities, progress, and emerging issues; (2) encourage the exchange of protocols and best practices; (3) agree on standard operating procedures, quality standards, and a roadmap to reach IRDiRC goals; and (4) identify projects and contribute to their implementation all within their scientific area.

In September 2012, Dr. Paul Lasko, Scientific Director of the Canadian Institutes of Health Research (CIHR) Institute of Genetics,[6] was selected to take over from Dr. Draghia-Akli as Chair of the Consortium Assembly, starting in 2013. Subsequently, the European Commission developed the SUPPORT-IRDiRC[7] contract mechanism to reinforce coordination via organizational and communication support to IRDiRC and its members. The contract was awarded to the French Institute of Health and Medical Research (INSERM, US14)[8] in October 2012 and enabled the creation of the Scientific Secretariat, a small group of coordinators, project managers, and communication managers dedicated to the IRDiRC mission. The Scientific Secretariat supports cooperation and coordination between and amongst all members, establishes standard policies and guidelines aimed at accelerating RD research, and thereby contributes to the timely achievement of IRDiRC goals.

The first IRDiRC scientific conference took place in Dublin, Ireland in April 2013, organized by the European Commission, and attended by more than 400 participants. Researchers, clinicians, patient groups and representatives of public and private organizations met to assess the work of the 3-year old consortium and officially hand-over chairmanship [7]. In November 2014, the second IRDiRC Conference was organized by IRDiRC and BGI[9] in Shenzhen, China. Over 600 participants attended the conference, which provided the opportunity for Chinese and international stakeholders active in the field of RD research to forge links.[10] The third IRDiRC Conference is planned for February 2017 in Paris, France.[11]

Beginning in March 2015, Task Forces were established to tackle specific time-limited topics identified by the Scientific Committees as important to advancing IRDiRC goals. Current Task Forces include: Matchmaker Exchange (joint effort with Global Alliance for Genomics and Health (GA4GH)[12]), Automatable Discovery and Access (joint effort with GA4GH), Privacy-Preserving Record Linkage (joint effort with GA4GH), Patient-Centered Outcome Measures, Small Population Clinical Trials, International Consortium of Human Phenotype Terminologies, and Data Mining and Repurposing. Task Forces are formed as new areas of focus and need are identified and are comprised of mostly external subject-matter experts in addition to IRDiRC representative members. In the fall of 2015, an Operating Committee was implemented to manage the preparation and advancement of IRDiRC activities, process information, and enable more effective management of the Consortium.

In December 2015, Dr. Christopher P. Austin, Director of the National Center for Advancing Translational Sciences, US National Institutes of Health (NCATS, NIH),[13] was selected as the next Chair of the Consortium Assembly, starting in

[6] http://www.cihr-irsc.gc.ca/e/193.html

[7] http://www.irdirc.org/support/index.html

[8] http://english.inserm.fr/

[9] http://www.bgi.com/us/

[10] http://www.irdirc.org/second-irdirc-conference-shenzhen/

[11] http://irdirc-conference.org/

[12] http://genomicsandhealth.org/

[13] https://ncats.nih.gov/

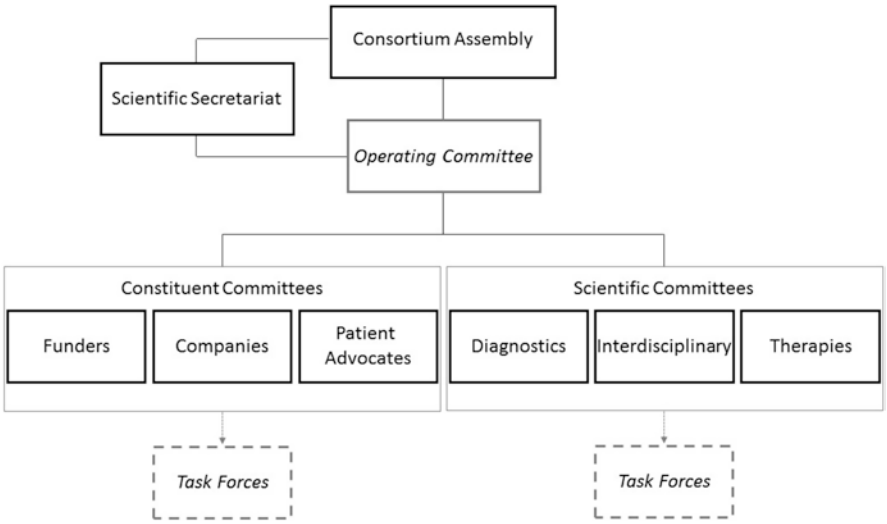

Fig. 20.2 International Rare Diseases Research Consortium (IRDiRC) governance structure

2016. IRDiRC had experienced substantial growth in its membership and activities from 2010–2016. To adapt to the growth in size and diversity of its members and functions, the Executive Committee was renamed the Consortium Assembly in the spring of 2016 to more accurately reflect its function as a gathering of all the Consortium's members, focused on information exchange and efforts to develop and coordinate scientific and policy efforts that aim to advance IRDiRC goals. In addition, three Constituent Committees were formed around the three major stakeholders of the Consortium: (1) Funders, (2) Companies, and (3) Patient Advocates. These groups work to coordinate activities, identify roadblocks to progress, and designate priorities in their respective constituent space, all to contribute to IRDiRC goals (Fig. 20.2).

20.3 Collaborative Models

It is important to note that no funds are available through IRDiRC itself to support RD research. All of the funding agency members support basic, clinical, and translational research projects in the RD realm. The mission of IRDiRC is to encourage coordination and collaboration, minimize duplication, and promote the sharing of resources, research infrastructure, and experiences within the RD research community. Therefore, by enabling research coordination and development of scientific and operational best practices, IRDiRC pushes the field of RD research forward.

20.4 Policies and Guidelines Applied to IRDiRC Activities

Much of IRDiRC's work is focused on strengthening international cooperation to enable exponential progress in the field of RD research. Coordination of efforts and avoidance of unintended duplication are key to maximizing the aggregate impact of global investments in RD research and accelerating progress in:

- International sharing of information, data, and samples
- Best practices in clinical/care for RD patients
- Mechanisms to decrease duration of the "diagnostic odyssey"
- Platforms for facile establishment of registries and natural history for RDs
- Strengthened links between academia and industry, so that industry can better capitalize on academic research results
- Understanding common molecular or pathogenic pathways across diseases to provide therapeutic approaches applicable to multiple RDs [4]
- Application of small patient population approaches developed for RD to personalized medicine
- Comprehensive RD enumeration and classification, utilizing standard terms of reference and common ontologies
- Harmonized regulatory requirements across countries
- Creation of links among teams working on similar issues to provide improved sharing of resources and to reduce redundancy

To guide its work toward these goals, IRDiRC developed Consortium Policies and Guidelines. A **consortium policy** is a principle which Consortium members agree to follow. **Consortium guidelines** refer to recommendations made by IRDiRC Scientific Committees, Working Groups, and Task Forces that offer advice as to "best practices" at a given time. A summary of those principles and guidelines is presented here [11, 15].

- **Generalized Principles –** Much of RD research is currently fragmented and compartmentalized. This leads to a lack of integration, duplication of efforts, and thinking in "silos", all of which hinder progress toward better diagnosis and therapy for RD patients. Different regulatory, legal, and ethical systems can be barriers to collaboration, as well. Small patient numbers and lack of clinical outcomes that are generally accepted and relevant to regulations pose particular difficulties to clinical trials for RD. There is an urgent need for sharing approaches that will enhance the development of better diagnoses and therapies. Such integration requires the direct involvement of all stakeholders including, but not limited to patients and members of the patient advocacy community, health care providers, academic research scientists, pharmaceutical industry members, and regulatory professionals. Patient involvement is particularly integral to the planning and development of the research plan, informed consent documents, and understanding the impact of research on people living with RD. It is essential to recognize and address the needs of all these stakeholders with the key outcome

of improved health through better diagnosis and therapies for people living with RD worldwide.

- **Policies**
  - **Policy 1:** RD research should be collaborative. Resources, data, and results should be shared among IRDiRC research projects and made publicly available to the broader community, and duplication should be avoided.
  - **Policy 2:** RD research should involve patients and/or their representatives in all relevant aspects of the research.
  - **Policy 3:** International, national, regional, and local legislation/regulations need to be adhered to with respect to data protection and ethical approvals.
- **Guidelines**
  - **Guideline 1:** The impact of research on people living with RD should be a key consideration for each project. Best ethical practices for ensuring the interest of the individuals living with RD should be applied.
  - **Guideline 2:** Information about IRDiRC and associated research projects should be disseminated and made available to the RD communities and the public.
  - **Guideline 3:** Education, training, and awareness of stakeholders should be encouraged by IRDiRC.

- **Data Sharing and Standards –** To achieve the goals of IRDiRC, integration and analysis of data from multiple sources is essential. Such data and resources include: patient and family material (extracted DNA, cell lines, pathological samples), technical protocols, informatics infrastructure and analysis tools, phenotypes, genomic variants, other 'omic' data (including transcriptomic, metabolomic, biomarkers), natural histories, and clinical trial data. It is critical to the overall success of IRDiRC that datasets obtained from one project be directly comparable to datasets obtained from another project, even if generated using a different approach or technology. The process of information retrieval and analysis could also be greatly accelerated if different databases used a single set of standards for collecting, storing, annotating, and communicating data. Data producers and funding agencies also acknowledge their role in performing and facilitating rapid data release of initial analyses or when significant findings (either positive or negative) become known. Timely publication and sustainability of datasets are a high priority to IRDiRC.
  - **Policies**
    - **Policy 4:** Research projects should adhere to standards endorsed by IRDiRC.
    - **Policy 5:** Data producers acknowledge their responsibilities to release data rapidly and to publish initial analyses in a timely manner. IRDiRC members will encourage and facilitate rapid data release.

- **Guidelines**
  - **Guideline 4:** Data generated from research projects, including source data, should be deposited in appropriate open or controlled access public databases.

- **Ontologies –** Ontologies are structured, automated representations of knowledge and provide computer-readable classifications of the entities within a domain and their relationships to one another. They are increasingly being used to define standards, controlled vocabularies for different fields in science and medicine, and are utilized for data integration, harmonization, organization, searching, and analysis. To be successful, an ontology must be widely used with appropriate annotation of data. Multiple ontologies are required to describe all relevant aspects of the field of RD. Two of the most applicable kinds of ontologies to RD clinical research and medicine are ontologies of phenotypic features (signs, symptoms, and findings of diseases) and ontologies of diseases and disease groups (nosologies). Additional ontologies and standards are required for other areas of RD research, including standards for mutation nomenclature and reporting of diagnostic results, ontologies and standards to support biobanking, clinical trials, natural history studies, laboratory values and bioimaging results, and RD medications and treatments. It is important that ontologies be interoperable; this is best achieved if there is minimal overlap in the concepts covered by the ontologies (orthogonality) and if the ontologies are semantically compatible with one another. To achieve broad use, the developers and managers of RD ontologies must be responsive to the community and must strive to reflect community needs and norms. IRDiRC aims to facilitate integration and interoperability across different ontologies, thereby facilitating diagnosis, clinical use, and optimal treatment regimen.
  - **Policies**
    - **Policy 6:** IRDiRC members will promote the harmonization, interoperability and open access of ontologies to be applied to databases, registries, and biobanks.
  - **Guidelines**
    - **Guideline 5:** Ontologies utilized by RD research projects should build upon existing best practice and allow integration and interoperability across different ontologies, including those for model organisms. Ontologies should include a RD classification ontology (nosology), a phenotype ontology with comprehensive coverage of RD manifestations including laboratory values and imaging, as well as ontologies to support biobanking, clinical trials, and research.

- **Diagnostics –** An accurate molecular diagnosis is essential for informed patient management and family counseling, as well as for RD research including natural history studies, biomarker identification, collection of information from patient

registries, and clinical trials. There are approximately 8000 RDs [6] and the relevant gene is known for only about 4500 of these diseases [16], thus around 3500 are without a defined molecular pathogenesis. In addition, a significant fraction of RD patients that have a defined molecular pathogenesis lack a molecular diagnosis due to issues related to accessibility of diagnostic testing. To meet the stated goals, IRDiRC continues to focus on the discovery of genes for the 3500 phenotypes that are currently without an associated disease gene. As data continues to be generated from different sources, we are gaining the ability to interpret genomic variation. A genotype-phenotype database that collects and curates information on all variants causing specific human disease phenotypes is essential to the provision of accurate and reliable diagnostics for RD. International efforts to establish guidelines for the clinical reporting of genomic sequencing in a clinical setting, including the approach to incidental findings, will expedite the delivery of high-throughput and cost-effective testing to the RD patient community as a whole. IRDiRC activities enable the discovery of all the genes that underlie RD and facilitate the development of diagnostic testing for all RD. IRDiRC supports the establishment and maintenance of a well-curated list of all RDs maintained by organizations such as Orphanet[14] and the Genetic and Rare Diseases Information Center.[15]

- **Policies**
  - **Policy 7:** IRDiRC members should promote the discovery of all the genes that underlie RD and facilitate the development of diagnostic testing for most RD.
  - **Policy 8:** Research projects should contribute to the development and evolution of standards for RD diagnostic testing and reporting.
- **Guidelines**
  - **Guideline 6:** Research projects should coordinate with existing efforts to produce a well-curated and interoperable inventory of RD.

- **Biomarkers –** A biomarker is a measureable biological characteristic that is an indicator of normal biological and pathogenic processes and/or response to therapeutic or other interventions. Biomarkers are central to the future of medicine. They can be used to monitor the effects of medical interventions including therapeutic responses in diagnostic and prognostic tests, and can better contribute to defining the target population more likely to respond to a particular therapy. They are usually linked to changes in particular aspects of a complex biological system. However, it should be emphasized that using biomarkers in biomedical research has several limitations as they may or may not be correlated with clinical outcomes. The work needed to understand the relationship of biomarker changes to either a clinical outcome or other aspects of a biological system is

[14] http://www.orpha.net/consor/cgi-bin/index.php

[15] https://rarediseases.info.nih.gov/

often substantial. For regulatory purposes, it is essential to differentiate treatment effects from the natural course of a disease during the lifespan. Therefore, early dialogue with regulatory authorities is essential and will facilitate successful biomarker qualification and regulation resulting in a speedier completion of product development, clinical trials, and regulatory review.

- **Policies**
  - **Policy 9:** Research projects should establish criteria and standards for evaluation, qualification, and validation of biomarkers.
- **Guidelines**
  - **Guideline 7:** The use of biomarkers in RD therapeutic development should be discussed and agreed with regulatory authorities through established procedures.

- **Patient Registries –** Patient registries are organized databases where patient information, including demographic, medical, and family history information are collected, stored, and available for retrieval via standardized and secure methods. Patient registries are increasingly recognized as crucial tools for RD research. They have been found useful in identifying research hypotheses, recruiting for participation in natural history studies and other clinical trials, identification of different phenotypes and genotypes, determining clinical endpoints or biomarkers, monitoring the pathogenesis of a disorder over a lifespan, and supporting the safety and efficacy evaluation of potential therapies. For most RD, no single institution, and in many cases no single country, has sufficient numbers of patients and resources to recruit adequate cohorts of patients to conduct clinical and translational research. Identifying patients with specific genotypes and phenotypes is a major constraint to patient recruitment into research and clinical trials. Patient registries are often used as part of regulatory decisions and post-marketing surveillance requirements. In addition, they may play an important role in identifying best clinical practices and providing health care to RD patients in the context of reference and specialist networks. To meet the full potential of patient registries, there remains a clear need for their standardization, coordination, and further development. In particular, patient registries must overcome the following challenges to develop their full potential in RD research: (a) lack of harmonization due to the high variability among registries according to RD coding systems, geographical coverage, and type of data collected; (b) lack of data sharing since only a minority share data with other databases, biobanks or centers of expertise; (c) lack of sustainability since RD patient registries often expire due to lack of commitment from data providers, lack of funding, or study termination, leading to loss of data and investment; and, (d) lack of utility for research owing to absence of quality control, standardized data elements, and genetic data.

- **Policies**
  - **Policy 10:** RD patient registries should aim to be global in geographic scope and practice. Interoperability and harmonization between RD patient registries should be consistently pursued. Linking to and data transfer into existing platforms should be considered "best practice". Registries should be broad and not focused exclusively around a single therapeutic intervention or product.
- **Guidelines**
  - **Guideline 8:** RD patient registries should be linked with data and biological specimens in biobanks, natural history studies and clinical trials and should include measures of quality control and updating.
  - **Guideline 9:** Patients and/or their representatives should be involved in the governance of RD registries.

- **Biobanks –** Biobanks are collections of biomaterials with associated data. Biobanking is an essential tool to provide access to high quality human biomaterial and data for fundamental and translational research. RD research benefits from the provision of human biomaterials through biobanks, and each human sample from a person with RD has a high value as it may hold the key to answering an important research question. The rarity and diversity of RDs and their associated biomaterials present specific challenges and opportunities for biobanking, requiring transnational collaboration and harmonization. Legacy samples, small collections, or even individual samples may be extremely precious for RD research. Such samples include primary cell, tissue, DNA, RNA, serum, urine, CSF, human induced pluripotent stem cell (hiPSC) lines, and others. Collection, storage, and dissemination of biomaterials often requires specialist input and appropriate quality standards. RD biobanks rely on the active participation of patients and patient organizations. Providing and managing information and access to valuable biological samples through a simple and reliable process is crucial for RD research. It underpins the development of new diagnostic techniques, biomarker development, identification of potential therapeutic targets and testing therapeutic response. Biobanks are important tools for RD research and as such, there remains a clear need for policy interoperability, standardization, coordination, and further development of RD biobanks. Biobanks need to overcome the following challenges to develop their full potential in RD research: (a) lack of policy and IT harmonization; (b) lack of biomaterial and data sharing; (c) lack of sustainability; and, (d) lack of utility for research.
  - **Policies**
    - **Policy 11**: RD biobanks should aim to be global in geographic scope and **practice**. Interoperability and harmonization between RD biobanks should be consistently pursued. Linking to and data transfer into existing platforms should be considered "best practice". Sharing and distributing of biomaterials among RD biobanks is highly encouraged.

- **Guidelines**
  - **Guideline 10:** RD biobanks are essential resources and should be sustainable. RD research studies should utilize biobanks for processing and storage of biomaterials and should include methods of quality control and updating.
  - **Guideline 11:** Patients and/or their representatives should be involved in the governance of RD biobanks

- **Natural History –** Understanding the natural history and evolution of a disease is an essential step not only in drug development, but also in better understanding the needs of patients and in care improvement. The pathogenesis, clinical manifestations, natural evolution and prognosis of many RDs are still poorly or incompletely understood. Performing natural history studies will facilitate the identification of disease characteristics that can be used when planning and conducting clinical investigations for RD therapies. Moreover, this knowledge will serve to define a trial's target population, develop biomarkers for disease progression and therapeutic response, determine appropriate surrogate and relevant clinical endpoints, and determine study duration. Ideally, natural history studies should be global in scope and can involve patients at any age although it is recommended to include younger patients. It is well recognized that RDs are highly diverse in nature and that there is no one set of data elements that can be recommended for data collection in all natural history RD studies; rather the disease characteristics should reflect the prominent features of the RD.
  - **Policies**
    - **Policy 12:** Research projects should contribute to the development and evolution of a set of standards for RD natural history studies. The outcomes of natural history studies should be considered in the design of clinical research.
  - **Guidelines**
    - **Guideline 12:** Patients and/or their representatives should be involved in defining the objectives, design, outreach, and analysis of clinical research and natural history studies.

- **Therapeutics –** Orphan designation procedures have brought a large number of investigational products into the development pipeline. Incentives associated with orphan designation play a major role in stimulating orphan product research and can be beneficial to industry-sponsored and investigator-driven clinical research. Recently PhRMA indicated there are 650 compounds in active investigation as orphan products [17]. Combined efforts are required of investigators, industry, patient representatives, research institutions, and regulatory authorities to overcome bottlenecks associated with biomedical research in low-prevalence conditions. Clinical trials on RDs represent a major challenge for the development of RD therapies intended to treat, cure, prevent or diagnose patients affected

by a RD. Small patient populations, together with geographical dispersion add additional complexity to the design and performance of trials aimed at providing efficacy and safety information to support marketing authorization and approval of these therapies. Delays in obtaining proper genetic and clinical diagnoses still exist for many RDs. In addition, there is still a lack of adequate epidemiological and medical knowledge on the natural history of many RD. The design and specific methodological aspects of a study need to be carefully discussed with all relevant partners. Training of investigators and patient representatives will ensure a better understanding of regulatory, methodological, and ethical requirements. Equally, adequate support should be given to existing infrastructures for clinical research, which take into account the intrinsic characteristics of rarity and may develop common and harmonized practices to submit, monitor and report multicenter and multinational rare disease clinical trials.

- **Policies**
  - **Policy 13:** IRDiRC members will encourage the development of therapies that could be approved by 2020, while respecting each funding entity's strategic research agenda (including products with an existing orphan designation, the repurposing of already marketed drugs, or funding preclinical orphan development intended to substantiate proof-of-concept).
- **Guidelines**
  - **Guideline 13:** Clinical investigations supported by IRDiRC funders should meet requirements set by regulatory agencies.
  - **Guideline 14:** Adequate scientific and regulatory information about **clinical** research should be exchanged by researchers.
  - **Guideline 15:** IRDiRC members should promote collaborative multinational studies, with common study procedures and harmonized policies for regulatory and ethical requirements.

- **Models –** Cellular models provide insight into the function of genes and the mechanisms underlying rare diseases. Experimental organisms such as yeast, *C. elegans*, fruit flies, zebrafish, and mice have long been critical for uncovering the molecular mechanisms fundamental to life, thereby providing a shortcut to understanding human biology. Currently, we only understand the biological function of a fraction of human genes. Cellular systems and model organisms can be manipulated experimentally much more readily than humans for both ethical and technical reasons, allowing important questions that cannot be addressed in patients to be addressed. Model organisms enable experimental interventions that can establish causal mechanisms of gene action, thereby putting disease genes into biological context. The generation of analogous mutations in a model organism or the substitution of a wild-type version of the gene with the human variant can provide a clear indication that the suspected variant is indeed causative for disease. The deep pathological insight that model organisms can yield facilitates the development of targeted

therapeutics. Lastly, studies of therapeutic interventions require model systems to demonstrate efficacy and identify potentially harmful effects. Global coordination of model organism research is important to ensure that pre-clinical studies based on validated animal models are robust, reproducible, and sufficiently powered in multiple models to provide evidence of efficacy prior to proceeding to clinical trials.

- **Policies**
  - **Policy 14:** IRDiRC members should promote coordination between human and model systems research in RD.
- **Guidelines**
  - **Guideline 16:** Prior to proceeding to clinical trials, experimentation **providing** multiple lines of evidence should be robust, reproducible and sufficiently powered.

- **Publication and Intellectual Property –** IRDiRC research results should be rapidly shared and made highly visible to the scientific, health care, patient and pharmaceutical communities. Their utility must be clearly demonstrated and potential users must have the opportunity to receive training in the techniques and tools developed. This includes negative results, which can be as important for the RD field as new scientific breakthroughs. A high level of visibility in scientific meetings and through scientific publications is necessary. The scientific impact of IRDiRC research projects should be maximized by pursuing opportunities for publication. Publications in lay journals may be prepared in order to attract maximum attention to RDs. Funders should encourage open access and provide resources for publication fees when required to ensure public access. Publication does not negate the need to share full data sets and data not used in publications. Data from pre-clinical research and clinical trials should be made available in publicly accessible repositories, such as ClinicalTrials.gov, for the RD community. Intellectual Property (IP) is an important factor for the public and the private sector, in particular to cover the significant cost of developing new therapies. Issues related to IP rights need to be assessed and handled in accordance with fundamental ethical rules and principles. Tools to handle IP issues may include exploitation and technological implementation plans, non-exclusive licensing, patenting, knowledge property rights and pre-existing know-how. In many instances, confidentiality agreements may be required between the parties involved. IRDiRC adheres to the principle that research outcomes should be freely accessible under non-exclusive licenses to the research and patient community.
  - **Policies**
    - **Policy 15:** Research projects should publish their results in a timely manner in peer-reviewed scientific journals, preferably with open access.

- **Guidelines**
  - **Guideline 17:** Research publications should appropriately acknowledge research funding and the use of infrastructures such as biobanks and registries, as well as the contribution of patients and their representatives.
  - **Guideline 18:** IP issues and confidentiality agreements need to be balanced with the need to share information for the benefit of research and the patient community.
  - **Guideline 19:** RD research should be published even where its outcomes are **negative** or do not show convincing results, including clinical trials.

- **Communication on IRDiRC –** Through research projects, IRDiRC will facilitate the generation of new knowledge, tools and resources and stimulate debate. Its outputs require high visibility to a range of stakeholders and a clear strategy to train and educate a next generation of scientists and other users. Target groups include the global scientific community both within and outside the RD field, professionals involved in healthcare including diagnostics and the delivery of new therapies, policymakers involved in health care planning at national and international levels, the pharmaceutical industry, and the RD patient communities. In addition, there is a strong imperative to raise awareness of this area with the general public and increase its profile in the media. The goals of an external dissemination strategy are to promote international academic and industrial cross-fertilization, both within and outside IRDiRC, and to provide information on IRDiRC research to other research projects, the scientific community, industrial groups, government bodies, policymakers and the general public, including patients. IRDiRC communication will be built on the principles of openness, public accessibility, transparency, inclusivity and timeliness. IRDiRC will communicate through various means, in particular through electronic communications and the internet as well as paper-based versions.
  - **Policies**
    - **Policy 16:** IRDiRC members will disseminate relevant information on their research project portfolio through adequate and timely measures, in particular via the IRDiRC website.
  - **Guidelines**
    - **Guideline 20:** IRDiRC shall publish its mission statem ent, list of member organizations and list of associated projects. IRDiRC shall publish non-confidential proceedings, as well as the minutes and approved documents of its Consortium Assembly, the Scientific Committees, the Working Groups, and the Task Forces.
    - **Guideline 21:** IRDiRC associated projects and IRDiRC member organizations should make reference to IRDiRC, where appropriate, on organizational websites, information material, and presentations.
    - **Guideline 22:** IRDiRC will promote active exchanges, events and activities between stakeholders, including patient organizations.

20.5 Areas of Emphasis – Scientific Committees and Task Forces

The members of IRDiRC support research projects that contribute to the Consortium objectives and goals. These projects have strong translational potential and are frequently international in scope, not always covered by national initiatives. IRDiRC had several Working Groups in the past, e.g. on registries and bioinformatics. The Working Groups were replaced by the Scientific Committees around overarching scientific areas and ***ad hoc*** Task Forces for specific topics. The Scientific Committees advise the Consortium Assembly on research priorities and progress, encourage exchange of best practices, and agree on procedures to reach IRDiRC goals in their scientific area. The Task Forces are time-limited and tackle specific topics identified by the Scientific Committees as important to advancing IRDiRC goals. They have an anticipated period of activity of around 1–1.5 years to enable active deliberation and recommendation formation. Below is a snapshot of the current Scientific Committees and Task Forces.

The **Diagnostics Scientific Committee** advises on research related to the diagnoses of RD.

- Current Chairmanship
  - Kym Boycott (Chair): Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Canada
  - Gareth Baynam (Vice-Chair): Genetic Services of Western Australia, King Edward Memorial Hospital & Western Australian Register of Developmental Anomalies, Australia
- Task Forces
  - **Matchmaker Exchange (MME)** – Due to the need for data sharing in the RD community to uncover causes of disease within the genome, MME is a federated network connecting databases of genotypes and rare phenotypes using a common application programming interface. The MME Task Force is a joint IRDiRC and Global Alliance for Genomics and Health (GA4GH)[16] effort that aims to provide data sharing tools for clinical geneticists to match unsolved genome and exome sequence cases. It also aims to ensure optimal collaboration between projects contributing to the interpretation of variants of matching phenotypes and variants. As the MME network grows, additional databases that support internal matching will join the effort. A special issue of Human Mutation was published in October 2015 on the effort [3] and their work is ongoing.
  - **International Consortium of Human Phenotype Terminologies (ICHPT)** – Due to the increased role of informatics and electronic health records in RD research and clinical care, there is a need for standards to achieve interoperability

[16] http://genomicsandhealth.org/

between databases. In particular, the ICHPT aimed to provide the community with standards to enable the linking of phenotype and genotype databases for RD. A workshop was held in September 2012 for researchers, clinicians, and leaders within the genetic and RD community to explore the current state of terminologies and determine the best path forward for establishing common terminologies all with the goal of serving the needs of the multitude of stakeholders. A second workshop was held in October 2013 to finalize the proposal, terms, and dissemination strategy. The outcome of this work – the list of terms and their mapping – is available on the IRDiRC website [13].

The **Interdisciplinary Scientific Committee** provides expertise on cross-cutting aspects of RD research.

- Current Chairmanship
  - Petra Kaufmann (Chair): National Center for Advancing Translational Sciences (NCATS), NIH, USA
  - Domenica Taruscio (Vice-Chair): Istituto Superiore di Sanità, Italy
- Task Forces
  - **Automatable Discovery and Access (ADA)** – Clinical data are essential to advance knowledge on the natural history of RDs and should be widely accessible to researchers and clinicians to maximize output. One of the obstacles to do so is the necessity to respect the scope of consent expressed by each patient with regard to his/her data. As most databases tend to be interoperable, it is now necessary to associate clinical data with the scope of consent given by each patient. The ADA Task Force is a joint IRDiRC and GA4GH effort that aims to associate clinical data with the scope of consent given by a patient, develop standardized and computer-readable data use types in consent forms, and align a user's permission against permitted data use type. The ADA Matrix is a standardized way to represent consent and other conditions that apply to a resource, making such information unambiguous and computer-readable. The first version of the ADA Matrix was open for comments from the public for 30 days in September 2016. The work is ongoing.
  - **Privacy-Preserving Record Linkage (PPRL)** – Patients are often enrolled in multiple independent research projects and the value of the datasets generated is increased if they can be linked together at the individual participant level. It is often difficult to know when two datasets contain the same individual, however, when research projects are run by different investigators or organizations. Additionally, identifying information about the individual usually cannot be shared to ensure data protection. The PPRL Task Force is a joint IRDiRC and GA4GH effort that aims to develop participant unique identifiers for research data sharing across multiple projects and institutions. It also aims to generate guidelines on the ethical, legal, and technical requirements of patient identifiers in RD research and recommendations for the most practical approach that maximizes uptake while also complying with regulations. A workshop is being held in December 2016 and work is ongoing.

The **Therapies Scientific Committee** advises on research related to research and development for therapies for RDs.

- Current Chairmanship
  - Diego Ardigò (Chair): Chiesi Farmaceutici S.p.A., Italy
  - Virginie Hivert (Vice-Chair): EURORDIS-Rare Diseases Europe, France
- Task Forces
  - **Patient Centered Outcome Measures (PCOM)** – Clinical trial outcome measures are vital, but many trials, particularly on RDs, do not yet include standardized outcomes in clinical data. This insufficient attention to the selection of outcomes can lead to a waste of the generated data and research, and inefficiencies in the drug development and regulatory review processes. Additionally, patient-centered outcome measures continue to gain considerable emphasis as useful research tools to assess patient response to treatments. The development and adoption of these research measurements have been essential in accelerating research and development in RD. The PCOM Task Force aims to place patients and their families at the center of decisions about the criteria in health assessment rather than leaving it solely to the clinician. The PCOM Task Force aims to boost the development and adoption of patient-centered outcome measures and explore how they can be expanded to target RD research in order to improve feasibility and quality of trials. A workshop was held in November 2015 and recommendations were developed [10] that can be accessed on the IRDiRC website. A publication is upcoming.
  - **Small Population Clinical Trials (SPCT)** – Clinical research and trials in RDs is particularly complex due to the low disease prevalence, small and heterogeneous patient populations, difficulty to recruit, disease severity, and lack of knowledge about disease natural history. The field needs to develop cost-effective, novel, rigorous controlled study designs and analyses to assess treatment efficacy in heterogeneous small populations. The SPCT Task Force aims to boost consensus about non-conventional statistical methods used for small population clinical trials. It also aims to boost acceptance of such methods by coordinating with related regulatory agencies and consortia. A workshop was held in March 2016 and recommendations were developed [12] that can be accessed on the IRDiRC website. A publication is upcoming.
  - **Data Mining/Repurposing (DMR)** – With the spike of scientific and technological developments along with advances in genetics analysis and disease mechanisms, RD research is ripe for breakthroughs and treatments. Initiatives, both academic and commercial, have proliferated recently targeted at making the most of the existing data and knowledge to identify new therapeutic targets and to repurpose drugs. The DMR Task Force aims to gather the expertise at a global level and identify opportunities for collaborations, especially public/private ones, to speed up the exploitation of these new discovery tools. A workshop was held in November 2016 and work is ongoing.

20.6 IRDiRC Recognized Resources

IRDiRC was launched to foster international collaboration and coordination of resources in RD research. Some of the basic tenets of IRDiRC include the need for collaboration, involvement of patients in all pertinent aspects of research, and the importance of sharing data and resources. As such, IRDiRC introduced a quality indicator in March 2015 called 'IRDiRC Recommended' to highlight resources which, if more broadly used, would accelerate advances in RD research. Early in 2016, this indicator was renamed 'IRDiRC Recognized Resources' to more accurately reflect the goal of the initiative: highlighting resources for RD research that are publicly available and that researchers in the RD community have deemed useful [14]. Resources that have obtained this designation underwent a peer-review process by IRDiRC Scientific Committee members and IRDiRC-independent researchers, who are often users of the resources themselves. These resources are expected to help accelerate the pace of discoveries and translation into clinical applications. To date, the label has been given to 17 resources including five guidelines, five platforms, and three reference databases, and an advisory committee. A full, updated listing of these resources can be found on the IRDiRC website.[17]

20.7 Conclusion and Prospects

As IRDiRC approaches the end of its fifth year, its two main initial objectives – to contribute to the development of 200 new therapies and the means to diagnose most RDs – have largely been achieved. This presents IRDiRC with the exciting opportunity to set new and even more ambitious goals for the next phase of the Consortium, focused on quantal improvement in the efficiency and effectiveness of RD understanding, diagnosis, and treatment [1, 2, 5]. At the same time, new partners are joining IRDiRC, furthering the realization of the IRDiRC founders' goal of a truly global RD research community. The combination of new IRDiRC goals and expanded IRDiRC membership portends a new era of collaboration and accomplishment in global efforts to bring the promise of science to all patients with rare diseases.

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[17] http://www.irdirc.org/activities/irdirc-recognized-resources/

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Chapter 21
Prospects of Pluripotent and Adult Stem Cells for Rare Diseases

Javier García-Castro and Ilyas Singeç

Abstract Rare diseases are highly diverse and complex regarding molecular underpinning and clinical manifestation and afflict millions of patients worldwide. The lack of appropriate model systems with face and construct validity and the limited availability of live tissues and cells from patients has largely hampered the understanding of underlying disease mechanisms. As a consequence, there are no adequate treatment options available for the vast majority of rare diseases. Over the last decade, remarkable progress in pluripotent and adult stem cell biology and the advent of powerful genomic technologies opened up exciting new avenues for the investigation, diagnosis, and personalized therapy of intractable human diseases. Utilizing the entire range of available stem cell types will continue to cross-fertilize different research areas and leverage the investigation of rare diseases based on evidence-based medicine. Standardized cell engineering and manufacturing from inexhaustible stem cell sources should lay the foundation for next-generation drug discovery and cell therapies that are broadly applicable in regenerative medicine. In this chapter we discuss how patient- and disease-specific iPS cells as well as adult stem cells are changing the pace of biomedical research and the translational landscape.

Keywords Pluripotent stem cells • Adult stem cells • iPS • Cellular therapy • Regenerative medicine • Clinical trial

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21.1 The Stem Cell Continuum in Ontogeny

Human development starts with the fertilized egg representing the earliest totipotent embryo state. The totipotent embryo undergoes multiple cell divisions and develops into the blastocyst-stage embryo containing the inner cell mass (ICM) surrounded by trophectodermal tissue. The ICM will give rise to the embryo proper while trophectoderm produces the placenta. The ICM consists of remarkably plastic self-renewing pluripotent stem cells that have the potential to generate all cell types of the human body. During gastrulation the ICM produces the three germ layers (ectoderm, mesoderm, endoderm), which will then generate tissue-specific multipotent stem cells as the building blocks of organs such as neural stem cells, liver stem cells, muscle stem cells, and others. After organogenesis, multipotent stem cells are maintained in various organs in discrete locations ("stem cell niche") throughout adult life and contribute to normal tissue homeostasis or repair following injury. These adult stem cells typically give rise to the cell types of the organ of origin. For instance, multipotent neural stem cells generate the three main neural lineages which are neurons, astrocytes, and oligodendrocytes. In general, across these different developmental stages, cell potential and plasticity become gradually restricted while lineage-commitment and cellular specialization increase over time. The molecular mechanisms that control this intricate and precisely controlled spatiotemporal interplay between gene silencing and gene activation is continuing to fascinate both developmental and stem cell biologists. More recent work using forced expression of specific transcription factors has demonstrated that fully differentiated cells (e.g. fibroblasts, blood cells) can be reprogrammed and de-differentiated into the pluripotent state, the so-called induced pluripotent stem cells (iPS cells; see below). Although at lower efficiency and without indefinite self-renewal capacity, somatic cells such as fibroblasts can be converted directly into induced neurons, cardiomyocytes, and other cell types (lineage programming).

21.2 Pluripotent Stem Cells

Major technical improvements in cell culture and recombinant protein technologies have transformed stem cell biology over the last few decades. The isolation, long-term expansion, and cryopreservation of various stem cell types is now a routine practice in many laboratories. The landmark achievement of establishing human embryonic stem (hES) cell lines by J. Thomson and colleagues [37] has enabled studying the mechanisms of pluripotency, early human development, and the differentiation process of multiple cell lineages in basic research laboratories. Pluripotent cells can be expanded indefinitely under appropriate cell culture conditions (self-renewal) and differentiated into many functional cell types of ectodermal, mesodermal, and endodermal lineages (pluripotency). Notably, hES cells do not undergo senescence while in the pluripotent state, which explains that many cell

lines have been successfully cultured and widely shared for almost two decades. Human ES cells were directly derived from blastocyst-stage embryos and despite of their vast biomedical potential, their routine use has been complicated by ethical concerns and scientifically limited by the fact that patient-and disease-specific cell lines cannot be generated in a streamlined fashion for drug discovery and regenerative medicine applications. In addition, safety issues due to potential tumorigenicity (i.e. uncontrolled cell growth after transplantating undifferentiated or genomically unstable cells) and the allogeneic use of established hES cell lines in combination with immunosuppression have been be long-standing unresolved challenges for broad clinical use.

The revolutionary discovery by Shinya Yamanaka and colleagues that fibroblasts and other somatic cells can be reverted back to a pluripotent state by four defined transcription factors (OCT4, SOX2, KLF4, C-MYC) has transformed biomedical research and concepts of developmental biology. These induced pluripotent stem cells are indistinguishable from hES cells with regard to morphology, molecular characteristics, developmental potential, and functional differentiation into mature cell types. Because the generation of iPS cell lines from somatic cells (e.g. skin cells, blood cells) of healthy individuals and diseased patients is an easily scalable process, large amounts of cellular material can be produced for disease research, tissue engineering, and regenerative medicine. It is therefore apparent that iPS cells are of tremendous immediate value for basic and translational research as well as future diagnostic and therapeutic purposes.

The first iPS cell lines were established a decade ago by Shinya Yamanaka and colleagues [35, 36] and the field has made significant progress by improving reprogramming technologies and protocols and by gaining fundamental insights into the molecular mechanisms of the reprogramming process itself [33]. For instance, while initially most iPS cell lines were derived by means of retroviruses that randomly integrate into the genome, the field has now moved on to using non-integrating Sendai virus, plasmids, or synthetic mRNAs [31, 42].

21.3 The Potential of iPS Cells for Rare Diseases

Significant progress has been made in iPS cell biology over the past decade and there is enormous potential that this technology brings to rare diseases. Indeed, the pathophysiology of many rare diseases are currently not well-understood and treatment options are limited. Having routine access to physiologically relevant human cell types has been a major obstacle for basic and translational research. In the context of rare diseases, cellular material from affected individuals is scarce and obtaining them for research purposes is often times a serendipitous event. The derivation of precious patient material from clinical or postmortem samples in a standardized and reproducible fashion has not been possible for the vast majority of rare diseases. Therefore, patient- and disease-specific iPS cells as an inexhaustible on-demand resource is a powerful technology, which is ideally suited to innovate the

approach of studying and treating rare diseases. Moreover, since the differentiation process of iPS cells recapitulates important aspects of human development, this strategy can be exploited for interrogating the different stages of normal development and disease states, including cell maturation and aging, otherwise not accessible for experimentation. Establishing cell-based models enables dissecting the pathophysiology and molecular underpinnings of rare human diseases under defined *in vitro* conditions [11, 18]. Over the last decade such "disease-in-a-dish models" have been reported for a number of disorders with monogenic and complex polygenic inheritance. Identification and characterization of robust disease signatures and specific phenotypes by integrated multi-omics methods (e.g. functional genomics, quantitative proteomics, metabolomics) and application of biologically meaningful functional assays will provide new insights and opportunities for disease modification and targeted treatments. Such therapeutic interventions could modulate or correct cellular phenotypes, pathways or cell signaling hubs by using small molecules identified by high-throughput and high-content chemical screening of large libraries using disease-relevant cell types. Another important question that could be systematically studied using controlled differentiation of iPS cells is why certain cell types are more vulnerable or resistant than others in genetic diseases. Such information will be highly informative and useful for improved disease classification including advanced patient selection criteria for clinical trials. Furthermore, using streamlined iPS cell production and differentiation in concert with standardized high-throughput technologies might help to carry out predictive studies ("clinical-trials-in-a-dish"), which could save time and the enormous costs and resources associated with clinical trials. This *ex vivo* approach could also help with better risk-benefit assessment and reduce the burden on patients and the health care systems.

In parallel to advances in iPS cell biology and cellular reprogramming, other powerful technologies emerged over the recent years. For instance, whole genome-sequencing, synthetic RNAs, and genome editing tools can be combined with stem cell strategies for better understanding and treating rare diseases. The wealth of genomic data derived by affordable whole genome-sequencing technologies and global initiatives for data analysis and sharing (e.g. genome-wide association studies) are impactful resources for personalized medicine. Efficient dosing and delivery of modified messenger RNAs are currently being developed into therapeutic modalities and can lead to expression of critically missing proteins and ameliorate disease symptoms [30, 34]. Moreover, availability of gene editing tools allow site-specific and genome-wide manipulations and can correct underlying genetic defects (e.g. point mutations, deletions) and may even cure some monogenic diseases [23, 26, 40].

The advent of the iPS cell technology represents an unique opportunity for regenerative medicine and the development of next-generation cellular therapies. Rare diseases in particular will benefit from new cell therapeutic strategies aimed at replacing lost cells or using stem cells or their differentiated progeny as vehicles that provide trophic support and missing gene products (e.g. enzyme replacement, detoxification) to diseased cells and tissues. Importantly, the application of

patient-specific cells will enable autologous cell therapies thereby circumventing immune rejection and the unwanted effects associated with the use of immunosuppressive drugs.

21.4 Current Challenges in the iPS Cell Field

Although remarkable progress has been made, major challenges remain to be addressed to firmly establish the iPS cell technology in drug discovery and clinical applications. The use of pluripotent stem cells always raises issues about safety, since grafting of undifferentiated cells can result in uncontrolled overgrowth and or give rise to large tumors *in vivo* [12, 29]. Strict quality control and quality assurance of material derived from pluripotent stem cells is therefore of critical importance before any clinical application is initiated. Cell sorting by utilizing both positive and negative selection criteria (e.g. cell surface markers that are only expressed by pluripotent cells such as SSEA3, SSEA4, TRA 1–60, TRA 1–80) can help to remove unwanted phenotypes. For instance, the tight-junction protein claudin-6 is expressed by human pluripotent cells and downregulated during early differentiation (Fig. 21.1). Using a panel of distinct and reliable markers will therefore help to avoid that undifferentiated cell types contaminate the cell suspension that will ultimately be transplanted.

Another key challenge is the lack of highly reproducible and controlled differentiation protocols that generate pure populations of relevant cell types. This is in part due to the fact that multi-step differentiation across various developmental stages is difficult to control because of cellular heterogeneity that quickly emerge when culture conditions are not optimal. Similarly, key cell signaling pathways that need to be activated or inhibited in combinatorial patterns have not been systematically elucidated using rigorous quantitative biology methods. Notably, pathways that control cell fate in human pluripotent stem cell cultures can be quite different than the knowledge accumulated in animal models. Moreover, the use of undefined culture conditions and mouse feeder cells can further complicate the formulation of highly robust differentiation protocols but also impede the cell manufacturing criteria that is pivotal for clinical translation and approval by regulatory agencies.

Scaling up cell numbers in a reproducible fashion without compromising quality is important to ensure that enough cellular material can be produced at will. Along these lines, the use of small molecules targeting specific receptors or cell signaling molecules instead of recombinant proteins can help to save costs and further increase the consistency of cell differentiation protocols. For instance, efficient neural induction of pluripotent stem cells can be achieved by using different combinations of small molecules [7, 32]. Ongoing high-throughput screening of large chemical libraries and the use of specific reporter cell lines will help to further advance small molecule-based directed cell differentiation.

A well-accepted problem in iPS cell differentiation is that the vast majority of cells do not fully mature and remain at a state that is fetal-like even after prolonged

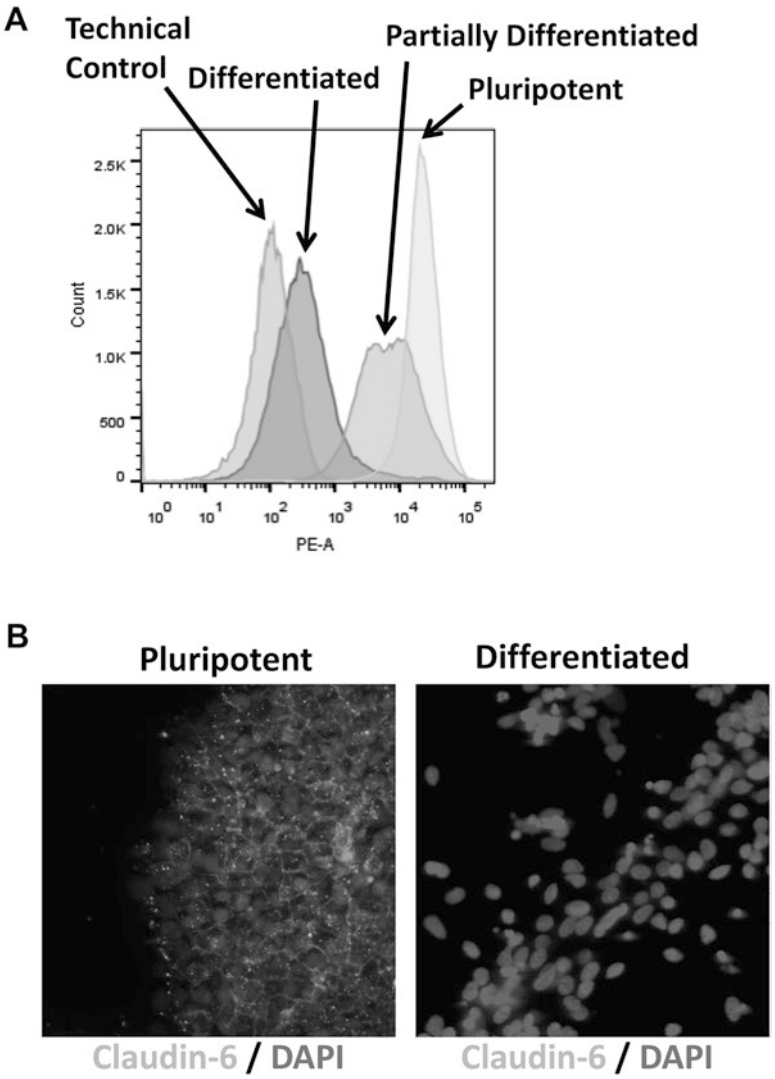

Fig. 21.1 Tight junction protein claudin-6 is exclusively expressed by pluripotent embryonic stem cells and downregulated during early differentiation. Specific markers such as claudin-6 can help to avoid grafting of undifferentiated cells in future cell therapies. (**a)** Fluorescence-activated cell sorting (FACS) analysis of claudin-6 in pluripotent, partly differentiated (embryoid bodies), and differentiated cells (small molecule-based neural induction according to Singec et al. 2016). Technical control shows pluripotent cells stained with the secondary antibody only. Antibody source: R&D Systems, Cat. No. MAB3656. (**b)** Immunocytochemistry against claudin-6 confirms expression by pluripotent cells and absence of claudin-6 in differentiated cells

in vitro culture. How to mature human cells and monitor long-term functionality and stability is among the most formidable challenges in the iPS cell field. Again, the identification of quantitative endpoints and informed manipulation of cross-talking cell signaling pathways by means of small molecules and optimized cell culture conditions (e.g. cell differentiation at low oxygen, appropriate extracellular matrix, three-dimensional cultures) should result in substantial progress with significance for clinical translation.

To address the above-mentioned complex challenges that the iPS cell field is currently facing, the National Institutes of Health (NIH) has launched the Stem Cell Translation Laboratory (SCTL) within the National Center for Advancing Translational Sciences (NCATS). This effort is part of the NIH Regenerative Medicine Program (RMP) and the main goal is to bring the iPS cell technology closer to clinical application and human biology-oriented drug discovery (https://commonfund.nih.gov/stemcells/index).

21.5 Examples of How iPS Cells Impact Rare Disease Research

Patient- and disease-specific iPS cells are uniquely suited to provide new information on the molecular and cellular mechanisms of a broad range of rare diseases. Cellular models of rare diseases are already providing actionable insights into molecular signatures and phenotypes, which can be identified and carefully characterized. Moreover, in proof-of-principle experiments several groups have reported that disease phenotypes can be corrected by using chemical or genetic approaches. For instance, Lee et al. generated iPS cells from patients with familial dysautonomia (FD) and studied underlying disease mechanisms [20]. FD is a rare disease causing peripheral neuropathy due to a point mutation in the IKBKAP gene, which is involved in transcriptional elongation. In affected patients this mutation leads to depletion of autonomic and sensory neurons. Directed differentiation of patient iPS cells into neural crest cells, the relevant cell lineage for this disease, served as an appropriate *in vitro* model to detect abnormal neurogenic differentiation and defective cell migration. The same authors then carried out large-scale chemical screening and identified compounds that rescued IKBKAP expression [21]. In a different study, iPS cells were derived from patients with LEOPARD syndrome [5]. These patients carry a mutation in the PTPN11 gene, which encodes the SHP2 phosphatase. In LEOPARD syndrome multiple organs are affected and the disease is characterized by lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness. Hence, depending on the rare disease under investigation and the clinical manifestation, the use of iPS cells and discovery of a disease-modifying drug could have significant beneficial effects on multiple organ systems. Cellular models established for many other rare diseases cannot be discussed here due to space limitation but the

following examples provide some insights into the broad potential of this technology: Rett syndrome [24], Williams syndrome [6], spinal muscular atrophy [10], Hutchinson-Gilford progeria syndrome [22, 44], Friedreich's ataxia [19], Fragile X syndrome [27], fibrodysplasia ossificans progressive [4], Jervell and Lange-Nielsen syndrome [2], Shwachman-Diamond syndrome [39], epidermolysis bullosa [14]. Given the relative ease of generating iPS cells and their versatile biomedical use, it is clear that many more disease-specific cell lines will be established and shared among the scientific community in the coming years [43].

21.6 Adult Stem Cells

Adult humans have limited regenerative capacity for repairing their tissues and organs after injury or in the context of disease. Restoration can be achieved either through the activation of somatic stem cells residing in specialized microenvironments (stem cell niche) or by inducing differentiated cells to proliferate [15]. These adult human stem cells, that are intrinsic to various tissues, are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue lineage as a consequence of physiologic cell turnover or tissue damage [16]. The clinical use of adult stem cells holds great promise, although the application of most adult stem cell types are still in the early phase of clinical trials. The most widely studied adult stem cells are hematopoietic stem cells (HSCs), which have been investigated since 1959 and are in routine clinical use for HSC transplantation (HSCT) [41]. HSCT refers to a procedure in which HSCs are infused to restore bone marrow function in patients. However, virtually all HSCT are carried out with either non-purified, mixed cell populations (mobilized peripheral blood, cord blood, or bone marrow) or cell populations that have been enriched for HSCs but have not been fully purified [9]. HSCT can be applied in an autologous fashion, which involves harvesting the patient's own HSC and then re-admininstering them, after leukemic patients have received myeloablative chemotherapy. Alternatively, allogeneic HSCT uses HSCs from a donor which might be either HLA (human leukocyte antigen)-matched or unmatched. However, patients who received allogeneic HSCT are at risk of developing graft-versus-host disease (GVHD). In those patients, immune cells of the allograft can induce an acute and/or chronic immune reaction against the host. GVHD remains one of the major challenges in allogeneic HSCT [17]. Interestingly, Prochymal/TEMCELL, the first allogenic MSC treatment approved in Canada, New Zealand and Japan is a cell therapy intended for the management of acute GVHD in children who are unresponsive to steroids (http://www.mesoblast.com).

A systematic review described the effectiveness, benefits, and adverse effects of using HSCT to treat rare diseases but currently no guidelines or recommendations are available that are based on extensive clinical studies (www.effectivehealthcare.ahrq.gov). The application of HSCT is often performed as uncontrolled single-arm studies or case reports, with the exception of some rare solid tumors, because HSCT

is mostly offered to patients with poor prognosis or those who have been refractory to other treatments. A summary of the rare diseases for which HSCT has been evaluated is presented in Table 21.1.

In vivo gene therapy treatment shows good results in certain rare diseases. For instance, Glybera is a treatment for lipoprotein lipase deficiency (LPLD), thereby representing one of the first gene therapies that have been approved [3]. Moreover, combination of gene and cell therapy have increased the range of possible clinical applications, for instance, the combination of gene therapy with HSCT. In fact, patients who received first gene therapy treatments for primary immune deficiencies (PIDs) still show robust and sustained immune recovery after 10–15 years. Using this approach, autologous HSC are isolated, *ex vivo* cultured and transduced with a therapeutic vector aimed at genetically modifying them. These "gene-corrected" cells are then re-administered to the patient as part of an "autologous gene-modified HSCT" strategy [3]. Great progress has been made in the treatment of some PIDs and metabolic disorders by means of gene therapy of X-linked severe combined immunodeficiency (SCID), adenosine deaminase deficiency (ADA), Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD), Fanconi anaemia, childhood cerebral adrenoleukodystrophy (CCALD), metachromatic leukodystrophies (MLDs) and X-linked lymphoproliferative syndrome (XLP). A similar dermal transplantation strategy using gene-corrected epidermal stem cells is used in several clinical trials with Netherton syndrome (NS) and epidermolysis bullosa (EB) patients [3]. Also, hepatocyte transplantation is currently performed in patients with metabolic disorders, such as familial hyper-cholesterolemia, through injection of hepatocytes into the portal venous system intended for liver or spleen engraftment. Allogenic and autologous hepatocytes, transduced with the low-density lipoprotein receptor gene, have been transplanted and showed some promising results [38].

Other approaches based on cell therapy are in early stages of clinical development. These therapeutic interventions focus on the administration of relevant cells in patients with a specific disease and clinical symptoms. Depending on the context, cells can be administered at different stages of maturation, either as stem/progenitor cells or at more differentiated states.

The European Medicines Agency (EMA) has approved Holoclar, the first advanced therapy medicinal product containing stem cells, as a treatment for moderate-to-severe limbal stem cell deficiency (LSCD) that can result in blindness. Hence, LSCD can now be treated with by translanting autologous limbal stem cells after they were isolated by biopsy and successfully expanded *ex vivo*. The majority of patients treated with Holoclar showed stable corneal epithelium restoration with functional improvement of vision (www.ema.europe.eu: EU/3/08/579). However, autologous cells from patients with rare diseases that carry the same mutation and their application might be of limited therapeutic value if the underlying genetic defect is not corrected. Notably, treatment of amyotrophic lateral sclerosis (ALS; also called Lou Gehrig's disease) using autologous mesenchymal stem cells (MSCs), capable of expressing neurotrophic factors, was tested in Phase I/II clinical trials.

Table 21.1 List of rare diseases for which HSCT has been evaluated

Disease	Outcome	Results	Strength of evidence
Anaplastic astrocytoma	Overall survival	Improves 5-year overall survival (40%, n = 10) when compared with patients who receive conventional therapy (0%, n = 71).	Low
Rhabdomyosarcoma	Overall survival	Associated with higher treatment-related mortality than conventional therapy and leads to shorter overall survival	Low
Ependymoma	Overall survival	No benefit with a single HSCT when compared with conventional therapy.	Moderate
Rhabdomyosarcoma	Overall survival	No benefit with a single HSCT when compared with conventional therapy.	Moderate
Ewing's sarcoma	Overall survival	No benefit with a single HSCT when compared with conventional therapy.	Low
Retinoblastoma	Overall survival	No benefit with a single HSCT when compared with conventional therapy.	Low
Wilms' tumor	Overall survival	No benefit with a single autologous HSCT when compared with conventional therapy.	Low
Wolman disease	Overall survival	Significant benefit with a single HSCT when compared with conventional therapy.	High
Niemann-Pick disease type A	Overall survival	No benefit was conferred with a single hematopoietic stem-cell transplantation when compared with conventional therapy.	Low
Mucopolysaccharidosis type II (Hunter Syndrome)	Neurodevelopmental/Neurocognitive	Benefit for both the attenuated and severe forms	Low
Mucopolysaccharidosis type III (Sanfilippo Syndrome)	Neurodevelopmental/Neurocognitive	No benefit from HSCT	Low
Gaucher disease type III	Neurodevelopmental/Neurocognitive	No benefit from HSCT	Low

Farber disease type 2/3	Subcutaneous nodules and joints with limited range of motion	Reduced number of subcutaneous nodules and joints with limited range of motion at 0.7 to 1.3 years of follow up.	High
Type-1 diabetes mellitus	Insulin independence	Extended interval of insulin independence with a single autologous nonmyeloablative HSCT	Moderate
Lupus erythematosus	Extended drug-free clinical remission	An extended drug-free clinical remission can be achieved after intense immune suppression and autologous HSCT.	Moderate
Juvenile idiopathic arthritis	Extended drug-free clinical remission	An extended drug-free clinical remission can be achieved after immune suppression and autologous HSCT.	Moderate
Systemic sclerosis	Extended drug-free clinical remission	An extended drug-free clinical remission can be achieved after immune suppression and autologous HSCT.	Moderate
Multiple sclerosis	Extended drug-free clinical remission	An extended drug-free clinical remission can be achieved after immune suppression and autologous HSCT.	Moderate
Pediatric crohn's disease	Extended drug-free clinical remission	An extended drug-free clinical remission can be achieved after immune suppression and autologous HSCT.	Moderate

Adapted from Ratko TA, Belinson SE, Brown HM, et al. AHRQ Comparative Effectiveness Review No. 48. Available at www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm

Evidences: **High**, further research is very unlikely to change the confidence in the estimate of effect. **Moderate**, further research may change the confidence in the estimate of effect and may change the estimate. **Low**, further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. **Insufficient**, evidence either is unavailable or does not permit a conclusion

Measuring trial endpoints showed a promising effect on disease progression as demonstrated by several scores in patients after intrathecal injection of MSCs [28].

Depending on the underlying disease, allogenic cells might restore the damaged tissue, enzyme deficiency or cellular function necessary to obtain a therapeutic response. For example, allogenic transplantation of myoblasts is under development for muscular dystrophy including X-linked Duchenne muscular dystrophy (DMD), so far with only little improvement of muscle function in DMD. Among the challenges are multiple cell injections that are required for a therapeutic effect and the need for immunosuppression [38]. As mentioned above, immune rejection of grafted cells is a major challenge in allogenic transplantation strategies and necessitates the identification of HLA-compatible donors. MSCs are a versatile cell population that are capable of differentiating into multiple cell lineages, exhibit significant *ex vivo* expansion potential, and show remarkable hypo-immunogenic or immune-evasive characteristics [1]. Currently, there are more than 300 registered clinical trials in different phases aimed at evaluating the clinical potential of MSC-based cell therapies throughout different countries.

Horwitz and colleagues carried out clinical studies with MSC in children affected with type III osteogenesis imperfecta (OI). This study included six children at the age of 2–4 years that received two infusions of HLA-matched MSCs. The outcome was MSC engraftment and an increase in linear growth velocities [13], albeit only for a limited time. MSC inoculation has been used also as prenatal transplantation in OI [8]. There are also preliminary data suggesting that MSCs may be helpful in treating patients with lysosomal storage disorders, such as metachromatic leukodystrophy, Hurler syndrome (mucopolysaccharidosis type I), and Hunter syndrome (mucopolysaccharidosis type II). MSC administration resulted in improvements in bone mineralization and nerve conduction velocity [25]. Similarly, MSCs infusion resulted in significant improvements in muscle strength, facial expressivity, ventilator-free breathing ability, and ability to speak in spinal muscular atrophy type I. Unfortunately, clinical improvement was not observed beyond 6–7 months and led to the discontinuation of the trial [25]. In cerebral palsy patients allogeneic umbilical cord-derived MSCs administered intravenously resulted in improved muscle tone, strength, speech, memory, attention, or cognition in a dose-dependent manner, while no worsening of symptoms was observed. Moreover, in autism-spectrum disorder (ASD), significant improvement of symptoms were observed after treatment with MSC but these cleary remain preliminary observations [25].

Neural stem cells (NSCs) are another type of somatic stem cell that can be isolated and utilized for cell therapy purposes. NSC may be derived from different sources including the fetal, neonatal or adult brain. These cells self-renew and differentiate into neurons, astrocytes, and oligodendrocytes and are used for various indications. Clinical trials have been undertaken for the use of fetal NSCs for lysosomal storage diseases. Children at an advanced stage of Batten's disease (neuronal ceroid lipofuscinosis) tolerated treatment with high doses of NSCs injected into multiple brain regions as part of a Phase I safety study. The transplanted cells provided widespread enzyme replacement and neuroprotection likely through multifactorial beneficial effects, the so-called chaperone effects. The same company also

carried out a Phase 1 clinical trial using fetal NSC transplantation for Pelizaeus-Merzbacher disease (PMD), a myelination disorder that affects male children [38]. Fetal NSCs as transplant material are also in clinical trials for the treatment of ALS and are injected into multiple sites of the lumbar spinal cord. It has been reported that NSC engraftment was well-tolerated and no adverse effects were observed [38].

21.7 Outlook

To fully exploit the potential of various types of stem cells for rare diseases, it is necessary to continue investigating them in parallel by using the ever-increasing toolkit of cutting-edge technologies. A range of self-renewing pluripotent and multipotent cells can now be derived from different sources, dramatically expanded *in vitro*, cryopreserved, and successfully applied. Importantly, for therapeutic purposes the most appropriate stem cell type can be selected and specifically tailored for any disease of interest. As data is being accumulated in basic research and clinical trials, stem cell technologies will become an essential part of evidence-based medicine and result in novel clinical treatment options for many rare and neglected diseases.

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Chapter 22
Personalized Medicine: What's in it for Rare Diseases?

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Abstract Personalised Medicine has become a reality over the last years. The emergence of 'omics' and big data has started revolutionizing healthcare. New 'omics' technologies lead to a better molecular characterization of diseases and a new understanding of the complexity of diseases. The approach of PM is already

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successfully applied in different healthcare areas such as oncology, cardiology, nutrition and for rare diseases. However, health systems across the EU are often still promoting the 'one-size fits all' approach, even if it is known that patients do greatly vary in their molecular characteristics and response to drugs and other interventions. To make use of the full potentials of PM in the next years ahead several challenges need to be addressed such as the integration of big data, patient empowerment, translation of basic to clinical research, bringing the innovation to the market and shaping sustainable healthcare systems.

Keywords Personalized medicine • Rare disease • Health data cooperatives • Actionable big data analytics • Systematic early dialogue • Managed entry agreement

22.1 Introduction

Over the last decades medical treatment in Europe has been based on the concept of evidence based medicine (EBM), which intends that decision making in medical practice is informed by the most reliable scientific information combined with individual expertise of the health professional, as well as patient preferences [3]. In practice, patients mainly receive treatments and medication that have been assessed and tested regarding efficiency and safety in well-designed Randomized Clinical Trials (RCTs), the gold standard in clinical research [52]. Nevertheless, this approach does not take into account the individual molecular characteristics of the patients, which are of great importance for the effectiveness and safety of therapies. Patients do not respond to therapies and drugs in the same way [24, 32, 49] due to differences in genomic and epigenomic profile [36]. Therefore, the traditional approach of EBM has been critizied as an ineffective 'one-size fits all' healthcare approach [32]. Furthermore, patients who receive drugs that do not fit their needs will either continue to carry the burden of the current health condition or even suffer from more severe health problems due to the accompanied side effects such as adverse drug reactions (ADRs). For example, evidence indicated that the 'one-size fits all' approach in cancer treatment is effective in 25% of the cases [57], however 75% of cancer therapies and treatments are not effective and patients suffer from ADRs and a loss of quality of life during treatment [57].

Not only do the patients suffer from ineffective treatments or even ADRs, the current approach also results in economic inefficiency of healthcare systems across Europe. In addition to the rising morbidity, demographic changes and the burden of non-communicable diseases (NCDs), the low treatment response rate creates an economic burden of more than EUR 100 billion each year [32].

Another traditional approach in health care is the classification of diseases into common diseases (CDs) and rare diseases (RDs) [45]. In Europe diseases that affect

less than 5 patients per 10,000 citizens are defined as rare diseases. Across the EU, approximately 30 million European citizens are suffering from RDs. However, emerging 'omics technologies' which enable sequencing of the human genome have first proven that patients have unique molecular characteristics [33] and second, that each mutation of a tumor is different [55]. Therefore, this new understanding of the complexity of diseases allows to classify diseases more accurate based on their genetic characteristics [44] using next generation sequencing. This results in a new understanding of diseases which makes no differences between CDs or RDs. Finally, according to Boycott et al. [4] the large majority of disease causing gene mutations will be discovered by 2020.

At this point, the approach of personalised medicine (PM) joins the discussions. Emerging technologies such as Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES) or Low-Coverage Sequencing (LCS) identified the need for better understanding of the molecular basis of disease and evened the path for PM. Based on molecular interindividual differences, PM applies an understanding that all diseases become rare diseases due to the uniqueness of each patient. For the purpose of the article, we apply this understanding and we do not differentiate between CDs and RDs.

22.2 What Does Personalised Medicine Mean?

Lately, PM is an often-used buzz word mentioned in discussions regarding healthcare and medicine. PM is an approach that is defined in many different ways among stakeholders and healthcare professionals [18]. Within the literature terms such as genomic medicine, stratified medicine or precision medicine are used interchangeably to describe the approach of PM [55]. Those terms arouse expectations of great medical advances even it is not fully clarified what personalised medicine means.

Since there is no uniform definition of PM, professionals differ in their understanding of the approach of PM, which consequently leads to misunderstandings and miscommunications [53]. While some experts only perceive treatments that are based on genetic analysis and biomarkers as PM [48], others describe PM as an approach in which the healthcare professional bases his treatment decision by taking into account the health status of the patient and the individual circumstances of the patient. In those cases, it is often referred to as individualized medicine [47].

For the purpose of this paper we refer to the definition of PM of the Horizon2020 Advisory Group for Societal Challenge "Health, Demographic Change and Wellbeing" of the European Commission. The Advisory group defines the concept of PM as 'a medical model using characteristics of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' [15]. This definition implies the understanding that the healthcare approaches are moving away from the traditional 'one-size fits all' approach.

22.3 Potentials of Personalised Medicine

By adjusting treatments to the unique molecular characteristics of the patients, PM has the potential to make treatments more effective and to decrease the economic burden. In order to identify the biological characteristics of the patient and their predispositions to a certain disease, PM applies 'omics technologies' [1, 36] such as 'genomics, epigenomics, proteomics, metabolomics, lipidomics' and incorporates real life data of the patients such as environmental and lifestyle information [7, 25]. All together, environmental, biological and lifestyle information adds up to an explosion of data soon reaching dimensions of "big data" [2].

PM is already applied successfully in various different healthcare fields [36] and therefore no longer seen as an abstract approach. Over the last decade 'omics technologies' and PM have had the greatest impact on oncology and cancer therapies [55] as well as other medical fields including rare diseases [36, 47], cardiology [59] and also for the treatment of infectious diseases [20].

Nevertheless, there is still potential for healthcare systems across Europe to further strengthen the uptake and implementation of PM [47]. Healthcare systems are not making full use of the potential of PM due to several barriers [25, 33, 47] and prefer to apply the traditional healthcare approach rather than PM. One reason is the complex and slow moving nature of health care systems as well as the lack of illustrating evidence that is needed to demonstrate the benefit of the PM approach.

22.4 Personalised Medicine on the European Union Agenda

As one of the main drivers of PM across Europe and beyond, the European Commission (EC) addresses challenges regarding PM, biobanking and 'omics-technologies' in several reports that have been published since 2013 [13, 14]. Furthermore, over the last 10 years, the European Commission committed around 1 billion Euros of funding to advance 'omics technologies' and PM [14].

One milestone that has been achieved regarding PM, is the launch of the 'Council Conclusions on Personalised medicine for patients' in December 2015 by the Luxembourg Presidency of the Council of the European Union (EU).

Furthermore, with the launch of the 'International Consortium of Personalised Medicine (ICPerMed)' in November 2016, European countries aim to coordinate health research policy to advance the implementation of PM [12]. The initiative brings together the EC, and health research funders and policy making organisations from 28 countries and five regions across Europe and Canada. Within the next few years a roadmap of research action will be defined, which is based on the 'Strategic Research and Innovation Agenda (SRIA)' developed by the EC funded Coordination and Support Action (CSA) PerMed: 'Shaping Europe's Vision for Personalised Medicine' [47]. The CSA PerMed consisted of partners representing European and national key decision makers in research and research policy,

healthcare and industry, as well as patient organisations. The PerMed SRIA lists five key challenges and provides 35 recommendations at national and EU level to address those challenges. The following five key challenges for the implementation of PM were identified: 'Developing Awareness and Empowerment, Integrating Big Data and ICT Solutions; Translating Basic to Clinical Research and Beyond, Bridging Innovation to the Market, Shaping Sustainable Healthcare' [12, 47].

22.5 Challenges to Implement Personalised Medicine into Healthcare Systems

The five key challenges of the PerMed SRIA need to be tackled and solved to promote the effective, efficient and timely implementation of PM in European healthcare systems in a socially acceptable manner. At the moment, aspects such as the integration of big data, the design of clinical trials, financing and reimbursement mechanisms and the active role of the patient/citizen in the decision-making process need to be addressed [9, 25]. In this book chapter, we present the five PerMed challenges and discuss the impact of PM on rare diseases (RDs). Furthermore, we suggest potential solutions.

22.5.1 Challenge 1 – Developing Awareness and Empowerment

> *Successful implementation of PM will be achieved only if all stakeholders, including patients and healthcare professionals, are empowered and develop the required awareness about PM. The crucial first step is to provide the best available evidence that supports the clinical and personal utility of PM, as well as its economic value to health systems, and to enable better understanding of how the changes brought by PM will impact public health for the benefit of individual citizens and society. Models that enable sharing, ownership and the development of a sense of responsibility towards personal health data, as well as the improvement of PM health literacy, will need to be generated along with suitable common principles, appropriate policy and regulatory frameworks.*[47].

Innovative treatments and therapies emerging in the field of PM are often challenging healthcare professionals (HCPs). HCPs feel overwhelmed and overloaded by the amount of new information, tools and technologies, which PM provides, to support their decision making process [27, 36]. This is due to the fact that across the EU, most of the curricula for HCPs are not up-to-date and do not include the new insights and understandings of the complexity of diseases arising from PM [9, 25, 46]. Issues that are elementary components of PM such as ICT solutions, companion diagnostics, the use of 'omics' technologies are often not addressed [36]. Furthermore, great differences and variations occur between the EU Member States and differences exist at national, regional and local level [27]. Thus, there is not only an urgent

need to update current curricula to the new understanding of the complexity of diseases to new innovative therapies and diagnostic tools. Of similar importance is that HCPs are also trained in the legal, economic and ethical implications of PM.

Besides the essential role of HCP education in the implementation of PM, patients and citizens are the key stakeholders that need to be empowered and health literate. The patient is often seen as a passive recipient within the healthcare system [5, 43]. For example, patients are rarely scrutinizing the decisions of their general practitioners (GPs) since they trust in their GPs [5]. To strengthen the uptake of PM it is of great importance to change the role of the patient from a passive recipient to an actively involved stakeholder of the decision-making process of his/her health interventions including prevention, diagnostics and therapies [8, 43, 47]. Health literacy is an important component of the approach of PM. Kickbusch and colleagues (2006) defined health literacy as 'the ability to make sound health decision (s) in the context of everyday life, – at home, in the community, at the workplace, the healthcare system, the market place and the political arena' [31]. Health literacy has gained increasing recognition by the European Institutions and is included in several of their policy documents [56]. The first European health literacy survey was conducted in 2011 as part of the European Health Literacy Project (HLS-EU) in order to measure the level of health literacy within eight Member States (MS) of the EU [56]. The results of the survey highlighted that the level of health literacy greatly differs among the participating countries. One key result of the survey was that people with a lower health literacy level are more likely to suffer from a lower health status compared to people with higher levels of health literacy [5, 56]. Patient empowerment and health literacy are key components of the approach of PM.

22.5.2 Solution – Good Governance via Health Data Cooperatives

As potential solution to overcome the challenge of patient empowerment and health literacy across the EU we would like to propose the concept of health data cooperatives (HDC). In order to empower and literate patients to strengthen the uptake of PM, HDCs could be a democratic solution as it is suggested by Hafen and his colleagues [24]. HDCs not only promise to integrate big data in an effective, efficient, timely and socially acceptable way, it also promises to empower the patients/citizens by being part of and actively involved in the decision-making processes of the HDC. HDC will make patients/citizens proactive consumers of health also called 'prosumers'. Patients/citizens will be actively involved in research ('citizen science') and be able to actively participate in the decision-making process regarding their health and treatment ('learning by doing'). It can be expected that empowered and literate patients/citizens will be the key in improving the diffusion of PM within the EU and its MS. Furthermore, in comparison to already existing health registers as for example rare disease registries, HDCs are owned and controlled by its

members or in other words it is controlled by the citizens. By joining the HDC model, the citizen are not only in the driver's seat, citizens become citoyens. Since the economic value of personal data is immensely increasing and the world largest companies show increasingly interest in the collection of personal data and health data, the risk to suffer from misuse of the data by third parties, HDCs give the patient/citizen the responsibility for the storing, analyzing and sharing of their health data [24]. As a collective, society as such is the beneficiary of both the economic as well as the health value of the health related data and information. Furthermore, by each member having one vote, HDC members decide how the revenues generated by granting third parties access to their data that they agreed to share (respectively the data commons), should be invested (e.g., in research, in public health, in education, in community outreach etc.) [24].

22.5.3 Challenge 2 – Integrating Big Data and ICT Solutions

> *The development of PM will rely heavily on integrated 'big data' analytics and ICT solutions to generate the required knowledge and infrastructure to support the new approaches. Technologies for data capture and management and development of high quality databases will be instrumental, but there will also be a requirement for strategies to make sense of this big data for known and future purposes. Translational research infrastructures and data harmonisation of structured, semi-structured and unstructured data will be a central component of such strategies and should lead to new analytical methods and modelling approaches as well as innovative decision support tools such as in silico simulations to support physicians' decisions. To integrate all these aspects, further European big data and 'big science' frameworks need to be created and supported by suitable legislation.* [47].

The world is challenged by a flood of information. In 2020, there will be approximately 5.200 gigabytes of information of each individual across the globe [50]. The European Commission describes this flood of information as 'the big data paradigm' [11]. According to the European Commission 'a defining characteristic of today's data-rich society is the collection, storage, processing and analysis of immense amounts of data' [11]. The world's largest companies such as Apple, Microsoft and Google are more and more interested in the collection and storage of health data [23]. The economic value of personal information is steadily increasing in Europe and beyond [24, 51].

By applying 'big data' in healthcare and public health a new understanding of the complexity of diseases did evolve over the last year [1, 37]. The analytics of big data make it possible to develop new medicines and drugs which are based on the individual molecular characteristics by integrating genomic information, lifestyle data and environmental information [37]. However, there is still room for improvements to make full use of the potential of big data because the majority of information is unstructured [29], inaccessible and stored in silos [24]. Since health and 'omics data are collected by an increasing variety of sources, the data collection is no longer seen as problem. The storage, analysis and integration of big data is currently challenging the professionals and healthcare systems traditional ways of working [1].

Big Data is commonly defined through its four V's: Volume, Velocity, Variety, Veracity [39]. According to a study by IDC [21, 28] the volume of data will double about every 2 years and will reach 40,000 Exabyte in 2020. This will be more than 5200 gigabytes per person in 2020. 500 petabytes are currently generated in medicine only due to medical imaging and it is predicted that this number increases 50-fold until 2020 [42]. The 'omics revolution adds to the exponentially increasing data volume and given mobile technologies and sensors, the amount of data per person that can be captured in the future is expected to be in the order of 1100 terabytes during the person's lifetime [40]. Only 10% of this data will be clinical data, 30% are 'omics data and the majority with 60% will be associated with exogenous data that captures lifestyle data, environmental data, behavioral data etc. The exponential increasing volume of data also indicates the speed that data is being generated, the second V of big data. Just a simple example illustrates that data is generated in real time: Each patient in an intensive care unit generates continuous, real time data through all monitoring devices [41]. In our daily lives, mobile sensors are already capturing real time data continuously. The speed in which next generation sequencing can measure the human genome has increased drastically. Furthermore, continued progress in 'omics technologies' and new technological developments that allowed to drastically reduce the costs of the sequencing of the human genome [33]. Since 2001, the costs were cut from US $ 100 million per human genome to around US $ 1.000 in 2013 [55]. The increasing speed and lower costs now enable clinical routine use of the technology [60].

However, the other two V's of Big Data are currently posing the largest challenge. The Variety of medical data has a wide spectrum as indicated before ranging from doctor's letters, radiology reports, laboratory reports, 'omics data to mobile sensor data and even social media. To integrate and correlate all this data with the published knowledge and guidelines as well as best practices and human expertise poses a very large challenge to gain meaningful insight from big data. The more we can integrate lifestyle data from wearables for example as well as social media data or environmental data, the 4th V, Veracity should be considered when carrying out the analysis, e. g. it should be asked how much a twitter feed or google search data can be trusted.

22.5.4 A Solution – Creating Fuzziness and Making Big Data Analytics Actionable

Considering the characteristics and value of Big Data in medicine, it's application is an essential step towards individualized medicine. Cognitive computing and computer tools in general become unreplaceable in how we treat patients especially in the context of rare disease. Mechanistic models with predictive power will soon be able to simulate clincal trials and predict the associated benefits for patient welfare and economy. Many other areas (e.g. the automobile and aviation industries) have already transformed towards a data driven mindset and rely on modelling

techniques to improve quality, decrease costs, accelerate development and reduce risks. Often, undiagnosed patients and patients with rare disease suffer from lack of democratization of knowledge meaning that every doctor should have the wealth and expertise of the medical profession at their fingertips. Furthermore, an increased virtualisation of the drug development process – with virtual clinical trials as one of the key components as well as more personalised therapy and prevention strategies based on patient modelling – might, in our ageing societies, very well be the only alternative to increased rationing of health care provision [32]. At the same time, services and data bases like Orphanet, OMIM, FindZebra, Isabel Healthcare and the IBM Watson technology, to name but a few, will support the physicians in finding the correct diagnosis and serve as assistants to accelerate differential diagnostics in individuals where there is no choice but to look at PM to diagnose and treat the rare disease.

Furthermore, also in this context good governance frameworks such as health data cooperatives (HDCs) will not only improve health literacy and empower patients, the integration of big data into a single system will improve the drug development process for rare disease and consequently will improve access to treatments for RDs .

22.5.5 Challenge 3 – Translating Basic to Clinical Research and Beyond

> *In order for PM to reach its anticipated impact on human health and wellbeing, translation of discoveries and communication across the continuum of research are required. A Europe-wide process to evaluate and validate biomarkers, together with longitudinal and in-depth studies to further characterise diseases and their progression would support on-going efforts towards this integration and reclassifcation. The development of new clinical trial designs that are adapted to these new approaches and the integration of preclinical testing with innovative clinical trials may further improve the effectiveness of interventions. Collaborative pre-competitive and transdisciplinary research and cross-sector collaborations need to be promoted and supported by suitable funding mechanisms in order to truly bridge all steps of the PM research continuum.* [47].

The new understanding of the complexity of diseases and that individuals show unique molecular characteristics is challenging the ways of working regarding the design of clinical trials. Clinical trials have been seen as the gold standard for many years but the traditional design of clinical trials is not applicable for the era of personalised medicine [36]. The traditional approach of designing clinical trials ignores the complexity of diseases [32] and the importance of the integration of big data [8], even in cases when it is known that patients differ in their response rates to drugs. Developments in epigenomic and genomic studies have led to a new human diseases classification [38]. Since patients' pools are becoming smaller, current clinical trial designs with up to thousands of participants cannot be sustained. N-of-1-trials are often seen as new design for clinical trials in the era of PM [36, 54]. The idea of N = 1 trials is that each individual/patient will be used as his/her own control/reference point. Since each patient will act as his/her own reference point, continuous data collection of health information over years or when it is possible lifelong is

needed. Data collection is a dynamic and changing process and therefore it allows intra-individual follow ups and comparisons [36].

As already mentioned above, many of the common conditions we know will be broken down into small subsets of disease with small patient populations that may fit into the definition of rare diseases. This will be possible due to the better understanding of the molecular causes of disease, the development of new biomarkers – static and dynamic- to define the characteristics of each patient, the possibility to integrate different data sources from each individual patient, and other scientific and technological developments. Therefore, we will no longer speak of "cancer" but "triple negative breast cancer", or "PIK3CA mutated squamous cell lung cancer". Centuries ago infectious diseases were considered as one big pot of diseases and nowadays we differentiate very clearly each of them with their differing pathogens and their dramatic differences, the same is already happening or will happen soon in oncology and many other diseases that are still clustered.

Rare or orphan diseases have been facing the challenge of small populations for all long time. They were challenged by clinical trials with low statistical power, the impossibility to gather enough evidence for marketing authorization applications, the indifference from drug developers due to the limited market and disseminated patients with difficulty to establish contact, between each others. In the cluster of rare diseases, all stakeholders joined forces and learned from each other to establish new pathways and overcome these challenges. Instead of reinventing the wheel, we should look at sources and methods developed in the field of rare diseases and apply them to PM, as fo example rare disease registers and registries. Such registries make it possible to pool data to gather a sufficient sample size for epidemiological and clinical research even in times of smaller patient populations.

22.5.6 A Solution – Making use of Registries

Traditional dieases registries in the sense of 'common disease regisistries' such as cancer registries and rare disease registries have been used many years to collect data and information about diseases and rare diseases and their treatments across Europe. Furthermore, they have served as key tool to assess clinical outcomes and for the assessment of technologies. Rare disease registries are often built up on national or local level to map RDs in certain areas and to collect information regarding the incidence and prevalence of different RDs in those selected areas. Beside general rare disease registers which are holding information and data on many different RDs, registries which are focusing on one specific rare disease also exist in the EU. Data for those disease registries are mostly obtained on a voluntary basis, observational studies and clinical data.

Traditional disease registries and rare disease registers are important tools for making use of PM and further strengthen the implementation of PM in healthcare systems across the EU. For example, often patients that are suffering from rare conditions are lacking access to adequate care. Further, their obtain health data is col-

lected and stored in silos and accordingly inaccessible or incompatible with other data sources.

Pancreatic cancer can be placed at the interface between rare and common diseases. Its incidence is increasing due to factors including demographic change. Pancreas cancer, (still) defined as a rare cancer, has the lowest survival rate of any cancer. Death rates from pancreas cancer are rising across Europe and beyond while those from all other cancers continue to fall. It is predicted that in 2030 pancreas cancer will be the second most frequent cancer. There is no option to control pancreas cancer incidence or mortality by primary or secondary (screening) prevention and only minor advances have been done recently in tertiary prevention under the umbrella of personalised treatment. Recently, the EC identified pancreas cancer as a tracer in bridging "rare" and "common diseases".

As demonstrated for the case of pancreas cancer, harmonized registries including the traditional disease registries as well as rare disease registries, will be major facilitators to understand the complexity of diseases, to conduct clinical trials, to improve the drug development process and to strengthen the uptake of PM across the EU.

22.5.7 Challenge 4 – Bringing Innovation to the Market

> *Bringing innovative PM solutions to the market presents a new set of challenges, including the issue of uncertainty. There will be opportunities to support the development of new risk-based approaches for the evaluation of PM in a context that encourages systematic early dialogue with all stakeholders, including regulators, funders and inno-vators, providing guidance for companies to enter the market for PM. As is the case for the research continuum, partnerships and innovation networks need to encourage cross-disciplinary and cross-border collaboration, and these would benefit from a transparent 'open Innovation'. Finally, research on appropriate policy, regulatory and legal frameworks would ensure that the new challenges associated with PM are adequately addressed from these perspectives.* [47].

In order to place an innovative product in a timely effective way on the market, the inherent uncertainties of innovation need to be considered. The implementation of an innovation to the market has traditionally been seen as a liner process "from research and development to regulatory approval, and then to health technology assessment (HTA) and on to the final reimbursement and implementation decision" [47].

However, the traditional market authorization processes, are not suitable for the approval of PM. The standard development process of drugs takes in average more than 10 years and costs up to a billion dollars [35]. The new understanding of the complexity of diseases makes it possible to design drugs that are more targeted to the patient's needs and therefore more effective than 'one-size fits all' drugs.

22.5.8 A Solution – Flexible Market Authorization Methods

Since large phase III clinical trials are not feasible, requirements for marketing authorizations need to adapt to the characteristics of PM. Approaches such as the adaptive pathways pilot launched by the European Medicines Agency (EMA) in 2014 open the way to promising new flexible marketing authorization methods for PM drugs. Furthermore, the consortium working on 'Medicines Adaptive Pathways to Patients pilots (MAPPs)', lead by the EMA, are evaluating important open questions for the further development and application of flexible marketing authorization methods [35]. MAPPs 'refer to flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits' [16].

Curently underlying outdated regulation is one of the main bottlenecks for the implementation of PM. Most of the relevant legislations and regulations such as for example the data protection regulation and medical devices regulation are currently under revision or have been recently revised.Hopefully the updated versions help to strengthen the uptake and implementation of PM [8, 9]. However, this may be a potracted process, since the revision and regulation in Europe is often an extremely complicated and complex task [9].

In contrast, the clinical trial regulation, which was released in 2014, is a perfect and rare example, how a regulation can be quickly revised. Improved and close collaboration and systematic early dialogue between all relevant stakeholders such as legislators, industry and other interest groups, made this possible [9].

Another regulation that is currently under revision is the data protection regulation [25]. During the time when the data protection regulation was published, it was not foreseeable how fast 'omics technologies' and the sequencing of the human will change the landscape of collecting, storing and analyzing personal data. To strengthen the uptake of PM, it is of great importance that the revised data protection regulation considers the increasing amount of available data and the different technologies by which the data is collected [9]. On the one hand the revision needs to take into account the protection of individuals and their personal information against misuse and stigmatization by third parties [26] and on the other hand research needs to be conducted without being hindered by overregulation. Moreover, harmonization of regulations and legislation is an essential step that is needed to strengthen the uptake of PM [36].

Furthermore, regarding the regulation of rare diseases, we should go one step beyond and asks ourselves if rare diseases should still be considered as a special group of diseases needing special pathways in the future? As we have seen, many conditions will divide into smaller clusters of disease and fit into the definition of rare diseases. Therefore, we will no longer need to develop special regulations for rare diseases. If we develop and apply them for the entire spectrum of new subconditions they will in any case be applicable for rare diseases.

22.5.9 A Solution – Systematic Early Dialogue

Systematic early dialogue (SED) is of great importance to bring the innovation in a timely effective way to the market. SED between the innovators, the end-users and the decision-makers ensures that innovators consider regulatory issues and reimbursement evaluation needs during the development process and will consequently lead to a more efficient innovation process [36]. SED between all stakeholders decreases the risk of duplication and misalignment of expectations and decreases the time to bring the innovation on the market. In conclusion,by applying SED, the risk that the innovation will end in the 'Death Valley of innovations' will decrease [35]. Furthermore, it brings the view of patients and HCPs into the review process and it provides guidance and clarity for the innovators throughout the whole innovation process.

22.5.10 Challenge 5 – Shaping Sustainable Healthcare

> *PM needs to rely on a knowledgeable healthcare system that is able to adapt to these new approaches in a timely and socially acceptable way, and that enables the partici- pation of all stakeholders to increase PM's effectiveness and effciency. Patients and the citizen will play an increasingly important role in adopting and controlling the use of data from electronic health records and in developing prospective surveillance and monitoring systems for personal health data. To ensure the effectiveness of the healthcare system, health economics research relating to PM needs to be supported. In addition a exible framework for pricing and reimbursement equitable for all patients needs to be developed, leading to an overall healthcare nancing strategy that covers all aspects of PM*. [47].

Reimbursement questions and quality and data integration are important factors, which need to be considered to build and shape sustainable healthcare systems.

Not only is there a need to change the design of clinical trials, to revise outdated regulation and to find ICT solutions to better ingrate big data, there is also an urgent demand to adapt financing and reimbursement mechanisms across Europe and beyond [36]. The traditional reimbursement and pricing mechanisms which are currently in place are making the uptake and diffusion of PM often difficult. Moreover, it is argued by critics that PM will impose rather a higher economic burden for healthcare systems than making healthcare systems more efficient due to the high costs of PM [58]. Since reimbursement systems across Europe are restrictive to pay for PM, EC Member States greatly vary in their ability to provide access to innovative therapies and medicines [17, 22, 30].

There is a clear lack of harmonization across the EU, due to the fact that the decisions with regard to pricing and reimbursement of pharmaceutical products and diagnostic tools are the responsibilities of the Member States and therefore made on a national or local level [22]. On the other hand, regulatory decisions are the responsibility of the EU [22]. Consequently, the EU is challenged 27 different pricing and

reimbursement mechanisms and health technology assessments [34]. Even within countries different mechanisms exist such for example as it is the case in UK. To further strengthen the uptake of PM, harmonization is urgently needed regarding pricing and reimbursement tools across the EU, as proposed in the ENVI report on a harmonized EU assessment of the Added Therapeutic Value of Medicines [6].

22.5.11 A Solution – Managed Entry Agreements

One of the big question marks remains the issue of pricing and reimbursement. For this area, we still need to develop new methods beyond the ones existing for orphan drugs. The sustainability of healthcare systems will be challenged if the incentives and pricing strategies developed for orphan drugs are extrapolated to all PMs. New risk methods must be developed for pricing and reimbursement. The Managed Entry Agreements negotiated between individual EU countries and pharmaceutical companies offer good examples of possible risk-sharing mechanisms. However, their results should be evaluated and they must become transparent before they can be implemented on a larger scale [19].

22.5.12 A Solution – European Reference Networks

The European Commission established for rare diseases so called 'European reference networks' (ERNs) to integrate information on rare disease into one single system across the EU. According to the European Commission those ERNs "should serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN should also reflect the need for services and expertise to be distributed across the EU" [10]. The Directive 2011/24/EU on the application of patients' rights in cross-border healthcare sets the rules for patients right to access safe and good quality treatment across the European borders and reimbursement roles. The directive provides a firm basis for increased cooperation between national health authorities. Some provisions address rare diseases. Article 12 foresees enhances cooperation of Member States including the criteria and conditions for ERNs for healthcare providers. The directive aims to identify already established centres of expertise and to encourage voluntary participation of healthcare providers in the future of ERNs.

ERNs can be seen as pilots to integrate information on rare diseases into one single system. If we will manage to integrate information on RDs on a European wide level into a single system by using ERNs, we will be able to harmonize data integration for other sectors as well. Improving data integration will greatly improve the drug development process and consequently the access to drugs for rare conditions.

22.6 Conclusions

Emerging technologies such as Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES) or Low-Coverage Sequencing (LCS) have proven that recent failures in stratified medicine show the need for better understanding of the molecular basis of rare diseases (RDs). The continuing advances in scientific knowledge will facilitate the move from the current stratified approach, which relies on static biomarkers of a RD, to a truly individualized treatment, which considers the combination of dynamic biomarkers, dynamic risk profiles, RD heterogeneity in time and space, the ever changing environment, epigenomics and many other factors that modulate RD phenotype and response to treatment. For example, big data analytics (e.g. IBM Watson) has been identified as a tool for the management of RDs and solving the challenges in the monitoring of a RD of an individual patient over time and space, i.e. taking into account the dynamics of individual patient information.

Conclusions can be drawn, that, on the one hand, the field of RDs has stimulated and pushed discussions and solutions in other fields. On the other hand, the final 5 challenges for personalised medicine, which had been identified by the PerMed SRIA, apply to all diseases including RDs. Since the vision of PM implies that the idea of common diseases will be replaced by unique disease profiles, there are no specific research and policy needs for RDs. This result has enormous implications for European and national policymakers. Instead of asking for separate regulations for RDs, it asks for future regulations and infrastructures (e.g. ERNs), which apply to all diseases in the same way. Rare cancers had been identified as a best practice example and role model to prepare and guide EU Member States in that direction.

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Chapter 23
Microphysiological Systems (Tissue Chips) and their Utility for Rare Disease Research

Lucie A. Low and Danilo A. Tagle

Abstract The scientific and technological development of microphysiological systems (MPS) modeling organs-on-chips, or "tissue chips" (TCs), has progressed rapidly over the past decade. Stem cell research and microfluidic concepts have combined to lead to the development of microphysiological platforms representing an ever-expanding list of different human organ systems. In the context of rare diseases, these bioengineered microfluidics platforms hold promise for modeling of disorders and could prove useful in the screening and efficacy testing of existing therapeutics. Additionally, they have the potential for replacing and refining animal use for new drugs and clinical treatments, or could even act as surrogate human systems for testing of new therapeutics in the future, which could be particularly useful in populations of rare disease sufferers. This chapter will discuss the current state of tissue chip research, and challenges facing the field. Additionally, we will discuss how these devices are being used to model basic cellular and molecular phenotypes of rare diseases, holding promise to provide new tools for understanding of disease pathologies and screening and efficacy testing of potential therapeutics for drug discovery.

Keywords Modeling organs-on-chips • Tissue chips • Microphysiological systems • Cell culture techniques • Drug toxicity • Drug safety • Organs-on-chips

23.1 Introduction

The drug development process is a time-consuming, risky and expensive process and suffers from extremely high attrition rates – it can cost billions of dollars over longer than a decade to get one single FDA-approved drug from a list of thousands. Even if candidate targets reach phase I clinical trials in humans, over 90% then fail

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either due to toxicities in human tissues that had not been predicted from preclinical tests, or from a lack of efficacy for the indicated disorder [26]. Clearly current *in vitro* and *in vivo* models are poorly predictive of human responses, and better models are needed.

The need is even greater in rare disease populations. While the definition of "rare" differs between countries, less than 5% of the 7000 currently identified rare diseases have effective treatments [9, 24]. There are a number of reasons for this. Firstly, the low prevalence of these disorders means pathologies are often poorly understood, if recognized and diagnosed at all. Populations may be geographically and demographically diverse, or in countries where healthcare providers cannot access reliable, updated information, patient materials, cell lines or treatment regimens, if these are even established. Natural history studies are often missing in these disorders, and current information may be limited to case studies or investigations in very small populations, therefore not reflecting the heterogeneity of patient populations, which tend towards familial-specific mutations. Furthermore, investment by pharmaceutical companies is lower where profit margins are likely to be reduced i.e. for smaller consumer pools, and where development of "orphan" drugs may not lead to commercialization. This combination of factors can lead to untreated or poorly managed patients, with the disease burden also affecting the family, friends, and colleagues of sufferers.

The issue of translational gaps between drug development and approval are of huge interest to the healthcare systems and the pharmaceutical industry worldwide, and improved models for safety and efficacy testing are critical for public health progress [23]. Many public and governmental funding agencies, including the Food and Drug Administration (FDA), National Institutes of Health (NIH) and Defense Advanced Research Projects Agency (DARPA) in the US, have recognized these needs and over the last decade have invested in programs to develop microphysiological systems (MPS) as tools to address these problems [8]. The premise of these systems is to model functional organ representations on "chips" (a term stemming from the original lithography fabrication technique, similar to that used for computer chip fabrication), often utilizing microfluidic technology to deliver fluids to human tissues on bioengineered platforms. These platforms can be used to model both healthy systems and those in a disease state, meaning not only can the pathology of a disease be better studied but also potential treatments for it tested safely and rigorously in human cellular systems. A main goal of many of these programs is to move towards the linkage of organ platforms to create a "human-on-a-chip", whereby linked organ systems can predict *in vivo* systemic responses i.e. sequential processing of a drug through the gut, then liver, then kidney, which can more accurately model the adsorption, distribution, metabolism and excretion profile (ADME) of a drug, plus its metabolites, in ways currently not possible. Looking to the future, these integrated human organ systems could provide tools for *in vitro* "clinical trials on chips", which could have multiple benefits for rare disease populations, circumvent the tainting of clinical trial patient cohorts, and mitigate the health risks associated with taking part in clinical trials in these vulnerable patient populations.

23.2 Progress and Challenges in the Field

For drug toxicity and safety screens, classical 2-dimensional cell culture methods have historically been used, together with animal (mainly rodent) studies. These have been very successful in predicting toxicity of compounds, with cell culture techniques being straightforward, reliable, cheap, as well as capable of being subjected to high throughput screens of thousands of compounds and dosages. However, they are not physiologically accurate as they lack the endothelial cellular scaffolding support, heterogeneous cell populations, and biomechanical forces found *in vivo*. A move towards 3-D modeling *in vitro* is widely acknowledged as preferable to provide better predictive models, and much progress has been made towards this aim from the development and use of 3-D organoids and MPS platforms. 3-D organoids are self-assembling tissue structures where induced pluripotent stem cells (iPSCs) are cultured and prompted to differentiate via supply of appropriate growth factors, then allowed to self-assemble into organ tissues of interest over time, often around a cellular scaffold or by the 'hanging drop' method (see [17] for a review). Organoid systems are amenable to high throughput screening, but the lack of vasculature and fluid exchange capabilities in these systems creates hypoxic tissues in central regions of the organoids that limits their physiological relevance. In contrast, 3-D microphysiological platforms are bioengineered to create physiologically relevant tissues with fluid flow to cells delivering nutrients and removing cellular waste, while subjecting cells to shear and stretch forces which mimic the cellular environment *in vivo*. These biologically-inspired designs are more complex and currently less amenable to high throughput screening, but have the advantages of allowing for real-time cellular monitoring or imaging through inclusion of 'reporter' cells in the milieu or readout electrodes embedded in the designs. For example, inclusion of virally transfected cells which fluoresce in the presence of apoptotic or hypoxic factors can allow real-time updates on cellular health and function [30]. Additionally, the platforms can give readouts on a number of "-omics" outcomes (genomics, proteomics, metabolomics), generating diverse data sets that are potentially highly informative, for example for machine learning algorithms for toxicity screening [28].

One of the early "organs-on-chips" was the lung chip [13–15], which mimicked the alveolar-capillary border of the lung by the co-culture of human alveolar epithelial cells and pulmonary microvascular endothelial cells on opposite sides of a flexible porous membrane. Cells were introduced into the appropriate chambers, and allowed to adhere to the porous membrane over the course of 16 days. When a vacuum was then applied to two air chambers running parallel to the cell chambers, the membrane would stretch and relax, hence mimicking the mechanical forces of breathing. This chip was used to model pulmonary inflammatory responses to the proinflammatory mediator tumor necrosis factor α (TNF-α), and also show the phagocytosis by neutrophils of foreign *E.Coli* bacteria introduced into the platform. Since this highly publicized work, the plethora of organs represented on "chips" has expanded to include liver (7), vasculature [10, 25, 27, 32], muscle (cardiac [2, 22, 33]

and skeletal [6, 19], kidney [35], reproductive tissues including ovary, uterus, cervix and fallopian tube [3, 18, 37], testes, blood-brain barrier [5], skin [1], gut [11, 16] and bone [7], amongst many others (see [4] for a review).

23.2.1 Use of Stem Cell Sources in MPS Platforms

The revolution in stem cell technology from the discovery that human induced pluripotent stem cells (iPSCs) could be generated from adult cells [29, 36] has led to the prospect of using iPSCs to seed these platforms. This has a number of advantages. Firstly, it eliminates the need for primary tissues from donors or patients, which are difficult and invasive to obtain, or not possible in some cases (i.e. brain). Second, using appropriate protocols allows cell differentiation into multiple cell types within the organ system of interest, creating a physiologically relevant heterogeneous cellular environment. Thirdly, it provides a renewable cell source for platform seeding, enabling wider reproducibility and therefore utility of the platforms for the research communities. Finally, it allows disease modeling as adult iPS cells e.g. from blood or skin can be created from individuals with specific pathologies, and used to populate organ platforms and create diseased organ model systems *in vitro*. This last point is particularly advantageous for rare disease sufferers as it allows non-invasive organ modeling, study of disease pathologies, and potential therapeutic screening and testing of promising therapeutics with no risk to the patient. This type of precision individualized medicine has not been possible to this point and could prove extremely useful for rare disease populations.

Caveats exist with the nascent iPSC field, however. Not all tissues are easy to create and differentiate appropriately, and even if differentiation is relatively straightforward, there is a lack of standardized protocols within the field, making reproducibility between laboratories difficult. Furthermore, some iPSC-derived cell types (for example, cardiomyocytes) do not display mature phenotypes, or may show properties different to primary tissues and embryonically derived stem cells [6]. These are issues that remain to be resolved for the whole stem cell field, and are being addressed by the research community in ongoing studies.

23.2.2 Challenges Currently Facing the MPS Field

In order for the potential utility for organ chips to be optimized in future years, the coupling of these systems will be important. However, physical coupling is complex in microfluidic platforms, with both biological and technical challenges to address. Biologically, common media (a “blood mimetic”) must be developed that is capable of supporting multiple cell types in different systems. Many of these cell types have been terminally differentiated in a particular differentiation media and are often then not compatible with other cell types. Additionally, cell numbers need to be

scaled relative to each other to represent the relative organ sizes and function of the human body, and inclusion of immune components will be important for predictive and biologically relevant models. Technical challenges include the elimination of bubble formation between coupled microfluidic platforms, and choosing the appropriate material for platform construction – currently, many platforms are fabricated from the clear, flexible plastic polydimethylsiloxane (PDMS), which is highly lipophilic and therefore can influence drug dosages studies as compounds are lost [20, 34]. Additionally, complex modeling and mechanics are needed to work out how to scale local perfusion within a system to flow rates between organ platforms to allow organ crosstalk – for example, some tissues need faster or slower fluid exchange according to their biological function. These challenges, however, are not insurmountable, and work continues apace to address them within the field. Currently, functional coupling studies are underway between some systems, with the effluent from one system collected and introduced into the next, i.e., effluent from a liver system being introduced to a kidney system to investigate the nephrotoxicity of metabolized compounds.

23.3 Tissue Chips for Rare Disease Research

Tissue chips could be utilized in a number of ways for rare disease research. For example, they could be used to model diseases, either by inducing known genetic mutations into healthy cells for monogenic disorders such as sickle cell anemia, or by populating platforms with iPSCs from patient groups. This disease modeling opens many avenues for advancing the understanding of disease pathologies at the molecular and cellular levels, as well as being used for drug toxicity and efficacy screening tests, and testing of promising therapeutic compounds in human 3-D *in vitro* systems.

23.3.1 Tissue Chips for Toxicity Screening

The use of tissue chips for monitoring of hepatotoxicity, nephrotoxicity and neurotoxicity, amongst others, could help uncover unexpected adverse effects of potential therapeutic compounds in rare disease populations. For example, developmental neurotoxicity is an important issue in compound development, and chemical safety screens may currently include intergenerational studies in animal models in order to monitor long-term effects. However, these are time-consuming and costly. MPS systems may be useful alternatives for these studies. Schwartz et al. [28] created "neurospheroids" in an MPS platform that contained neural, microglial and endothelial cell precursors on a hydrogel scaffold which self-assembled into 3-D constructs. 240 of these constructs were then treated with 34 known toxic chemicals and 26 known non-toxic compounds, and the resulting RNA-Seq data gathered from

the treatments used to create a predictive model of neural toxicity using algorithms fed into a machine learning system. The model later correctly classified the toxicity of 9 of 10 compounds in a blinded trial (with the final compound later found to be a false positive). This type of research holds promise for high-throughput developmental neurotoxicity screening of potentially therapeutic compounds in neurospheroids created from patients-derived iPSCs.

Tissue chips could also be used to screen orphan drugs – the drugs developed by pharmaceutical companies which are not commercialized due to the limited profitability of that drug for treating small populations. The Orphan Drug Act of 1983 in the US (and similar legal Acts in other countries) designated these drugs, vaccines and diagnostic agents as "orphans" and offers tax incentives, an exclusive 7 year marketing period following approval, aid with FDA approval processes and R&D grants to help these drugs move towards commercialization. Screening orphan drugs through tissue chips seeded with cells from a rare disease population could rapidly and radically change the status of these orphans and bring them closer to treating patient populations. Additionally, tissue chips could be useful for screening of multiple existing and licensed drugs to see if these drugs could be repurposed for rare diseases.

23.3.2 Modeling of Rare Diseases on Tissue Chips

A number of platforms are already in use to model rare diseases, and insights into disease pathology are being gained. For example, the cardiac abnormalities associated with Barth syndrome, a rare X-chromosome-linked myopathy, have been modeled using a "heart on a chip" [33]. The researchers generated iPSCs from two patients with Barth syndrome, which is caused by a mutation of the *TAZ* gene and leads to muscle and cardiac weakness, growth delays and immune deficiencies. With these iPSCs, they then created muscular thin films (MTFs) of cardiomyocytes on specially designed chips and left cells in culture for 5 days, after which MTF constructs were "peeled" from their glass coverslips and allowed to take on a curved shape. Stimulation of these films with electrodes caused contraction of the heart muscle cells, the degree of which was quantified by measuring the twitching of the films. As expected, MTFs from Barth syndrome patients did not contract as strongly as those from control healthy subjects, recapitulating the phenotype of cardiac muscle from Barth syndrome patients. Importantly, the investigators then used Cas-9 gene editing techniques to restore *TAZ* function in patient-derived cardiomyocytes, and showed that this could increase the twitch contractility of the MTFs – an important step in validating that the microphysiological system was accurately representing the *in vivo* phenotype, but also paving the way for investigation of novel gene editing techniques such as CRISPR-Cas9 for preclinical research on other diseases.

Ewing's sarcoma is a rare bone cancer that affects fewer than 1000 children and adolescents in the US per year, and is another example where MPS systems can

model the disease in a more physiologically relevant system than 2-D cell culture. Marturano-Kruik et al. [21] describe a protocol for bioengineering bone tumors by infusing tumor cell aggregates into a human bone MPS engineered from the patient's mesenchymal stem cells, which is then subject to biophysical stimuli such as mechanical compression during prolonged (<4 weeks) periods of culture. Unlike any current 2-D cell culture or organoid model, this provides the tumor cells, osteoblasts and supporting cells of the bone and extracellular matrix the opportunity for crosstalk, as well as exerting the same compression stresses that would be present on bone tissue *in vivo.* This model results in strong upregulation of cancer-related genes, expression of hypoxic and glycolytic tumor phenotypes, and the enhanced vascularization that is characteristic of tumors [31], suggesting that this could be an extremely useful model for future therapeutic testing.

The National Center for Advancing Translational Science (NCATS) recently provided supplemental funding for members of its Tissue Chip for Drug Screening program to develop and adapt MPS systems for modeling rare diseases, in collaboration with the physicians, patients and research teams of the Rare Disease Clinical Research Network (RDCRN). Projects funded by these collaborations include: the creation of tissue engineered blood vessels (TEBVs, [10]) from patient-derived iPSCs which recapitulate the fatal atherosclerosis of Hutchinson-Gilford progeria syndrome; the modeling of hereditary hemorrhagic telangiectasia (HHT), a rare dominant genetic disorder characterized by the presence of vascular malformations, in a vascular microphysiological system [25]; the muscle weakness of Glycogen Storage Disease type III (Cori disease) in bioengineered skeletal muscle myobundles; the brain tumors characteristic of the genetic disorder Tuberous sclerosis in a "neurovascular unit" [5]; and modeling of the rare childhood liver disease Alpers Huttenlocher syndrome using a liver sinusoid chip [30]. This exciting application of MPS technology promises to help advance the understanding of the underlying pathologies of these diseases, but also will allow future screening of a multitude of different drugs on the platforms that may be useful therapeutically but cannot be tested *in vivo,* opening up avenues for repurposing of existing drugs in many disease states.

23.3.3 "Clinical Trials on Chips" for Rare Diseases

Finally, tissue chips hold promise for use in "clinical trials on chips" for rare disease populations. Currently, the lack of appropriate models for safety and efficacy screening at the preclinical stage of drug trials means that phenotypic pathologies and disease-related metabolism differences in patient populations may not be uncovered before drugs are administered to individuals enrolled in clinical trials, increasing the risk of unanticipated adverse reactions such as nephrotoxicity leading to acute kidney injury [12]. The connectivity of multiple organ chips populated with iPSCs from patients could recreate an individual's whole body phenotype *in vitro*

for therapeutic screening and treatment, reducing these risks by allowing drug effects to be studied non-invasively, and with no risk to the individual.

Biobanking of tissue samples from rare disease patients while alive or after death (after following of appropriate informed consent procedures) may also create "libraries" of patient populations that could help address another two issues facing rare disease research. One is that clinical trials can only be performed on patients currently living with the disease, leading to highly heterogeneous patient populations and small, statistically underpowered clinical trials. Additionally, patients are sometimes disqualified from taking part in multiple clinical trials, because to adequately evaluate a drug's response, it may have to be administered to a physiologically naïve individual who has not been exposed to a similar drug in the past. MPS platforms could be used not only to help uncover what effects previous clinical trials may have had on an individual's physiology, but also create chips from naïve (alive or deceased) patients. This would create chips from an ever-expanding population of rare disease patients, with the chips recreated many times and entered into multiple clinical trials. Additionally, this would increase the population size in any given trial, and therefore increase the statistical power of these currently small, often underpowered trials.

23.4 Conclusion

The applications of tissue chips mentioned above hold much potential for a number of endeavors which could aid in the diagnosis, understanding, and treatment of rare diseases. Drug development pipelines could be streamlined as target compounds could be tested for toxicity in early stages of development in more physiologically relevant models than 2-dimensional cell culture. Not only could this process screen out toxic compounds earlier during drug development, it could reduce the time and money spent on taking a drug to animal trials, and would be a better predictor of efficacy *in vivo*. While 2-D cell culture and animal studies will still be needed for the foreseeable future for high-throughput toxicity screening and whole-organism therapeutic testing, the use of tissue chips could also help reduce and refine the number of animals being tested during preclinical phases of drug development, as the toxicity and efficacy of candidates could be better modeled on MPS platforms before being tested in animals. This has important economic and ethical advantages.

However, challenges remain regarding population of platforms with patient-derived cells, as not all tissues readily differentiate from stem cells, and the low incidence of rare diseases means tissue sources can be difficult to obtain – even when a patient is identified, they are under no obligation to provide cells that can be used for research. As discussed, the biobanking of rare disease patients' cells may be helpful for researchers in future years, but adequate cell resources remain a challenge for the moment.

Furthermore, the development of these platforms is still at a relatively new stage, and while the field is burgeoning and new organ systems are being developed and added to an ever-expanding list, the challenges of cell sourcing and functional/physical coupling will require the investment of effort from a multitude of experts in a number of fields, including stem cell researchers, tissue bioengineers, microfluidics and biomaterials engineers, as well as clinicians and experts in multiple biological systems. In order for microphysiological platforms to live up to their potential in future years, collaboration and investment will be needed from these experts, as well as from a number of stakeholders at multiple levels, including research funding bodies, and the pharmaceutical and biotechnology industries. Rare disease patient advocacy groups can help by lobbying pharmaceutical companies to invest in moving towards the use of these platforms in their R&D processes, but reproducibility and validity of the platforms must be proven within the research community first, with support from government and private funding bodies. Expertise and input from the pharmaceutical and biotechnical industries will then be crucial in the coming years for the continued development of effective, reliable and cheap MPS platforms which can be validated by international regulatory bodies such as the Organisation for Economic Cooperation and Development (OECD), and then approved by bodies such as the FDA in the US for more widespread use and application for research and therapeutic development. The current interest and investment in MPS technology offers much promise in future years for rare disease research and treatment.

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Part VIII
Rare Diseases Epidemiology

Chapter 24
Epidemiology of Rare Lung Diseases: The Challenges and Opportunities to Improve Research and Knowledge

Cormac McCarthy, Beatriz Lara Gallego, Bruce C. Trapnell, and Francis X. McCormack

Abstract Rare lung diseases encompass a broad spectrum of conditions and affect an estimated 1.2–2.5 million people in North America and 1.5–3 million people in Europe. While individual rare lung diseases affect less than 1 in 2000 individuals, collectively they have a significant impact upon the population at large. Hence it is vital to understand firstly the epidemiology and subsequently the pathogenesis and clinical course of these disorders. Through a greater understanding of these aspects of disease, progress can be made in reducing symptoms, containing healthcare costs

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and utilizing resources efficiently. Furthermore, a greater understanding of the pathobiology of rare lung diseases can inform both the pathogenesis and management of more common pulmonary disorders.

In this chapter we review how epidemiological approaches and the utilization of patient registries has improved the knowledge and management of rare lung diseases. We further focus on the epidemiology of several of the more widely known rare pulmonary disorders, including idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF) and alpha-1 antitrypsin deficiency (AATD). To conclude we describe how patient advocacy groups and foundations have driven advances in research and management of ultra-rare lung diseases, namely, the major strides made in the management and understanding of lymphangioleiomyomatosis (LAM) and pulmonary alveolar proteinosis (PAP).

We conclude that the models used to study some of the rarest of diseases may be successfully adopted by other rare and common disease communities, leading to improved care and the possibility of novel therapeutic options.

Keywords Rare Lung Disease • Cystic Fibrosis • Alpha-1 Antitrypsin • Lymphangioleiomyomatosis • Pulmonary Alveolar Proteinosis • Idiopathic Pulmonary Fibrosis

24.1 Introduction

Rare lung diseases are a group of conditions that individually affect fewer than 1 in 2000 persons [127]; or for the ultra-rare disorders, fewer than 1 in 2 million individuals [45]. Collectively, however, these disorders affect quite a large number of patients; estimated at 1.2–2.5 million individuals in North America [43] and 1.5–3 million people in Europe [78, 127]. It is therefore important to understand pathogeneses and epidemiology [72] of these disorders, in order to reduce human suffering, contain healthcare costs and maximize efficiency of resource utilization. In addition, research into rare diseases often provides valuable insights into the pathogenesis of more common disorders [90]. As an example, azithromycin was recently adopted as a prophylactic agent to prevent exacerbations in chronic obstructive pulmonary disease (COPD) [3], almost a decade after studies of this anti-inflammatory antibiotic were shown to be beneficial in cystic fibrosis (CF) [116].

In this chapter we will discuss the epidemiology of rare lung diseases, with a focus on some of the more common and widely known members, including idiopathic pulmonary fibrosis (IPF), CF and alpha-1 antitrypsin deficiency (AATD). We will review how epidemiological approaches and patient registries have improved the knowledge of these conditions, and how these methods may benefit rarer lung diseases. Finally we will describe how the efforts of patient advocacy groups and foundations have led to advances in two rare lung diseases, lymphangioleiomyomatosis (LAM) and pulmonary alveolar proteinosis (PAP).

24.2 Rare Lung Disease: Diagnostic and Classification Challenges

Classifying all rare lung disease together under one heading is problematic, as some conditions are relatively more common, such as CF or AATD, while other diseases are quite rare, such as PAP, LAM or Hermansky-Pudlak syndrome (HPS). In addition, there is substantial variation among diseases in clinical features and manifestations, including age of onset, patterns of extra-pulmonary involvement, mode of inheritance and prognosis. Some conditions are caused by monogenic mutations (AATD, CF) which are amenable to screening [14, 71, 126], facilitating earlier diagnosis and intervention. Other conditions are multifactorial and have an unknown genetic basis (e.g. lymphangiomatosis), which can result in diagnostic delays and difficulties with classification [32]. Symptoms of rare lung diseases may be mistaken for those of more common conditions [66] as often happens with AATD; a disorder which can present clinically as one of the most common chronic respiratory conditions (COPD) and, despite its high penetrance, can vary considerably depending on the exposure to external factors such as tobacco smoke [122].

The principle of parsimony does not necessarily apply to rare diseases, and applying Occam's razor can be hazardous. For instance, the failure to realize that recurrent pneumothoraces may be due to LAM rather than primary spontaneous pneumothorax [54], may delay pleurodesis and place patients at risk of future morbidity. In cases where intervention has a clear impact on outcome, such as sirolimus treatment to slow progression in LAM, timely diagnosis is especially important to preserve lung function, limit unnecessary and invasive investigations and contain costs. Early referral to specialist centres for rare lung diseases can be helpful in this regard [42]. Correct coding and use of proper nomenclature impacts upon the ability to classify the epidemiology of these conditions [127], design appropriate clinical trials and optimise management.

24.3 Rare Disease Networks and Databases: Establishing Prevalence and Enabling Research

Estimates of the prevalence and incidence of rare disorders are made possible by the existence of networks, consortia and patient organisation alliances such as the National Institutes of Health Rare Diseases Clinical Research Network (NIH-RDCRN), European Organisation for Rare Diseases (EURODIS) and Orphanet. The prevalence of rare lung disease in Europe varies greatly, from 20 per 100,000 people for AATD to 0.15 per 100,000 people for HPS. The prevalence data of several rare lung diseases is listed in Table 24.1, gleaned from data obtained from Orphanet's 2016 report, which is compiled through a systematic survey of published and online sources [98]. These data help establish a clear picture of the

Table 24.1 Prevalence of rare lung diseases

Disease	Estimated Prevalence per 100,000	
Alpha-1 Antitrypsin Deficiency	20	*
Idiopathic Pulmonary Fibrosis	16.7	
Hereditary Haemorrhagic Telangiectasia (Rendu-Osler-Weber Disease)	16	*
Systemic Sclerosis	15.4	*
Bronchopulmonary Dysplasia	13	*
Sarcoidosis	12.5	
Small-Cell Lung Cancer	11.2	*
Tuberous Sclerosis	10	*
Granulomatosis with Polyangiitis	9	*
Cystic Fibrosis	7.4	*
Dermatomyositis, Polymysositis	7.1	*
Primary Ciliary Dyskinesia	5	*
Congenital Lobar Emphysema	4	
Acute Interstitial Pneumonia	3.8	*
Anisynthetase Syndrome	3.5	
Pulmonary Arterial Hypertension	3.3	*
Mesothelioma	3.1	*
Chronic Thromboembolic Pulmonary Hypertension	3	
Graft Versus Host Disease	2.3	*
Scimitar Syndrome	2	*
Hypereosinophilic Syndrome	1.5	*
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)	1.5	
Adult Pulmonary Langerhans Cell Histiocytosis	1.5	*
Legionellosis	1.1	*
Idiopathic and/or Familial Pulmonary Arterial Hypertension	1	*
Goodpasture Syndrome	0.64	
Birt-Hogg-Dubé Syndrome	0.5	*
Idiopathic (Autoimmune) Pulmonary Alveolar Proteinosis	0.5	
Relapsing Polychondritis	0.35	
X-linked Agammaglobulinaemia	0.22	
Lymphangioleiomyomatosis	0.15	
Hermansky-Pudlak Syndrome	0.15	
Dyskeratosis Congenita	0.1	*

* = European Data Only

natural history of rare lung diseases, and facilitate clinical trials and standardised care, aimed at improving patient satisfaction and outcomes [127].

The RDCRN is made up of 22 research consortia and maintains an online registry that supports international multicentre studies [92]. The Rare Lung Diseases Consortium (RLDC) is part of this network, which itself consists of 29 US and 18 international

clinics that contribute to both data collection and study recruitment, accelerate clinical research and improve medical care access for persons with rare lung diseases. The RLDC collaborates closely with several patient organisations including the LAM Foundation, PAP Foundation, Alpha-1 Foundation, HPS Network and Histiocytosis Association and others to provide educational resources and recruit for clinical trials. In rare lung disease research, the major obstacle to conducting a clinical trial is the small number of participants available for inclusion. The use of internet based communications by patient organisations is a novel and exciting method which has proven to be a useful strategy for trial recruitment [123]. Networks and patient registries increase the pool of patients available for research studies, and often include repositories for sample collection and distribution. (Tables 24.2 and 24.3).

Patient foundations and registries often engage in collection of self-reported data, which can be useful for demographic studies but is not generally sufficiently validated for rigorous studies involving prevalence, incidence, mortality and outcome data. Hospital coding data and insurance claims databases have proven to be useful in determining the prevalence of several rare diseases, including IPF [68, 96, 110]. Other methods have included surveying death certificates [22], supplemented with data from patient registries to improve accuracy [26]. The latter approach is based on the premise that combined approaches to epidemiological data collection are particularly well suited to the rare diseases.

Clinical trials are difficult to perform in rare diseases. Validation of optimal outcome measures of rare lung disease is vital, as is the identification of surrogate markers that accurately predict meaningful endpoints. Randomised control trials are not always feasible in rare conditions, and alternative study designs such as ‘n-of-1’ single patient, crossover and sequential approaches may be considered [11, 75]. In diseases where prognosis is poor, survival is the most important outcome to ascertain the efficacy of a new drug, but this is not always practical or feasible when conditions are extremely rare or survival is prolonged; in those cases use of clinical parameters which are predictive of survival are necessary surrogates. Examples of rare disease communities that have successfully conducted large epidemiological studies to discover powerful surrogates for survival include IPF [27] and CF [61]. In these diseases, pulmonary function and frequency of acute exacerbations [76] correlate with risk of death and are now used as outcome measures in pivotal trials, speeding the discovery of new treatments. Studies are desperately needed in other rare diseases, including those of much lower prevalence, to determine appropriate surrogates for each particular condition.

The study of the more common rare lung diseases including IPF, AATD and CF can inform the approach to ultra-rare conditions and drug development. For example, in AATD, a well-designed National Heart Lung and Blood Institute (NHLBI) Registry facilitated accurate description of key demographic and physiologic characteristics of AATD individuals [86], including patterns of lung function decline that are critical for the design of trials. One recent benefit of the Registry was the discovery of a promising surrogate for the efficacy of therapeutics, including augmentation therapy [16]. Furthermore, in AATD the information recorded in national registries has been useful in identifying differences in cohorts of patients in disease

Table 24.2 Patient organsiations/resources for rare lung disease

Organisation	Condition	Organisation	Condition
Rare Lung Disease Consortium (RLDC)	Collaboration of patient organizations, clinical investigators and NIH	Longfibrose patiënten vereniging	Idiopathic Pulmonary Fibrosis
www.rarediseasesnetwork.org/cms/rld		www.longfibrose.nl	
RareConnect by EURORDIS (European Rare Disease Organisation)	Information on a spectrum of rare diseases	PF Advocates	Idiopathic Pulmonary Fibrosis
www.rareconnect.org		www.pfadvocates.org	
National Organization for Rare Disorders (NORD)	Information on a spectrum of rare diseases	The Lymphangioleiomyomatosis (LAM) Foundation	Lymphangioleiomyomatosis
www.rarediseases.org		www.thelamfoundation.org	
Alpha-1 Foundation (USA)	Alpha-1 Antitrypsin Deficiency	LAM Health Project	Lymphangioleiomyomatosis
www.alpha1.org		www.lamhealthproject.org	
Alpha-1 UK Support Group	Alpha-1 Antitrypsin Deficiency	European LAM Federation	Lymphangioleiomyomatosis
www.alpha1.org.uk		www.europelamfederation.org	
Alpha One Foundation (Ireland)	Alpha-1 Antitrypsin Deficiency	LAM Action (UK)	Lymphangioleiomyomatosis
www.alpha1.ie		www. lamaction.org	
Alpha1 Netzwerk (Germany)alpha1-netzwerk.de	Alpha-1 Antitrypsin Deficiency	LAM France	Lymphangioleiomyomatosis
		www.francelam.org	
BHD Foundation	Birt-Hogg-Dubé Syndrome	LAM Japan	Lymphangioleiomyomatosis
www.bhdsyndrome.org		www.j-lam.net	
Cystic Fibrosis Foundation (USA)	Cystic Fibrosis	PCD Foundation	Primary Ciliary Dyskinesia
www.cff.org		www.pcdfoundation.org	
Cystic Fibrosis Trust (UK)	Cystic Fibrosis	PAP Foundation	Pulmonary Alveolar Proteinosis
www.cysticfibrosis.org.uk		www.papfoundation.org	
Cystic Fibrosis Canada	Cystic Fibrosis	Pulmonary Hypertension Association (PHA) USA	Pulmonary Hypertension
www.cysticfibrosis.ca		www.PHAssociation.org	

CF Europe	Cystic Fibrosis	Pulmonary Hypertension Association (PHA) UK	Pulmonary Hypertension
www.cf-europe.eu		www.phassociation.uk.com	
Hermansky-Pudlak Syndrome Network	Hermansky-Pudlak Syndrome	PHA Europe	Pulmonary Hypertension
www.hermansky-pudlak.org		www.phaeurope.org	
Pulmonary Fibrosis Foundation	Idiopathic Pulmonary Fibrosis	WASOG (World Association for Sarcoidosis and Other Granulomatous Disorders)	Sarcoidosis
www.pulmonaryfibrosis.org		www.wasog.org/index.php/patient-societies	
Pulmonary Fibrosis Trust	Idiopathic Pulmonary Fibrosis	EPOS (European Association of Patients Organizations of Sarcoidosis and other Granulomatous Disorders)	Sarcoidosis
www.pulmonaryfibrosistrust.org		www.sarcoidosis.biz	
Pulmonary Fibrosis UK group	Idiopathic Pulmonary Fibrosis	National Sarcoidosis Resource Center	Sarcoidosis
www.pulmonaryfibrosis.org.uk		www.nsrc-global.org	
The Coalition for Pulmonary Fibrosis	Idiopathic Pulmonary Fibrosis	Sarcoidosis and Interstitial Lung Association:	Sarcoidosis
www.coalitionforpf.org		www.sila.org.uk	
Action for Pulmonary Fibrosis	Idiopathic Pulmonary Fibrosis	Sarcoidosis Association	Sarcoidosis
www.actionpulmonaryfibrosis.org		www.sa-uk.org	
Irish Lung Fibrosis Foundation	Idiopathic Pulmonary Fibrosis	Sarcoidosis Network Foundation	Sarcoidosis
www.ilfa.ie		www.sarcoid-network.org	
Lungenfibrose eV	Idiopathic Pulmonary Fibrosis	Tuberous Sclerosis Alliance	Tuberous Sclerosis
www.lungenfibrose.de		www.tsalliance.org	
Canadian Pulmonary Fibrosis Foundation	Idiopathic Pulmonary Fibrosis		
www.cpff.ca			

Table 24.3 Rare lung disease registries

Registry	Approximate number of Patients	Year
Alpha-1 Registry (USA)	5426	2016
National Alpha-1 Antitrypsin Deficiency Registry (Ireland)	334	2016
Rare Lung Disease Consortium/Birt-Hogg-Dubé Registry	110	2016
European Cystic Fibrosis Society Patient Registry (Europe) (27 countries)	38,985	2013
Cystic Fibrosis Patient Registry (USA)	28,676	2014
UK Cystic Fibrosis Registry	10,583	2014
French Cystic Fibrosis CF Patient Registry	6,329	2013
Cystic Fibrosis Registry of Ireland	1,183	2014
Hermansky-Pudlak-Syndrome Network	1,223	2016
LAM Foundation	2,056	2016
National Registry for Pulmonary Alveolar Proteinosis	81	2016
Pulmonary Hypertension Association Registry	15,964	2016

severity, smoking exposure, access to treatment and frequency of phenotypes including very rare mutations [33, 100].

To understand the challenges of describing the epidemiology of individual rare lung diseases, we will focus on how IPF, CF and AATD may inform future work in other conditions. Following this we will briefly describe the challenges in extremely rare conditions and detail some of the exceptional progress in LAM and PAP.

24.4 Idiopathic Pulmonary Fibrosis: Epidemiological Challenges

Although idiopathic pulmonary fibrosis (IPF) is perhaps more widely known to the broader medical and lay communities than most rare lung diseases, many aspects of the approach to this disease require refinement. IPF is a complex disease that requires a multidisciplinary approach to ensure timely and accurate diagnosis [108]. When the correct diagnosis is delayed or missed, lags in specialist care are associated with increased risk of death [69]. The discovery and approval of novel treatments has sparked renewed interest in IPF clinical care and translational research. Prior to the year 2000, very few clinical trials had been performed in IPF, encompassing a total of only about 100 patients enrolled in small, low quality studies. Since that time, thousands of patients have been enrolled in randomized, controlled clinical studies [21, 127], leading to significant improvements in therapeutic options and a large body of data that is being used to inform trial design. The emergence of pirfenidone [21, 59, 62] and nintedanib [59, 114] as medications that have shown benefit in reducing pulmonary function decline in IPF has led to a greater focus on

the epidemiology and clinical course of IPF, including identification of the subsets of patients who may uniquely benefit from such novel treatments.

The epidemiology of IPF had been poorly described in the literature until recently. It was not until 1998 [60] that a clear definition of the disease was proposed and incorporated into the 2000 consensus diagnostic criteria, which were then subsequently updated [63, 108]. This confusion in accurately defining IPF compromised accurate epidemiologic data collection, as many patients were coded under alternative and often erroneous diagnoses. The reported prevalence range of IPF using these methods was therefore implausibly broad, spanning almost three logs from 0.7 per 100,000 to 63 per 100,000, and incidence figures ranging from 0.6 per 100,000 to 17.4 per 100,000 [106, 107]. The methods used to acquire epidemiological data in IPF have included accessing healthcare insurance claims and benefits databases [68, 96, 110], medical record linkage systems [99], primary care databases [41], surveys of pulmonary clinics [47, 58, 89], and death certificates and pathology reports [22]. These varied approaches led to conflicting reports of mortality rates and incidence, with the effect of increased age poorly accounted for [91]. Under recognition and misclassification [56] have plagued data collection based on extraction from death certificates and national registries [73]. Although the use of insurance claims databases may be more accurate for demographic and outcome data collection, this method is heavily dependent on correct initial coding, incompletely validated [29] and subject to overestimation of prevalence and various outcomes.

24.5 Evolving Management of IPF: Improving Epidemiological Data

While the epidemiology of IPF is still not well understood, it continually improving. Evidence for epidemiologic progress includes new, approved therapeutic options and better diagnostic and management strategies. Rapid and accurate methods of diagnosing IPF are now possible in the form of high resolution computed tomography (HRCT) imaging, which is considered diagnostic if the classic pattern of usual interstitial pneumonia characterised by subpleural, basilar-predominant reticular abnormality with honeycombing is identified [79, 108]. The recognition that the diagnosis can be made based on clinical criteria has reduced the need for lung biopsy [109]. Developments in bronchoscopic techniques such as transbronchial cryobiopsy have further improved the ability to accurately diagnose IPF by less invasive, non-surgical methods [5, 35, 67, 102]. More accurate diagnosis of IPF will also allow better data acquisition, that together with the growing portfolio of novel candidate therapies and biomarkers will be used to assess disease progression and prognosis [37] and design and accelerate trials. Accurate identification of IPF will, in turn, lead to better understanding the natural history of the disease, as well as its societal impact on health care use and costs [74]. The use of well-designed registries

have dramatically improved clinical trial recruitment in IPF. The NHLBI sponsored IPF Clinical Research Network (IPFnet) has screened over 1000 patients [23] for inclusion in clinical trials for a range of treatments including prednisolone, azathioprine, and N-acetylcysteine [6, 81], sildenafil [48] and warfarin [93], to name a few. While none of these medications showed any clinically significant benefit in trials, the use of IPFnet as a source for patient recruitment has provided a platform for future accurate epidemiological classification of IPF, and a template for other rare lung disease communities to emulate.

24.6 Cystic Fibrosis: A Model for Epidemiological Studies in Rare Disease

Cystic fibrosis is a rare disease caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR), and it is the most common life shortening autosomal recessive disorder in Caucasians. It is a multisystem disease, in which the major cause of mortality is due to pulmonary complications [111]. The genetic inheritance pattern in CF lends itself to screening at birth [31], which has led to a better understanding of the natural course of disease progression and facilitated collection of powerful epidemiological data. Although rapid and inexpensive genotyping for CFTR mutations is increasingly accessible and has greatly improved the diagnostic yields of newborn screening [126], on a world-wide basis the workhorse for diagnosis remains sweat chloride testing. Together these methods have the potential to identify almost all cases of CF in early infancy. This combination of early and accurate diagnosis, well understood molecular pathophysiology and powerful patient advocacy place CF at the vanguard of all models to study rare lung disease.

The incidence of CF ranges from approximately 1 in 350,000 in Japan [49, 139] to 1 in 3,500 live births in the USA [65] to approximately 1 in 1,353 in Ireland [30], which has the highest incidence and prevalence worldwide. Registry data has been essential for facilitating between-country comparisons of incidence, prevalence, survival and other outcomes [12, 52]. For instance, it is now clear that children and young adults born in the USA have better pulmonary function than those in the UK [38]. Observations such as these, which have been a direct result of development of informative registries, spur investigation into the underlying reasons for differences, facilitate interventions and provide opportunities for quality improvement.

24.6.1 Improved CF Care: The Benefits of Registries and Patient Foundations

Registries in CF are excellent sources of demographic data and have been used to great effect in outcome studies, for clinical trial recruitment and as prognostic markers. More so than in perhaps any other rare lung disease, CF patient registries have informed the natural history of disease progression and facilitated breakthrough discoveries.

The use of data from CF registries has helped to identify the association between particular genotypes and mortality risk [87], as well as the prediction of prognosis based on clinical parameters including FEV1, body mass index (BMI) and bacterial colonisation of sputum [76]. The impact of external factors such air pollutants [40], second-hand smoke exposure [18] and socioeconomic status [94, 121] on lung function decline, mortality and other outcome measures has also been gathered from registry studies. As CF is a multisystem disorder, the accurate collection of data is essential for predicting prognosis and measuring response to intervention, and registries are useful for capturing data on comorbidities, including osteoporosis, diabetes, pancreatic insufficiency and gastrointestinal complications, all of which impact upon disease progression [83].

While registries ideally should collect similar data in a standardized manner, major differences can occur internationally which may affect their use as validated sources of information regarding outcomes and prognosis. The European CF Demographics Registry Project compared data collected from 35 European countries' registries, including demographic data for 29,000 patients [85], and demonstrated significant variation between the age at death and proportion of patients diagnosed with CF in non-EU countries compared to EU countries, perhaps due to either under-diagnosis, premature mortality or differences in patient registration in the former. To tackle this difference in reporting the European CF Society (ECFS) has launched an initiative to develop standardised care programmes [19]. Improvements in care have been well demonstrated through collaboration between caregivers, patient foundations, registries and patients in several countries. In the USA, for instance, the CF Foundation developed extensive quality improvement programmes, setting key performance indicators for CF centres, and using registry data to create a transparent forum for quality improvement [119, 120]. The efforts have resulted in greater compliance with diabetes screening [104, 105], and improvement in BMI [128] and in overall care provision [130]. Furthermore, the use of clinical prediction tools in CF identifies patients for lung transplantation earlier [77] and predicts overall prognosis [82]. Registries have been essential for validating scoring systems, which in some cases have developed as candidates for surrogate outcome measures. They are also useful in cost analysis and assessing referral patterns [80]. Finally, CF registries are ideal sources of information to examine the long term effects and impact novel therapies have on outcomes, including survival, exacerbations and quality of life measures [131].

24.6.2 Cystic Fibrosis Registries and Novel Treatment Development

CF registry studies have shown survival benefits associated with long term use of nebulised dornase alfa (DNase) [137] and tobramycin [118]; cases in which short-term randomised control trials [36, 113] failed to reveal an effect. These examples highlight the utility of registry studies in assessing therapies in rare diseases with small study populations. Furthermore, collaborative studies employing CF registries have played a pivotal role in the development of novel drugs, in particular the CFTR potentiator ivacaftor [112].

The Cystic Fibrosis Foundation Therapeutics Development Network (TDN) has successfully conducted numerous clinical trials since its inception [39] and was instrumental in developing high-throughput screening to identify candidate drugs, and enrolling patients in phase I, II and III trials around the world. Apart from establishing a significant pool of over 20,000 patients from the USA and links to international sites, this network improved the integrity and efficiency of trial conduct and data collection and management. The subsequent development of ivacaftor has been revolutionary in CF care, demonstrating a significant improvement in inflammation, pulmonary function, exacerbation frequency and quality of life in a subset of patients with CF [101, 117]. These exciting results are transforming care in CF and are setting expectations for future novel and personalized medicine at a very high level for CF, and other genetic lung diseases. Network development and intelligent use of registry data in CF are exemplars for all rare lung diseases.

24.7 Alpha-1 Antitrypsin Deficiency: Epidemiological Findings of a Complex Genetic Condition

Alpha-1 antitrypsin (AAT) is a serine protease inhibitor produced in the liver, which is abundant in the blood stream and acts mainly in the lung to counteract neutrophil elastase. In AAT deficiency (AATD) there is an imbalance in the protease/antiprotease balance leading to parenchymal lung damage and emphysema. AATD is a multisystem disorder where polymerisation of mutated AAT can accumulate in hepatocytes leading to chronic liver disease and the rare occurrence of AATD associated panniculitis [34]. AAT is inherited in an autosomal codominant pattern with more than 50 known deficient alleles, the most common being those encoding the S and Z mutations, with prevalence varying markedly across continents and within countries.

Despite commendable attempts to characterize the genetic landscape of AAT worldwide, small studies have often fallen short and detailed genetic epidemiological studies are lacking in about half of all countries across the globe [25]. However, innovative tools used in other scientific areas of knowledge have been used to compensate this circumstance; Blanco *et al* used an informatics approach namely the ArcMap (ArcGGIS Geographical Information System, for Microsoft Windows)

based on the inverse distance weighting (IDW) multivariate interpolation method to develop detailed maps of the prevalence of S and Z alleles worldwide. This approach identified an unsuspected significance of S and Z allele frequencies in areas where AAT deficient allele prevalence had not been previously studied, highlighting these areas as priority targets for further screening and future trials [8].

Interestingly, these epidemiological studies supported the hypothesis that the Z mutation appeared in the Scandinavian Peninsula approximately 2000-6500 years ago and that Viking raids may have spread the Z allele. In contrast, the S allele may have originated in the Iberian Peninsula more than 9000 years ago and it shows the opposite distribution with a gradient south-north and west-east in Europe [9]. The approach to National registries in AATD have served as a platform to share knowledge about the condition, promote screening amongst at risk individuals and produce local guidelines regarding diagnoses and treatment, and serves as an exemplar for all rare diseases [14, 15, 24, 70].

24.8 Lymphangioleiomyomatosis: Excellence in Foundation Driven Developments in Care

Lymphangioleiomyomatosis (LAM) is a rare, progressive, cystic lung disease found almost exclusively in women [57, 115]. Similar to other rare lung diseases, the limited available epidemiological data about the disease has been acquired from federal and international registries and advocacy group sources, as well as case report series.

Data from the NHLBI LAM registry [115] and the Japanese LAM Registry [44] together with several large cases series from Europe [55, 136], Korea [95] and Japan [64] have been used to compile a demographic and epidemiologic picture for LAM. With such a rare disease, accurate prognostic information and survival data has been difficult to acquire due to the small, geographically disperse populations and variable study methodology. Mortality was initially reported to be very high, with early retrospective cohorts reporting 10-year survival rates of only approximately 20% [20, 125], but more recent studies have estimated the 10-year survival to be approximately 76-91% after symptom onset [44, 55, 88, 136]. Although the mean age at diagnosis is approximately 40-41 years [97, 115] cases in prepubertal individuals and octogenarians have also been reported [46]. Until recently it had been difficult to elucidate the factors that determine survival or predict prognosis in LAM, and there have been some associations made that are not intuitively obvious; for instance, pneumothorax as the initial presentation has been associated with favourable outcome [44, 129] while airflow obstruction which is responsive to bronchodilators is associated with pulmonary function decline [132].

The LAM Foundation, a disease specific patient advocacy organisation established in 1995, has been instrumental in accelerating advances in LAM. A population-based study conducted on 410 patients with LAM registered with the

LAM Foundation has been influential in defining the prognostic indicators in this previously poorly classified condition [97]. A study by Oprescu *et al* using the LAM Foundation registry and the National Death Index at the Centers for Disease Control (CDC) validated the prolonged survival reported in a few recent studies, with 86% of patients surviving at least 10 years [97], and was the first to specifically report federally-compiled causes of death. Respiratory failure accounted for 4.12% of deaths, while pulmonary infection and pneumothorax accounted for 11.76% and 2.94%, respectively [97]. While the 10-year survival was 86%, similar to previous Japanese and UK studies (76% and 91% respectively), the median survival was much better than previously estimated, with a median transplant-free survival of 29 years from symptom onset and 23 years from diagnosis [97]. Analysis of a population based cohort rather than a hospital and clinic based cohort is the likely explanation for differences.

The importance of defining prognosis in LAM is vital in determining treatment options, especially as novel therapeutics have become available in the last decade [84]. The LAM Foundation assisted in the recruitment and operations of the Multicenter International LAM Efficacy of Sirolimus (MILES) Trial [84], a landmark study for LAM and for the greater rare disease community in terms of conducting trials for orphan drug development. Sirolimus, which inhibits the mammalian target of rapamycin (mTOR) signalling pathway, was shown to significantly improve pulmonary function compared to placebo [84], as well as reduce blood levels of vascular endothelial growth factor D (VEGF-D), a lymphangiogenic growth factor [140], and improve quality of life in LAM patients. This trial raised additional questions about criteria for future patient selection, and the importance of identifying accurate prognostic factors and biomarkers to guide therapeutic decisions. Sirolimus has been demonstrated to improve CT measurements of gas trapping in LAM [4], and in a small study of 25 mild LAM patients with a history of chylothorax and/or lymphangioleiomyoma, to favorably impact the lymphatic manifestations of the disease [134]. VEGF-D has been demonstrated to perform well as a diagnostic, prognostic and predictive biomarker [84, 140]. This trial was conducted by the Rare Lung Diseases Consortium as an international, multicenter investigator initiated study without pharmaceutical company involvement in the conduct of the trial, and although not designed with a label change in mind, served as the sole basis for FDA approval.

The LAM Foundation has been cited as an ‘model to emulate’ by the New England Journal of Medicine [50] an exemplar among patient organisations that aspire to organize, support and educate those affected; to promote collaboration between the patient community, the NIH and medical researchers; and to fund the research that forms the basis for clinic trials. A decade of building and supporting a network of researchers and patients provided the platform for recruitment of patients for a pivotal, randomised control trial. Additionally, the LAM Foundation has identified specialty clinics around the world, which serve to focus care, nurture expertise and facilitate clinical trials.

24.9 Pulmonary Alveolar Proteinosis: Epidemiological Challenges and Opportunities to be Gained from Claims Databases

Another very rare lung disease that is instructive with respect to epidemiologic approaches is pulmonary alveolar proteinosis (PAP), a disease in which there have been great strides in our understanding of the natural history and molecular pathogenesis over recent years. PAP is characterised by the accumulation of surfactant within alveolar macrophages and alveoli, resulting in restrictive lung disease, varying degrees of hypoxemia and respiratory insufficiency, and an increased risk of pulmonary infection [124, 135]. PAP can be categorized as primary, secondary or congenital [114, 116]. The prevalence of primary or autoimmune PAP, which accounts for 90% of all cases, had been historically estimated at approximately 0.5 per 100,000 individuals [98, 135]. However, more recent data based on insurance sources suggest that the disorder may be tenfold more common than originally thought. The evolution in approaches to gathering epidemiologic data has been instructive.

The primary source of data regarding the clinical course and natural history of PAP has been large case series, including a meta-analysis by Seymour *et al* of 410 cases from published literature [124]. Other sources have included multicentre series from Japan (n=248) [51], China (n=241) [138] and single centre reports from the US (n=34) [103], Germany (n=70) [10], Israel (n=15) [7] and Italy (n=81) [13]. While these studies have been crucial in defining the progression and response to treatment in PAP, they have likely underestimated the prevalence of this rare condition. While prevalence has been previously reported as 3.7–6.2 per million patients [7, 51, 124] this is likely an underestimate. Through the use of de-identified claims data acquired from the OptumInsight database, (Table 24.4) which include outpatient, inpatient, emergency department and pharmacy dispensing data, we estimate that the prevalence of PAP at 6.87 per million. By identifying 164 newly diagnosed PAP patients who were continually enrolled with Optum for full medical and pharmacy benefits and a control group of age/gender matched individuals followed for 12 months, it was possible to define some features of the epidemiology of the disease. The prevalence was noted to increase with age, and the disease occurred equally in males and females with a bimodal peak at 45-54 years of age. Similar methods utilising the OptumInsight database have been employed to assess the long-term healthcare costs in IPF [28] .

Other sources of claims data are available and have been employed in a variety of diseases, both rare and common, to determine outcome and prevalence data. The National (Nationwide) Inpatient Sample (NIS) is a large inpatient care database in the US, containing data on more than seven million hospital stays, covering all payment sources. The large population size is ideal for determining prevalence estimates, enabling analysis of rare diseases, and aiding in calculations of economic burden, mortality and other outcome measures for individual conditions [17, 133]. MarketScan is a collection of databases, containing healthcare claims information from large employers, managed care organisations, and Medicare and Medicaid

Table 24.4 Patient and claims databases useful for research

Database	Brief Description
Centers for Medicare and Medicaid Services (CMS)	Quantitative information on Medicare and Medicaid programs
www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.html	Medicare and Medicaid claims data
OptumInsight	Contains de-identified claims data from commercially- insured patients from 2000 to present day.
www.optum.com/solutions/data-analytics.html	Links administrative data with claims and lab results, anonymizing data at patient level.
	Data set includes 8 million hospital claims, 1.2 billion lab results, 1.3 billion prescription claims, 2.8 billion outpatient claims for a patient population aged 19 to 64. Data on more than 90 million lives at any point and more than 13 million current lives.
The Health Improvement Network (THIN)	Includes the general practice electronic longitudinal medical records for a sample of patients in the UK
www.inps.co.uk/vision/health-improvement-network-thin	Useful for conducting long-term longitudinal observational studies.
	There are over 12.3 million patient records with acceptable recorded data.
	Population is representative of the national UK population in terms of age, gender, leading diagnoses and treatments.
The National Death Index (NDI)	A centralized database of death record information maintained by the National Center for Health Statistics (NCHS) to aid epidemiologists and other investigators with mortality ascertainment activities.
www.cdc.gov/nchs/ndi/index.htm	Death records are added annually, approximately 12 months after the end of a particular calendar year.
The National (Nationwide) Inpatient Sample (NIS)	The largest all-payer inpatient care database in the US with data on more than 7 million hospital stays.
www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp	Large sample size enables analyses of rare conditions, uncommon treatments, and special populations.
National Health Service Hospital Episode Statistics (HES)	Contains data on all admissions, outpatient appointments and emergency room attendances at National Health Service (NHS) hospitals in England.
www.digital.nhs.uk/hes	HES processes over 125 million admitted patient, outpatient and emergency room records per year.

programmes [1] which may also be useful in identifying rare disease prevalence and patterns. The Medicare database has been employed successfully to determine the prevalence of nontuberculous mycobacteria (NTM), a rare pulmonary infection, where an increasing prevalence rate was identified in a sample comprising 5% of Medicare beneficiaries over a 10 year period from 1997-2007, increasing from 20 to 47 cases per 100,000 individuals [2]. These databases are ideal sources to study rare disease, and are especially powerful in combination with registry and patient foundation data. Linking of society and registry data with claims databases has been useful in the facilitation of long term study in other fields [53], and hence similar links could be beneficial to rare lung disease research. (Table 24.4)

24.10 The Future of Rare Lung Disease: Registries and Foundations to Facilitate Research

The significant growth in the knowledge of rare diseases in general and the astounding progress in select conditions, including IPF, CF and LAM in particular, bodes well for future advances in rare lung diseases. The collaboration of researchers, expert clinicians, patient organisations and registries has made possible the huge leaps in understanding and therapeutic options; highlighting the value of collaborative approaches in rare diseases. Lessons learned from trial design and quality improvement in smaller populations, are often instructive for other disease communities. The excellent results of the CF Foundation, Alpha 1 Foundation and the LAM Foundation in educating, supporting and organizing patients, facilitating clinical trials through recruitment and direct participation in study operations, and funding research has proven to be a pivotal component of improving outcomes of patients with these conditions [39, 84, 112]. Through advocacy, optimization of resources, networking, coordination and development of registries, the conduct of clinical studies that have impact are uniquely possible in rare diseases. Similar cohesive strategies are required in other rare conditions including the ultra-rare disorders; but will require collaborative approaches to develop multicentre networks and expert-led clinics. The LAM Foundation and the Rare Lung Diseases Consortium, a network supported by the National Center for Accelerating Translational Research, are attempting to do just that using the platform of special centers for the care of LAM patients. The LAM Foundation and the RLDC have invited over a dozen rare lung disease communities to refer their patients to the LAM Clinics, now dubbed RLDC clinics. Recently, the third annual RLDC Conference was hosted by the RLDC and the LAM Foundation in Cincinnati, with 472 attendees from 35 states and 20 countries represented, from over a dozen rare lung disease communities and advocacy organizations. This collaborative approach to clinical care and conferences focuses rare lung disease patients to a limited number of academic health centers within major cities, nurtures expertise, improves quality and consistency of care, and

facilitates clinical trials. In this way, rare lung diseases are pooling resources and enabling breakthroughs in even the rarest of members.

In summary, studying the epidemiology of rare lung disease has historically been difficult and has produced mixed results, but the dawn of the information era is revolutionizing our approaches and expanding our opportunities. Models of successful registries and clinical studies by some of the rarest of diseases are available for adoption by other disease communities, including the common disorders, and promise to improve care and lead to new therapeutic options.

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Chapter 25
Rare Neurodegenerative Diseases: Clinical and Genetic Update

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Abstract More than 600 human disorders afflict the nervous system. Of these, neurodegenerative diseases are usually characterised by onset in late adulthood, progressive clinical course, and neuronal loss with regional specificity in the central nervous system. They include Alzheimer's disease and other less frequent dementias, brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and Prion diseases, among others. Neurodegeneration usually affects, but is not limited to, the cerebral cortex, intracranial white matter, basal ganglia, thalamus, hypothalamus, brain stem, and cerebellum. Although the majority of neurodegenerative diseases are sporadic, Mendelian inheritance is well documented. Intriguingly, the clinical presentations and neuropathological findings

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in inherited neurodegenerative forms are often indistinguishable from those of sporadic cases, suggesting that converging genomic signatures and pathophysiologic mechanisms underlie both hereditary and sporadic neurodegenerative diseases. Unfortunately, effective therapies for these diseases are scarce to non-existent. In this chapter, we highlight the clinical and genetic features associated with the rare inherited forms of neurodegenerative diseases, including ataxias, multiple system atrophy, spastic paraplegias, Parkinson's disease, dementias, motor neuron diseases, and rare metabolic disorders.

Keywords Genetic diagnosis • Neuromuscular • Metabolic disorders • Dementia • Ataxia • Movement disorders

25.1 Introduction

Rare diseases are highly heterogeneous life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are the result of a genetic pathological mutation, a few result from environmental exposures during pregnancy or later in life, often in combination with genetic susceptibility, and the others being rare cancers, auto-immune diseases, congenital malformations, toxic, and infectious diseases. There is also a great diversity in the age at which the first symptoms occur, but half of rare diseases can appear at birth or during childhood.

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Work over the last 25 years has resulted in the identification of genes responsible for ~50% of the estimated 7,000 rare monogenic diseases, and it is predicted that most of the remaining disease-causing genes will be identified by the year 2020. This acceleration in gene discovery is the result of the application of high-throughput next-generation sequencing technologies. We expect to rapidly move into a scenario where most families presenting with a rare disease may have a molecular diagnosis established, allowing adequate clinical follow-up and proper genetic counselling. Also, deciphering the genetic and molecular signatures underlying rare diseases will facilitate the design of new therapies that will hopefully interfere in an efficacious way in those pathogenic pathways.

There is a wide range of diseases that can be classified as neurodegenerative. Some are very rare, but all have a significant impact with a progressively increasing burden of management. Herein, we highlight the clinical and genetic features associated with those rare inherited forms of neurodegenerative diseases, including ataxias, multiple system atrophy, spastic paraplegias, Parkinson's disease, dementias, motor neuron diseases, and rare metabolic disorders.

25.2 Cerebellar Ataxias

Cerebellar ataxias represent a heterogeneous group of disorders characterised by progressive degeneration of the cerebellum often accompanied by a variety of neurological and systemic symptoms. Two main categories are distinguished: sporadic and hereditary ataxias. Sporadic ataxias may be symptomatic or idiopathic. Symptomatic ataxias are due to structural lesions or malformations in the cerebellum, toxics (alcohol; antiepileptic drugs: benzodiazepines; antidepressants: lithium; antineoplastics: cyclosporine; and amiodarone, procainamide, isoniazid, metronidazole, nitrofurantoin, among others; heavy metals: lead and mercury; and chemicals: for instance solvents and pesticides), hypothyroidism, diabetes, malabsortion due to celiac disease, vitamin E or B12 deficiencies, abetalipoproteinemia, paraneoplastic syndromes, demyelinating disorders, Whipple disease and post-viral/immune-mediated ataxia. Symptomatic ataxias can be handled and diagnosed with a detailed medical history and common ancillary tests. Idiopathic ataxias include the so-called idiopathic late-onset cerebellar ataxia (ILOCA) and multiple system atrophy (MSA).

Hereditary ataxias can present with autosomal dominant (SCA), autosomal recessive, X-linked or mitochondrial inheritance. Overall, they comprise about 60–75% of ataxias. They are diagnosed on family history, physical examination, neuroimaging, and genetic testing. This section focuses on hereditary and idiopathic ataxias (ILOSCA and MSA).

25.2.1 Autosomal Dominant Ataxias

Forty-three different genetic subtypes of spinocerebellar ataxia (SCA) are now distinguished. They are conventionally referred as SCAs regardless of whether or not they present with spinal pathology. In addition, the complex form dentatorubral-pallidoluysian atrophy (DRPLA) and eight episodic ataxias (EA) are usually included (Table 25.1; modified from [16, 32]. Together with the autosomal recessive ataxias, the minimum prevalence rate in European descend populations would be 6–7 per 100,000 people, which is comparable to Huntington's disease or motor neuron diseases [32].

25.2.1.1 SCAs

The prevalence of these diseases is not widely known and varies considerably among geographical areas due to founder effects. SCAs 1, 2, 3, 6 and 7 account up to 65% of all SCA worldwide cases [10], being SCA3 the most common subtype worldwide. The genotype still remains elusive in up to 40–50% of SCA families indicating a reservoir of yet to be characterised diseases.

Age of onset is quite variable usually presenting in adulthood, and the disease progresses over decades. Life span is shortened in SCAs 1, 2, 3 and 7 [16] Anticipation is observed in SCAs in which CAG repeat expansion occurs and it is a significant issue to be considered in the genetic counselling process.

Cerebellar dysfunction in SCAs is often associated with other clinical signs such as ophthalmoplegia, polyneuropathy, retinopathy, pyramidal and extrapyramidal features, dementia, chorea, seizures, and lower motor neuron signs. Despite the clinical overlap between different SCA genotypes some distinctive clinical features may help the clinician in pursuing direct genetic testing: marked slow saccades are associated with SCA2; ophthalmoplegia with SCA3; pyramidal signs with SCAs 1 and 3; polyneuropathy with SCAs 1, 4, 8, and 25; pigmentary retinopathy with SCA7; seizures with SCA10; cognitive impairment with SCAs 2, 12, 13, and 17; axial myoclonus with SCA14; chorea with SCA17; dysphonia and early calcification of dentate nucleus with SCA20; and lower motor neuron signs with SCAs 3 and 36 [8]. Conversely, the pure cerebellar phenotype has been mainly associated with SCAs 5, 6, 11, 14, 15/16, and 37 [39, 52].

SCAs are often subdivided into expanded exon-coding CAG repeat ataxias (SCAs 1, 2, 3, 6, 7, 17, and DRPLA); SCAs with mutations in non-coding regions (triplets and pentanucleotide repeat expansions: SCAs 8, 10, 12, 31, and 36); SCAs with conventional mutations in other identified genes, and SCAs with still unidentified loci.

This complex and expanded knowledge in SCAs has not yet led to find the ultimate common pathogenic mechanism. Basic scientific research has identified transcriptional dysregulation, protein aggregation and clearance, autophagy, alterations of calcium homeostasis, mitochondria defects, toxic RNA gain-of-function mecha-

nisms and activation of pro-apoptotic routes, amongst others, as the main mechanisms leading to cerebellar Purkinje cell death [31, 33]. Thus, several identified potential targets open the way to find effective treatments that may act during the early stages of neurodegeneration in SCAs [31, 33, 46, 48].

However, regardless of several trials in cells and animals models, available human therapeutic trials in SCA are scarce and only recently, some positive output has emerged. Valproate, an antiepileptic drug acting as an histone deacetylation inhibitor, improved locomotor function in an open trial in SCA3 [24]; and riluzole, a small-conductance potassium KC2 channel activator showed symptomatic benefits in a double-blind 12-months trial in a few SCAs and FRDA [45]. Nevertheless, no approved treatment to modify neurodegeneration is available yet for these diseases. Piracetam for myoclonus; L-Dopa for dystonia; baclofen and botulin toxin for spasticity; beta-blockers, benzodiazepines and even thalamic stimulation for intention tremor; anticholinergic drugs for hypersalivation; clonazepam for muscle cramps in addition to physical therapy, are commonly used and recommended as symptomatic treatments.

25.2.1.2 Episodic Ataxias (EA)

The episodic occurrence of symptoms differentiates EAs from SCAs [43]. Typically onset of EA occurs in childhood or early adulthood, however in E2, the most common form of EA, the onset may delay up to the fifth decade. Episodic ataxias can be provoked by exercise, emotional stress, startle or change of position. Tremor, muscle cramps, and stiffening may accompany the ataxia. Interictal and subclinical myokimia in face, arms, and legs may be seen in electromyography. Episodic ataxia 1 (EA1) presents with movement-induced attacks of ataxia that lasts less than 15 min and can appear up to 15 times a day. EA1 is caused by mutations in the potassium channel *KCNA1* gene. In contrast, EA2 attacks may last for hours and days and they are often associated with nausea, migraine headache, and sometimes hemiparesis, dystonia and tinnitus; permanent cerebellar interictal signs may develop along the course of EA2, especially nystagmus, followed by a progressive cerebellar syndrome. Emotional and physical stress, caffeine, alcohol, exercise, intercurrent illness and phenytoin may trigger the attacks. EA2 is associated with point mutations in the *CACNA1A* gene whereas missense mutations in the same gene are associated with familial hemiplegic migraine, and CAG repeat expansions with SCA6. Evident clinical overlap exists with EA2, even within families [54]. Acetazolamide is an effective therapy for most patients with EA2 and half of the patients with EA1; phenytoin and carbamazepine are alternative therapies in EA1, whereas valproate, flunarizine, topiramate, and 4-aminopyridine may be an option in case acetazolamide fails in EA2. Episodic ataxias subtypes 3, 4, 5, 6, and 7 represent the minority of phenotypical variations in EA and few patients have been identified. EA5 shows an EA2 phenotype and EA6 additionally presents with seizures [43] (Table 25.1).

25.2.1.3 Other

Other rare autosomal dominant disorders like hereditary spastic ataxia and sensory motor neuropathy with ataxia may also present with ataxia.

25.2.2 Autosomal Recessive Ataxias

The autosomal recessive ataxias constitute a group of heterogeneous and rare disorders involving many genetic defects caused by a myriad of mechanisms of pathogenesis, which are mainly commonly caused by loss of function of the gene products (Tables 25.2 and 25.3).

Friedreich ataxia (FRDA) is the most common recessively inherited ataxia with a prevalence of 1 in 50,000, followed by ataxia telangiectasia (AT) with a prevalence of 1 in 100,000 individuals [6]. Traditionally, neurologists take into account an age of onset of 25 years of age as a cut-off threshold to further screen these patients because only a minority of recessive and metabolic ataxias reveal an adult onset. In addition, all patients with a suspected recessive ataxia and negative screening should also be investigated for SCA.

25.2.2.1 FRDA

FRDA classically presents with ataxia, dysarthria, absent deep tendon reflexes, pyramidal signs, and an early-onset (<25 years). Cardiomyopathy, scoliosis, distal muscle atrophy, deafness, optic atrophy, and diabetes are common variable features. A milder phenotype with late-onset and a phenotype with spastic paraplegia without ataxia or polyneuropathy has also been reported. The underlying mutation consists of a GAA trinucleotide repeat expansion within the *FXN* gene (ranges: normal, 5–33 GAA repeats; mutable normal, 34–65 repeats; FRDA, 66–1,700). The expansion size accounts for less than 50% of the age of onset, and correlates more with the presence of diabetes and cardiomyopathy, particularly for larger alleles. Between 6 and 10% FRDA patients are compound heterozygotes for the GAA expansion. The *FXN* gene encodes for frataxin, a mitochondrial protein related to iron storage and sulphur-iron complexes biogenesis, thus being mitochondrial dysfunction a key feature underlying FRDA pathogenesis. Clinical trials with antioxidants [18, 22, 61], erythropoietin [29] and pioglitazone (ACTFRIE, unpublished data) have failed to prove any benefit.

25.2.2.2 Others

Once FRDA is excluded, an age-dependent screening for recessive ataxic syndromes and metabolic diseases is recommended (Table 25.2). It is important to note that some of these diseases are treatable [1]. Some clinical traits may help to direct the genetic test [6, 16]. Oculomotor apraxia is a common finding in ataxia telangiectasia (AT) and in ataxias presenting with oculomotor apraxia (AOA1, AOA2). Oculocutaneous telangiectases, choreoathetosis, dystonia, immunodeficiency, hypersensitivity to ionizing radiation, and predisposition to malignancy are also specific features for AT. Ataxia telangiectasia is due to mutations in the *ATM* gene, which encodes a protein related to DNA repair. The clinical disparity in AT is partly related to the relative preservation of ATM expression in some *ATM* mutations leading to milder phenotypes. As for AOAs 1 and 2, they both associate with polyneuropathy, and in addition AOA1 may show mild mental retardation. The aprataxin (APTX/AOA1) and the senataxin (SETX/AOA2) genes are both implicated in DNA repair pathways. Polyneuropathy is common in FRDA, vitamin E deficiency, abetalipoproteinemia, Refsum's disease, and late-onset hexosaminidase A deficiency that may present as a FRDA-like phenotype. Retinitis pigmentosa with anosmia, polyneuropathy, cerebellar ataxia, deafness, and ichthyosis is typical of Refsum's disease, while juvenile cataracts are a clinical hallmark of cerebrotendinous xantomatosis (CTX, sterol 27-hydroxylase deficiency) that will also present with tendon xanthomas, chronic diarrhea, ataxia, pyramidal signs, dementia, epilepsy, polyneuropathy, and white matter lesions on magnetic resonance imaging (MRI). In fact, MRI could also contribute to guide genetic testing [6]. White matter lesions are found in mitochondrial diseases and all leukodystrophies, such as the mentioned CTX, metachromatic leukodystrophy (arylsulfatase gene), and Krabbe disease (galactoceribrosidase deficiency).

A few other rare conditions may have an adult onset autosomal recessive ataxia such as Niemann-Pick C, a lipid storage disorder, often associated to dementia or psychiatric symptoms, and GM1 gangliosidosis that may associate with dystonia. Ataxia with a combination of migraine, epilepsy, myoclonus, late-onset ophthalmoplegia, and cognitive decline is presented in the autosomal recessive mitochondrial ataxic syndrome because of mutations in the *POLG* gene [13].

25.2.3 X-Linked Inherited Ataxias

Adult-onset adrenomyeloneuropathy is a mild form of adrenoleukodystrophy that typically presents in adult males (<50 year old) and is characterized by a progressive spastic paraparesia with sphincter and sexual dysfunction. Cerebellar ataxia may be present in up to 10% of these patients [6, 11]. White matter MRI lesions in the parietooccipital regions of the brain are commonly found. An increased level of very long chain fatty acids in plasma is diagnostic and the disease is due to mutations in the *ABCD1* gene. Conversely, in >50 year old males with suspected X-linked

ataxia, the fragile-X-associated tremor ataxia syndrome diagnostic should be considered. The syndrome combines progressive intention tremor, cerebellar ataxia, and white matter disease in the middle cerebellar peduncles. Additional features contributing to the diagnosis include executive function and memory deficits, parkinsonism, and additional MRI findings of global brain atrophy and white matter disease [14]. It has been reported in elderly male carriers of premutation allele (>200 CGG repeats) within the *FMR1* gene, and the diagnostic should be considered in all males with onset of ataxia above 50 years because the carrier frequency is high (1:810 males).

25.2.4 Mitochondrial Cerebellar Ataxia

Cerebellar ataxia is found in most subtypes of mitochondriopathies (MERFF, MELAS, NARP, Kearns-Sayre, Leigh and May-White syndromes). These are all multisystem disorders with involvement of peripheral and central nervous systems, heart, eyes, ears, guts, kidney and bone marrow as well as endocrine dysfunction.

25.2.5 Idiopathic Late-Onset Cerebellar Ataxia (ILOCA)

After exclusion of symptomatic cerebellar ataxia, a hereditary ataxia should be considered in patients younger than 50 even if the family history is negative. Recessive ataxias should be screened followed by SCAs. When all diagnostic tests are negative, the acronym ILOCA should be used.

25.2.6 Multiple System Atrophy (MSA)

MSA is the most common disease causing isolated late-onset cerebellar ataxia (30%) with a prevalence of 1.9–4.9 cases per 100,000 people. Clinical hallmarks include autonomic and urinary dysfunction, Parkinsonism, and cerebellar and corticospinal tract symptoms and signs. Diagnosis is considered possible, probable or definite according to established criteria [62]. It usually starts in the sixth decade with a mean survival of 6–9 years. Some patients show predominant Parkinsonism signs, some of them showing predominant cerebellar signs. MRI show olivopontocerebellar and putaminal atrophy, with hyperintensities of the pons and middle cerebellar peduncles in T2-weighted images. Pathologically, MSA is a α-synucleopathy with glial cytoplasmic inclusions. No effective treatment is available for MSA.

Table 25.1 Genetics of dominantly inherited autosomal spinocerebellar ataxias

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCA1	6p22.3	164400	*ATXN1*	3rd–4th decade (<10 to >60)	Pyramidal signs, peripheral neuropathy.
SCA2	12q24.12	183090	*ATXN2*	3rd–4th decade (<10 to >60)	Slow saccadic eye movements, peripheral neuropathy, dementia.
SCA3	14q32.12	109150	*ATXN3*	4th decade (10–70)	Pyramidal and extrapyramidal signs, lid retraction, nystagmus, decreased saccade velocity, amyotrophy, fasciculations, sensory loss.
SCA4	16q22.1	600223	Unknown	4th–7th decade (19–72)	Sensory axonal neuropathy, deafness, may be allelic with SCA31.
SCA5	11q13.2	600224	*SPTBN2*	3rd–4th decade (10–68)	Early onset, slow course, first reported in descendant of Abraham Lincoln.
SCA6	19p13.2	183086	*CACNA1A*	5th–6th decade (19–71)	Usually pure phenotype, sometimes episodic ataxia, very slow progression.
SCA7	3p14.1	164500	*ATXN7*	3rd–4th decade (0.5–60)	Visual loss with retinopathy.
SCA8	13q21	608768	*ATXN8OS*	4th decade (1–65)	Slowly progressive, sometimes hyperreflexia, decreased vibration sense; rarely, cognitive impairment.
SCA9	Unknown	612876	Unknown	Unpublished	Ophthalmoplegia, dysarthria, pyramidal and extrapyramidal tract signs, weakness, posterior column signs, parkinsonism, phenotype resembling multiple sclerosis.
SCA10	22q13.31	603516	*ATXN10*	4th decade (12–48)	Occasional seizures, most families are of Native American background.
SCA11	15q15.2	604432	*TTBK2*	Age 30 (15–70)	Usually pure mild phenotype, remain ambulatory.
SCA12	5q32	604326	*PPP2R2B*	4th decade (8–62)	Slowly progressive, hyperreflexia, subtle parkinsonism, cognitive/psychiatric disorder.
SCA13	19q13.33	605259	*KCNC3*	Childhood or adulthood	Mild intellectual disability, short stature.

(continued)

Table 25.1 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCA14	19q13.42	605361	*PRKCG*	3rd–4th decade (3–70)	Early axial myoclonus.
SCA15/ SCA16	3p26.1	606658	*ITPR1*	4th decade (7–66)	Pure ataxia, very slow progression, head tremor in Japanese family.
SCA17/ HDL4	6q27	607136	*TBP*	4th decade (3–55)	Mental retardation, occasional chorea, dystonia, myoclonus, epilepsy.
SCA18	7q22-q32	607458	*IFRD1*	Adolescence (12–25)	Early sensory-motor neuropathy, muscle weakness, atrophy, fasciculation, Babinski response.
SCA19/ SCA22	1p21-q21	607346	*KCND3*	4th decade (10–51)	Slowly progressive, rare cognitive impairment, myoclonus, hyperreflexia.
SCA20	11q12.2-11q13.3	608687	Unknown	5th decade (19–64)	Early dysarthria, spasmodic dysphonia, hyperreflexia, bradykinesia, calcification of the dentate nucleus.
SCA21	7p21.3-p15.1	607454	*TMEM240*	6–30	Mild cognitive impairment.
SCA23	20p13	610245	*PDYN*	5th–6th decade	Dysarthria, abnormal eye movements, reduced vibration and position sense.
SCA24	Unknown	–	Unknown	Unknown	No published data available.
SCA25	2p21-p15	608703	Unknown	1.5–39	Sensory neuropathy.
SCA26	19p13.3	609306	*EEF2*	26–60	Dysarthria, irregular visual pursuit.
SCA27	13q33.1	609307	*FGF14*	11 (7–20)	Early-onset tremor, dyskinesia, cognitive deficit.
SCA28	18p11.21	610246	*AFG3L2*	19.5 (12–36)	Nystagmus, ophthalmoparesis, ptosis, hyperreflexia.
SCA29	3p26	117360	*ITPR1*	Early childhood	Learning deficits.
SCA30	4q34.3-q35.1	613371	Unknown	(45–76)	Hyperreflexia.
SCA31	16q21-q22	117210	*BEAN/TK2*	5th–6th decade	Normal sensation.
SCA32	7q32-33	613909	Unknown	Adulthood	Variable mental impairment, azoospermia.
SCA33	Unknown	–	Unknown	No published data	No published data available.

SCA34	6q14	133190	*ELOVL4*	Cutaneous signs in childhood	Erythrokeratodermia in childhood. Allelic to Stargardt macular dystrophy 3 and autosomal recessive ichthyosis, spastic quadriplegia, and mental retardation.
SCA35	20p13	613908	*TGM6*	Age 43.7 (40–48)	Hyperreflexia, Babinski responses, spasmodic torticollis.
SCA36	20p13	614153	*NOP56*	Age 52.8±4.3	Muscle fasciculations, tongue atrophy, hyperreflexia.
SCA37	1p32	615945	*DAB1*	Age 48 (38–64)	Slowly progressive pure phenotype, early abnormal vertical saccades and pursuit.
SCA38	6p	615957	*ELOVL5*	(34–51)	Usually pure phenotype, slow saccades, few subjects with axonal neuropathy.
SCA39	11q21-11q22.3	–	*44 genes (7.5 Mb)*	40th decade	Ataxia with spasticity and mild mental retardation.
SCA40	14q32.2	616053	*CCDC88C*	4th decade	Ocular dysmetria, impaired vertical gaze, hyperreflexia, spastic paraparesia.
SCA41	4q27	616410	*TRPC3*	38	Gait instability and imbalance.
SCA42	17q21.33	616795	*CACNA1G*	9–78	Dysarthria, saccadic pursuit.
SCA43	3q25.2	617018	*MME*	42–68	Dysarthria, dysmetria, hypometric saccades.
SCA44	6q24.3	617691	*GRM1*	3rd to 6th decade	Gait and limbs ataxia, spasticity, hypermetric saccades.
EA1	12p13.32	160120	*KCNA1*	1st–2nd decade (2–15)	Myokimia, attacks lasting seconds to minutes; startle or exercise induced; no vertigo.
EA2	19p13.2	108500	*CACNA1A*	2–32	Nystagmus; attacks lasting minutes to hours; posture-change induced; vertigo; later, permanent ataxia.
EA3	1q42	606554	Unknown	1–52	Vestibular ataxia, vertigo, tinnitus, and interictal myokymia. Absence of interictal nystagmus.
EA4	Unknown	606552	Unknown	Early adulthood 6th decade	Recurrent attacks of vertigo, diplopia, oscillopsia, and ataxia beginning in early adulthood. Slowly progressive cerebellar ataxia occurred in some.

(continued)

Table 25.1 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
EA5	2q23.3	613855	*CACNB4*		Recurrent episodes of vertigo and ataxia. Spontaneous downbeat and gaze-evoked nystagmus, mild dysarthria and truncal ataxia.
EA6	5p13.2	612656	*SLC1A3*	Childhood	Allelic with SCA6 and hemiplegic migraine.
EA7	19q13	611907	Unknown	<20	Attacks (hours to days), with weakness and dysarthria, or vertigo, triggered by exercise and excitement; interictal migraine headaches.
EA8	1p36.13-p34.3	616055	Unknown	2	Twitching around the eyes, muscle weakness, intention tremor, myokymia.
ADSA	8p12-q12.1	608984	*RNF170*	28–55	Instability in the dark, Romberg sign, no cerebellar signs, preganglionic posterior columns abnormalities.
SPAX1	12p13	108600	*VAMP1*	1st–7th decades	Initial progressive leg spasticity, involuntary head jerk, dysarthria, dysphagia, ocular movement abnormalities.
ADCADN	6p21-23	604121	*DMNT1*	Adulthood	Deafness, narcolepsy, optic atrophy, primitive reflexes, pseudobulbar signs, incontinence, pyramidal signs, cataracts, nystagmus, ataxia, head tremor, resting tremor, mental deterioration, sensorimotor polyneuropathy.
CIAT/ ADHD	12q13	614306	*SCAN8A*	9–¿? A single pedigree with children and adults	Delayed psychomotor development, attention deficit disorder, esophoria, amblyopia, gaze-evoked nystagmus in childhood. Adult onset with emotional instability and mild cognitive impairment.

SCA Spinocerebellar ataxia, *EA* Episodic ataxia

Table 25.2 Autosomal recessive ataxias to be considered in adults

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
FRDA	9q21.11	229300	*FXN*	1st–2nd decade (4–40)	Hyporeflexia, babinski responses, sensory loss, cardiomyopathy.
AT	11q22.3	208900	*ATM*	1st decade	Telangiectasia, immune deficiency, cancer, increased α–fetoprotein.
ATLD1	11q21	604391	*MRE11A*	Early childhood	Oculomotor apraxia, chorea, distal muscle wasting.
ATLD2	20p12.3	615919	*PCNA*	Early childhood	Sensorineural hearing loss, conjunctival and cutaneous telangiectasia.
AVED	8q12.3	277460	*TTPA*	<50 (2–52)	Similar to FA, head titubation.
Abeta lipoproteinemia	4q23	200100	*MTP*	Childhood to young adulthood	Celiac syndrome, retinis pigmentosa, progressive ataxic neuropathy, acanthocytosis, serum cholesterol very low, serum beta lipoprotein absent.
AOA1	9p21.1	208920	*APTX*	Childhood, rare adulthood	Oculomotor apraxia, choreoathetosis, mild intellectual disability, hypoalbuminemia.
AOA2/SCAR1	9q34.13	606002	*SETX*	10–22	Oculomotor apraxia, sensory-motor polyneuropathy.
AOA3	17p13.1	615217	*PIK3R5*	1st decade	Oculomotor apraxia, increased alpha-fetoprotein, axonal sensory polyneuropathy.
AOA4	19q13.33	616267	*PNKP*	1st decade (1–9)	Oculomotor apraxia, distal muscle weakness and atrophy.
Refsum disease	10p13	266500	*PHYH*	1st–6th decade	Neuropathy, deafness, ichthyosis, retinopathy.
PHARC	20p11	612674	*ABHD12*	Full expression in adulthood	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, cataract.
MIRAS	15q26.1	607459	*POLG1*	Childhood to young adulthood	Nystagmus, dysarthria, epilepsy.
SANDO	15q26.1	607459	*POLG1*	Childhood to young adulthood	Abnormal eye movements, RRF, myopathy, dysphagia, neuropathy, myopathy.
CTX	2q35	213700	*CYP27A1*	Childhood to young adulthood	Thick tendons, cognitive decline, dystonia, white matter disease, cataract.

(continued)

Table 25.2 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
Adult Tay-Sachs	15q23	272800	*HEXA*	Young adulthood	Childhood clumsiness, proximal muscle weakness, ataxia, dysarthria, tremor, no cherry red spots, abnormal eye movements.
Adult GM1	3p22.3	230650	*GLB1*	Young adulthood	Variable phenotype. A form with ataxia, mental retardation, vertebral changes, mild visceromegaly.
Niemann-Pick C	18q11.2	257220	*NPC1*	Young adulthood	Mild intellectual impairment, supranuclear vertical gaze paresis, ataxia; later dementia/psychiatric symptoms; variably, seizures and extrapyramidal deficits.
SCAR3	6p21-23	271250	Unknown	Young adulthood, adulthood	Deafness, blindness.
SCAR4	1p36	607317	Unknown	Young adulthood	Pyramidal signs, sensorimotor neuropathy, striking eye movement abnormalities (overshooting horizontal saccades, macrosaccadic oscillations.
SCAR7	11p15	609270	*TPP1*	Childhood to young adulthood	Hyperreflexia, Babinski responses, saccadic pursuit, oculomotor apraxia, impaired neurocognitive function.
SCAR8	6q25.2	610743	*SYNE1*	Childhood to young adulthood	Pure phenotype in adult onset; motor neuron disease in children.
SCAR10	3p22.1-p22.3	613728	*ANO10*	Teenage to young adulthood	Hyperreflexia, mental retardation. Low CoQ10 plasma and muscle levels.
SCAR19/ Lichtenstein-Knorr disease	1p36.11	616291	*SLC9A1*	Childhood or young adulthood	Sensorineural hearing loss, dizziness.
SCAR26	19q13.31	617633	*XRCC1*	28	Oculomotor apraxia, sensory loss, distal polyneuropathy.
SPAX3	2q33.1	611390	*MARS2*	Birth to 59	Spasticity, cerebral palsy, dysarthria.

FRDA Friedreich ataxia, *AT* ataxia telangiectasia, *AOA* ataxia with oculomotor apraxia, *PHARC* polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract, *MIRAS* mitochondrial recessive ataxic syndrome, *SANDO* sensory ataxia, neuropathy, dysarthria and ophthalmoplegia, *CX* cerebrotendinous xanthomatosis, *RRF* ragged red fibers, *SCAR* spinocerebellar ataxia autosomal recessive

Table 25.3 Autosomal recessive ataxias with exclusive or predominantly onset in childhood

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
IOSCA Mitochondrial DNA depletion syndrome	10q24.31	271245	*C10ORF2*	Infancy	Finland. Neuropathy, athetosis, optic atrophy, deafness, ophthalmoplegia, seizures.
Marinesco-Sjögren syndrome	5q31.2	248800	*SIL1*	Infancy	Intellectual disability, cataract, hypotonia, short stature, myopathy.
Human Cayman ataxia	19p13.3	601238	*ATCAY*	Early childhood	Marked psychomotor retardation, hypotonia.
ARSACS	13q12.12	270550	*SACS/sacsin*	12–18 months	Dysarthria, spasticity, neuropathy, retinal striation.
SPAX5	18p11.21	614487	*AFG3L2*	Early childhood	Spasticity, oculomotor apraxia, dystonia, myoclonic epilepsy.
CoQ deficiency	1q42.13; 4q21.22-q21.23; 16q13; 10p12; 6q21	612016; 607426; 614654; 614651; 614652	*COQ8A;COQ2;COQ9; PDSS1;PDSS2*	Childhood	Seizures, cognitive decline, pyramidal signs, myopathy.
SCAN1	14q32.11	607250	*TDP1*	Late childhood	Sensory-motor neuropathy (Charcot-Marie-Tooth like)
SCAR2	9q34.3	213200	*PMPCA*	Infancy	Mental retardation.
SCAR5 Galloway-Mowat syndrome	15q25.2	251300	*WDR73*	Infancy	Microcephaly, CNS abnormalities, severe delayed psychomotor development, hiatal hernia, nephrotic syndrome, optic atrophy, seizures.
SCAR6	20q11-q13	608029	Unknown	Infancy	Non-progressive congenital ataxia, spasticity, short stature, pes planus.

(continued)

Table 25.3 (continued)

Name	Locus	OMIM	Gene	Average onset (range in years)	Distinguishing clinical features
SCAR9/ COQ10D4	1q42.13	612016	*ADCK3*	Childhood	Exercise intolerance, seizures, mental retardation.
SCAR11	1q32.2	614229	*SYT14*	Childhood	Psychomotor retardation in childhood; ataxia in fifties.
SCAR12	16q23.1-q23.2	614322	*WWOX*	Infancy	Seizures, mental retardation.
SCAR13	6q24.3	614831	*GRM1*	Infancy	Seizures, mental retardation, pyramidal signs, ophthalmological abnormalities (ptosis, esotropia, abduction deficits, nystagmus, hypometric saccades), short stature.
SCAR14	11q13	615386	*SPTBN2*	Infancy	Delayed psychomotor development, mental retardation, spasticity.
SCAR15	3q29	615705	*K1AA0226/RUBCN*	Infancy	Epilepsy, delayed motor development, cognitive deficits.
SCAR16	16p13.3	615768	*STUB1*	Teenage	Spasticity, sensory neuropathy.
SCAR17	10q24.31	616127	*CWF19L1*	Infancy	Non-progressive congenital cerebellar ataxia.
SCAR18	4q22	616204	*GRID2*	Infancy	Delayed psychomotor development, mental retardation.
SCAR20	6q14.3	616354	*SNX14*	Early infancy	Severely delayed psychomotor development, poor or absent speech, coarse facies.
SCAR21	11q13.1	616719	*SCYL1*	Infancy	Liver failure with liver fibrosis, mild learning disabilities, late neuropathy.

SCAR22	2q21.23	616948	*VWA3B*	Childhood	Normal development followed by intellectual disability, adult-onset ataxia.
SCAR23	6p22.3	616949	*TDP2*	Infancy	Seizures, intellectual disability.
SCAR24	3q22.1	617133	*UBA5*	5–8	Cataract, cerebellar gait and limb, speech disorders
SCAR25	6q21	617584	*ATG5*	Congenital	Inability to read or write, low IQ, truncal ataxia
SPAX4	10p11.23	613672	*MTPAP*	Early childhood	Optic atrophy, learning difficulties, cerebellar and spastic dysarthria
SPAX8	10q26.3	617560	*NKX6-2*	1 month to 5 years	Progressive until CNS myelination is complete, then stable.
CAMRQ1-4	9p24	224050	*VLDLR*	Infancy	Non-progressive congenital cerebellar ataxia, mental retardation, strabismus, seizures, short stature, cataracts.
	17p	610185	*WDR81*		
	8q11	613227	*CA8*		
	13q12	615268	*ATP8A2*		

IOSCA infantile onset spinocerebellar ataxia, *ARSACS* autosomal recessive spastic ataxia Charlevoix-Saguenay type, *SCAN* spinocerebellar ataxia with axonal neuropathy, *SCAR* spinocerebellar ataxia autosomal recessive, *CAMRQ* cerebellar ataxia, mental retardation dysequilibrium syndrome

25.3 Hereditary Spastic Paraplegias

The hereditary spastic paraplegias (HSPs) were first identified by Seeligmüller, Strümpell and Lorrain as an autosomal dominant disease, characterised by progressive spasticity and weakness of the lower limbs, with moderate loss of vibratory sense and bladder dysfunction. At that time, the neuropathological hallmark of the disease was also described as the degeneration of the longest spinal pathways, corticospinal tracts, and medial dorsal columns. The classification of HSPs is difficult and, throughout the years, several proposals have been made based on phenotype, mode of inheritance, and mutated gene (SPGs). All modes of hereditary transmission are found: autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), and mitochondrial inheritance. Clinically, the HSPs have been subdivided into pure and complex forms, according to the presence or absence of other neurological and extra-neurological features.

25.3.1 Clinical Manifestations

The initial symptoms in HSP patients include a feeling of stiffness, muscle cramps, inability to walk rapidly and frequent falls. In early-onset cases the disease is often expressed as delayed gait acquisition. Age-at-onset is highly variable, particularly for pure forms, ranging from the first year of life to the 8th decade, tending to be later in autosomal dominant forms and earlier in recessive ones. At disease onset, spasticity is usually noticeable only while walking. Over time, especially in complex forms, pyramidal signs may affect the upper limbs, though many patients show only tendon hyperreflexia that may include a brisk jaw reflex; weakness or spasticity of the upper limbs is rare, particularly in pure forms. In some patients with complex forms, dysarthria and dysphagia may present as a pseudobulbar state. Other manifestations include cognitive impairment (mental retardation or deterioration), epilepsy, optic atrophy, amyotrophies, neuropathy (usually axonal), ataxia and dystonia [15].

Until now, 89 loci and 75 genes have been identified: 20 autosomal dominant, 57 autosomal recessive, five X-linked, one with mitochondrial inheritance, and 6 with both dominant and recessive transmission (Table 25.4). A recent study has identified HSP mutations in genes associated with Parkinson (*ATP13A2/SPG78*), neuronal ceroid lipofuscinosis (*TPP1*), and the hereditary motor and sensory neuropathy (*DNMT1*), highlighting the genetic, in addition to the clinical, heterogeneity of spastic paraplegia [17].

Table 25.4 Genetics of spastic paraplegias

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG1	Xq28	303350	*L1CAM*	X-linked	Infancy	Ataxia, mental retardation, hydrocephalus.
SPG2	Xq22.2	312920	*PLP1*	X-linked	Infancy or childhood	Pure or with cerebellar dysfunction, hypotonia, dementia, seizures, mental retardation.
SPG3A	14q22.1	182600	*ATL1*	AD and AR	Before 10 (1–68)	Pure or rarely axonal neuropathy.
SPG4	2p22.3	182601	*SPAST*	AD	30 (1–80)	Pure or neuropathy, cognitive impairment, agitation.
SPG5A	8q21.3	270800	*CYP7B1*	AR	Variable (1–47)	Pure or cerebellar signs, nystagmus, cognitive impairment.
SPG6	15q11.1	600363	*NIPA1*	AD	16.5 (9–35)	Pure or rarely neuropathy.
SPG7	16q24.3	602783	*SPG7*	AD and AR	30 (25–42)	Pure or optic atrophy, supranuclear palsy, ataxic gait, pyramidal signs.
SPG8	8q24.13	603563	*KIAA0196*	AD	Adult onset (18–60)	Pure or atrophy of shins.
SPG9	10q24.1	601162	*ALDH18A1*	AD and AR	Variable (1–30)	Pure or amyotrophy, cataracts, neuropathy, gastroesophageal reflux.
SPG10	12q13	604187	*KIF5A*	AD	Variable (2–51)	Pure or neuropathy, amyotrophy.
SPG11	15q21.1	610844	*SPG11*	AR	Early variability (1–30)	Pure or amyotrophy, neuropathy, cognitive decline, cerebellar signs.
SPG12	19q13	604805	*RTN2*	AD	6.9 (5–22)	Pure.
SPG13	2q33.1	605280	*HSPD1*	AD	39 (17–68)	Pure or pyramidal signs.
SPG14	3q27-q28	605229	Unknown	AR	30	Pure or mental retardation, distal motor neuropathy.
SPG15	14q24.1	270700	*ZFYVE26*	AR	Infancy or childhood (5–19)	Pure or distal amyotrophy, cerebellar signs, ataxia, cognitive deterioration, axonal neuropathy.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG16	Xq11.2	300266	Unknown	X-linked	Infancy	Pure or quadriplegia, motor aphasia, mental retardation, pyramidal signs.
SPG17	11q13	270685	*BSCL2*	AD	Variable (2–60)	Neuropathy, distal limb muscle atrophy and weakness.
SPG18	8p11.2	611225	*ERLIN2*	AR	Infancy (1–6)	Mental retardation, contractures, primary lateral sclerosis.
SPG19	9q33-q34	607152	Unknown	AD	47 (36–55)	Pure.
SPG20	13q12.3	275900	*SPG20*	AR	Early childhood	Troyer syndrome, distal amyotrophy, cerebellar signs.
SPG21	15q22.31	248900	*SPG21*	AR	Adulthood	Mast syndrome, frontotemporal atrophy, pyramidal signs.
SPG22	Xq13.2	300523	*SLC16A2*	X-linked	Infancy	Mental retardation, dystonia, ataxia, quadriplegia.
SPG23	1q32.1	270750	*DSTYK*	AR	Early childhood	Hyperpigmentation, cognitive impairment, peripheral neuropathy.
SPG24	13q14	607584	Unknown	AR	Early onset	Pure.
SPG25	6q23-q24.1	608220	Unknown	AR	Adulthood (30–46)	Sensory or motor neuropathy, pyramidal signs secondary to spinal cord compression.
SPG26	12q13.3	609195	*B4GALNT1*	AR	Childhood (2–19)	Dystonia, ataxia, distal amyotrophy, mental retardation.
SPG27	10q22.1-q24.1	609041	Unknown	AR	Adulthood (25–45)	Pure or sensorimotor polyneuropathy, dysarthria, hyperactive bladder.
SPG28	14q22.1	609340	*DDHD1*	AR	Childhood (7–15)	Pure or pyramidal signs, distal sensory impairment in lower limbs.
SPG29	1p31.1-p21.1	609727	Unknown	AD	Infancy	Neonatal hyperbilirubinemia, auditory neuropathy, hiatal hernia.

SPG30	2q37.3	610357	*KIF1A*	AD/AR	Variable (10–39)	Pure axonal neuropathy or cerebellar signs.
SPG31	2p11.2	610250	*REEP1*	AD	30 (2–45)	Pure distal sensory loss, amyotrophy.
SPG32	14q12-q21	611252	Unknown	AR	Childhood	Mild mental retardation, cerebellar atrophy.
SPG33	10q24.2	610244	*ZFYVE27*	AD	Adulthood (42–50)	Pure.
SPG34	Xq24-q25	300750	Unknown	X-linked	Adulthood (10–25)	Pure.
SPG35	16q23.1	612319	*FA2H*	AR	(3–11)	Dystonia, optic atrophy, ataxia, cognitive decline, seizures.
SPG36	12q23-q24	613096	Unknown	AD	24 (14–33)	Demyelinating motor and sensory neuropathy.
SPG37	8p21.1-q13.3	611945	Unknown	AD	32 (8–60)	Pure.
SPG38	4p16-p15	612335	Unknown	AD	Young adulthood (16–19)	Pure.
SPG39	19p13.2	612020	*PNPLA6*	AR	1st decade	Distal muscle atrophy, axonal motor neuropathy.
SPG40	Reserved	–	–	AD	–	Pure.
SPG41	11p14.1-p11.2	613364	Unknown	AD	Young adulthood (16–19)	Pure.
SPG42	3q25.31	612539	*SLC33A1*	AD	Variable (4–42)	Pure.
SPG43	19q12	615043	*C19orf12*	AR	1st decade	Distal muscle atrophy and weakness, neuropathy.
SPG44	1q42.13	613206	*GJC2*	AR	1st–2nd decade	Cerebellar ataxia, cognitive impairment.
SPG45/ SPG65	10q24.32-q24.33	613162	*NT5C2*	AR	2nd year	Mental retardation, delayed motor development.
SPG46	9p13.3	614409	*GBA2*	AR	Childhood (2–16)	Cerebellar ataxia, cataracts, mental retardation.
SPG47	1p13.2	614066	*AP4B1*	AR	Birth	Mental retardation, seizures, dystonia.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
SPG48	7p22.1	613647	*AP5Z1*	AR	Adulthood (2–50)	Pure or complex with cognitive impairment or mental retardation.
SPG49	14q32.31	615031	*TECPR2*	AR	2nd year	Ataxia, brachycephaly, intellectual disability, hypoventilation, areflexia.
SPG50	7q22.1	612936	*AP4M1*	AR	Birth	Mental retardation, seizures, cerebellar atrophy, strabismus.
SPG51	15q21.2	613744	*AP4E1*	AR	Birth	Mental retardation, seizures, cerebellar atrophy, hypotonia.
SPG52	14q12	614067	*AP4S1*	AR	Birth	Mental retardation, microcephaly, axial hypotonia, lack of speech development, stereotypic laughter, shyness.
SPG53	8p22	614898	*VPS37A*	AR	Infancy (1–2)	Kyphosis, cognitive impairment, delayed speech.
SPG54	8p11.23	615033	*DDHD2*	AR	Infancy (0–2)	Mental retardation, short stature, strabismus, telecanthus.
SPG55	12q24.31	615035	*C12orf65*	AR	1st decade	Visual loss, optic atrophy, intellectual impairment, axonal neuropathy.
SPG56	4q25	615030	*CYP2U1*	AR	1st decade (0–8)	Pure or axonal neuropathy, dystonia, cognitive impairment.
SPG57	3q12.2	615658	*TFG*	AR	1st year	Optic atrophy, axonal and demyelinating sensorimotor neuropathy, muscle weakness and atrophy.
SPG58	17p13.2	611302	*KIF1C*	AR	Teenage	Pure or ataxia, dysarthria, distal muscle atrophy.
SPG59	15q21.2	603158	*USP8*	AR	Infancy	Nystagmus, mental retardation.
SPG60	3p22.2	612167	*WDR48*	AR	1st year	Nystagmus, neuropathy.

SPG61	16p12.3	615685	*ARL6IP1*	AR	Infancy	Acropathy, diffuse motor and sensory polyneuropathy.
SPG62	10q24.31	615681	*ERLIN1*	AR	Infancy	Pure
SPG63	1p13.3	615686	*AMPD2*	AR	Infancy	Short stature, amyotrophy.
SPG64	10q24.1	615683	*ENTPD1*	AR	Infancy	Amyotrophy, cerebellar signs, intellectual disability.
SPG66	5q32	610009	*ARSI*	AR	Infancy	Amyotrophy, sensory motor and polyneuropathy.
SPG67	2q33.1	611655	*PGAP1*	AR	Infancy	Amyotrophy.
SPG68	11q13.1	604806	*FLRT1*	AR	Infancy	Optic atrophy, amyotrophy, neuropathy.
SPG69	1q41	–	*RAB3GAP2*	AR	Infancy	Dysarthria, cataract, deafness, intellectual disability.
SPG70	12q13.3	156560	*MARS*	AR	Infancy	Amyotrophy, contractures.
SPG71	5p13.3	615635	*ZFR*	AR	Infancy	Pure.
SPG72	5q31.2	615625	*REEP2*	AD/AR	Infancy	Pure.
SPG73	19q13.33	616282	*CPT1C*	AD	Adulthood (19–48)	Muscle atrophy, urinary dysfunction, delayed central sensory evoked potentials.
SPG74	1q42.13	616451	*IBA57*	AR	1st decade	Optic atrophy, axonal peripheral neuropathy, distal leg muscle atrophy.
SPG75	19q13.12	616680	*MAG*	AR	Early childhood	Optic atrophy, distal muscle atrophy, cognitive impairment, cerebellar signs, peripheral neuropathy.
SPG76	11q13.1	616907	*CAPN1*	AR	28 (19–39)	Cerebellar signs, sensory axonal neuropathy.
SPG77	6p25.1	611592	*FARS2*	AR	Before 5	Pure.
SPG78	1p36.13	617225	*ATP13A2*	AR	Juvenile or adulthood	Cognitive decline, strabismus, sensory-motor polyneuropathy.
SPG79	4p13	615491	*UCHL1*	AR	5–10	Blindness, cerebellar ataxia.

(continued)

Table 25.4 (continued)

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
–	19p13.2	602378	*DNM2*	AD	Young Adulthood	Pure.
–	2p25.1	615759	*KIDINS220*	AD	1st year	Intellectual disability, nystagmus, obesity.
SPOAN	11q13.2	609541	*KLC2*	AR	Infancy	Optic atrophy and neuropathy.
–	6p21.1	–	*KLC4*	AR	Infancy	Hearing and vision loss, ataxic gait.
–	1q42.3	606897	*LYST*	AR	Adulthood (48–58)	Cerebellar ataxia, peripheral neuropathy.
–	5p15.2	256840	*CCT5*	AR	Infancy	Mutilating sensory neuropathy.
–	9p13.2	606489	*EXOSC3*	AR	Infancy	Cognitive disability, cerebellar signs, amyotrophy.
–	9q22.31	609797	*BICD2*	AD/AR	Infancy	Spinal muscular atrophy.
–	Mit	516060	*MT-ATP6*	AD	Adulthood (30–50)	Pain, axonal neuropathy.
–	1p36.22	607093	*MTHFR*	AR	Adulthood (29–50)	Polyneuropathy, behavioural changes, cognitive impairment, psychosis, seizures, leukoencephalopathy.
–	19p13.3	602662	*TUBB4A*	AD	Infancy	Pyramidal involvement, ataxia gait, dysdiadochokinesia.

SPG Spastic paraplegia, *AD* Autosomal dominant, *AR* Autosomal recessive

25.3.2 Prevalence

Prevalence of HSP varies widely among studies, probably due to a combination of factors, such as variable diagnostic criteria, epidemiological methodology, and population differences. Reported estimates vary from 0.1 to 9.6/100,000 in different series, 0.5–5.5/100,000 for dominant forms, and 0.0–5.3/100,000 for the recessive ones [9]. The most common dominant spastic paraplegia (SPG) in all series is SPG4, while SPG11 is the most frequent among the recessive HSPs.

25.3.3 Pathogenic Mechanisms

HSPs are among the most genetically heterogeneous diseases (Table 25.4). Many of the proteins involved act in the same cellular processes; nevertheless, the number of cellular mechanisms known to be affected continue growing and include: abnormal mitochondrial function, axonal transport dysfunction, alterations in lipid metabolism, abnormal DNA repair, alterations in membrane trafficking, organelle shaping and autophagy [12, 17]. Currently, no specific treatment exists to prevent, delay, or reverse progressive disability in patients with hereditary spastic paraplegia.

25.4 Inherited Parkinson's Disease

Parkinson's disease (PD) (OMIM 168600) is the second most common neurodegenerative disease after Alzheimer's, albeit the inherited forms are considered rare presenting with a much lower prevalence [21, 25]. PD is characterized by instability, rigidity, bradykinesia, postural tremor, and positive response from Levodopa (30%). Its prevalence is higher than 1% in individuals over 50 years and about 3% in those older than 75. The physiopathology includes loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies (LBs), except in a subtype of recessively inherited PD, *PARK2*, that courses without the typical ubiquitinated cell body inclusions. A direct relationship between several gene mutations and Parkinson's disease presenting with an autosomal dominant, recessive, and X-linked modes of inheritance has been demonstrated (Table 25.5).

In many cases there is a confirmed genetic linkage between some loci and Parkinson disease, but the gene has not been isolated as of yet for the following cases: PARK3 (2p13) (602404), PARK10 (1p32) (606852), and PARK11 (2q36) (607688). The PARK12 locus is located on Xq21- q25 (300557) and was the first case presenting with an X-linked mode of inheritance. Two additional genes have been associated with PD: SNCAIP (Synphilin-1, 5q23.1–q23.3) (603779), which codifies for a protein that interacts with α-synuclein. An unique mutation p.R621C within the *SNCAIP* gene in two sporadic cases with PD were identified demonstrating the

involvement of SNCAIP in PD [30]. In addition, a polymorphism within intron 6 of NR4A2 (Nuclear Receptor-related 1: NURR1) (2q22–q23) (601828) is present more frequently in affected patients than in healthy controls [64]. Two different mutations in Parkinson families, but not in sporadic cases [23], demonstrate the implication of NR4A2 in PD. However, other authors have not yet confirmed these findings.

25.4.1 Molecular Genetics Diagnosis

Traditionally the molecular genetics diagnosis in PD included the search for recurrent mutations within the genes implicated in Parkinson disease by DNA sequencing. If this approach was negative then, multiplex ligation-dependent probe amplification is used to look for gene dosage alterations in the *SNCA* gene. In the last years, implementation of next-generation sequencing enables the simultaneous analysis of a myriad of genes implicated in PD thus facilitating diagnosis (Table 25.5).

25.4.2 Autosomal Dominant Parkinson's Disease

25.4.2.1 SNCA/PARK1-4

Mutations in the *SNCA* gene on 4q21–23 coding for alpha-synuclein (OMIM 163890) were the first genetic defects identified causing PD [41]. Nevertheless, mutations within *SNCA* are rare, and thus far, only three different missense mutations as well as duplications and triplications of the entire gene have been reported. The *SNCA* gene contains 6 exons and spans 117 kb. The protein localises in presynaptic terminals and interacts *in vivo* with synphilin-1 resulting in characteristic eosinophilic inclusions. Of the three missense mutations identified to date, p.A53T is by far the most frequent mutation reported. Penetrance of the missense mutations appears to be high, 85% for p.A53T. Increase of the dosage of the *SNCA* gene in familial PD is associated with PARK4 [53]. Other known allelic variants including p.A30P, p.E46K, and the presence of polymorphisms within the gene promoter associate with major susceptibility to develop Parkinson's disease. These and other mutations are reported in the Parkinson's Disease Mutation Database (PDMTD; www.thepi.org/parkinson-s-disease-mutation-database).

25.4.2.2 LRRK2/PARK8

Mutations in the *LRRK2* gene are the most frequent cause of late-onset autosomal dominant and sporadic PD with a mutation frequency ranging from 2 to 40% [5, 36]. LRRK2 parkinsonism is clinically indistinguishable from idiopathic PD.

LRRK2 codifies the leucine-rich repeat kinase 2 Dardarin, a protein with 2,482 amino acids containing a leucine-rich repeat, as well as kinase, Ras, and WD40 domains. The multidomain protein structure supports for a multifactorial role of LRRK2 in the neurodegenerative pathogenesis. The gene contains 51 exons and spans 144 kb. More than 20 mutations over the different protein motifs have been identified. The more prevalent mutations include G2019S, R1441G, and I2020T. To date, the mutations identified in LRRK2 are missense, two of them corresponding to intronic nucleotide changes (source: PDMTD).

25.4.3 Autosomal Recessive Parkinson's Disease (ARPD)

25.4.3.1 PARKIN/PARK2

Parkin was the second identified PD gene and the first gene irrefutably causing an AR form of the disorder. Mutations in this gene trigger a disease onset usually in the third or fourth decade of the patients' life, with slowly progression and an excellent response to dopaminergic treatment. However, some of *Parkin*-mutation carriers have an onset even in childhood, and homozygous mutations in *Parkin* are the most frequent cause of juvenile PD (age of onset ≤21 years). The clinical phenotype of *Parkin*-, *PINK1*-, and *DJ-1*-linked PD is indistinguishable. Reported post-mortem examinations indicate that the substantia nigra shows neuronal loss and gliosis, however, it frequently lacks Lewy bodies. A large number (>100) and wide spectrum of *Parkin* mutations have been identified, including alterations in all 12 exons, across various ethnic groups (PDMTD). *Parkin* is one of the largest genes in the human genome, spanning 1.38 Mb in 12 exons. The gene codifies for a protein involved in the protein degradation pathway by the ubiquitin–proteasome system [20].

25.4.3.2 PINK1/PARK6

Mutations in the phosphatase and tensin homolog (*PTEN*)-induced putative kinase 1 (*PINK1*) gene are the second most common cause of AR early-onset PD (EOPD) after *Parkin* [58] and has been reported in sporadic cases as well. The frequency of *PINK1* mutations is in the range of 1–9%, with considerable variation across different ethnic groups. The gene contains 8 exons and spans 1.8 kb. More than 40 punctual, insertions or deletion mutations have been reported (PDMTD). PINK1 is a 581 amino acid ubiquitously expressed protein kinase. It consists of an amino-terminal 34 amino acid mitochondrial targeting motif, a conserved serine–threonine kinase domain (amino acids 156–509; exons 2–8), and a carboxy-terminal autoregulatory domain. Two-thirds of the reported mutations in PINK1 are loss-of-function mutations affecting the kinase domain, demonstrating the importance of PINK1's enzymatic activity in the pathogenesis of PD. Interestingly, recent studies provide evidence that PINK1 and Parkin function in a common pathway for sensing and

selectively eliminating damaged mitochondria from the mitochondrial network. PINK1 is stabilized on mitochondria with lower membrane potential, and as such, it recruits Parkin from the cytosol. Once recruited to mitochondria, Parkin becomes enzymatically active and initiates autophagic clearance of mitochondria by lysosomes, i.e., mitophagy.

25.4.3.3 DJ-1/PARK7

DJ-1 is the third gene associated with AR PD, and it is mutated in about 1–2% of EOPD cases [4, 37]. Given that *DJ-1*-linked PD seems to be rare, very few patients have been reported in the literature. However, about 10 different point mutations and exonic deletions have been described mostly in the homozygous or compound-heterozygous state. The function of *DJ-1* is not well known, yet it has been implicated as an oncogene and as a regulatory subunit of a RNA binding protein (RBP). The seven coding exons of the *DJ-1* gene encode for a 189-amino acid-long protein that is ubiquitously expressed and functions as a cellular sensor of oxidative stress. The DJ-1 protein forms a dimeric structure under physiologic conditions, and it seems that most of the disease-causing mutants (p.L166P, p.E64D, p.M26I, and p.D149A) heterodimerise with wild-type DJ-1. In addition, the mutated proteins are frequently not properly folded, unstable, and promptly degraded by the proteasome. Thus, their neuroprotective function and antioxidant activity are reduced. There is a genetic and biochemical association between DJ-1 and PINK1. On this regard, an early-onset PD Chinese family presenting with a digenic inheritance of mutations in both genes was identified [57]. It is believed that digenic inheritance occurs because the proteins codified by both genes are functionally related to produce the specific PD phenotype by an epistasis effect. Up to date, more than 25 missense, deletions, frameshift or duplication mutations in *DJ-1* have been reported (PDMTD).

25.4.3.4 ATP13A2/PARK9

Homozygous and compound-heterozygous mutations in *ATP13A2* have been found to cause an AR atypical form of PD named Kufor-Rakeb syndrome [42]. This syndrome has juvenile onset with rapid disease progression, accompanied by dementia, supranuclear gaze palsy, and pyramidal signs. *ATP13A2* is a large gene comprised of 29 exons coding for an 1,180-amino acid protein. The ATP13A2 protein is normally located in the lysosomal membrane and it contains ten transmembrane domains and an ATPase domain. About ten different pathogenic mutations have been identified in the homozygous or compound-heterozygous state, directly or indirectly affecting transmembrane domains. Most of the mutations produce truncated proteins that are unstable and are retained in the endoplasmic reticulum and subsequently degraded by the proteasome. No exonic deletions or deletions or multiplications of the entire gene have been found to date. Several single heterozygous missense mutations are known, but their role in PD pathogenicity is currently unclear.

25.4.4 Parkinsonism-Related Disorders

Neurodegeneration with brain iron accumulation (NBIA) is a genetically heterogeneous disorder characterized by progressive iron accumulation in the basal ganglia and other regions of the brain, resulting in extrapyramidal movements including Parkinsonism and dystonia. Age at onset, severity, and cognitive involvement are highly variable. Associated genes identified include *CP*, *FTL*, C19ORF12, *PLA2G6*, *PLAN*, *PANK2*, *WDR45*, and *COASY*. Mutations in *PANK2* account for most of the NBIA cases.

25.4.5 Mitochondrial Inheritance

Pathogenic mitochondrial DNA (mtDNA) mutations are also associated with PD. MtDNA is a 16,569 base pair length genome that encodes 13 genes for subunit components of the oxidative phosphorylation subunits (OXPHOS) and its own tRNAs and rRNAs. As hundreds to thousands copies of mtDNA reside in virtually each mammalian cell, a state of heteroplasmy arises when different mtDNA genotypes, such as wild type and mutant forms, co-exist within the same cell. Substantia nigra neurons from autopsies of normal aged people and PD patients harbour high levels of mutated mtDNA with large-scale deletions causing mitochondrial dysfunction. Furthermore, mitochondrial disease patients with mutations in polymerase γ, the polymerase responsible for mtDNA replication, excessively accumulate mtDNA mutations and also have an increased risk of developing PD. The many links between mitochondrial dysfunction and the pathogenesis of PD has stimulated interest in the roles of PINK1 and Parkin on mitophagy.

25.4.6 Multifactorial Inheritance

Vaughan et al. [59] proposed that nigral degeneration with the presence of Lewy bodies leading to the several clinical symptoms might represent a common final outcome of a multifactorial process of the disease due to genetic as well as environmental agents [59]. In these regard, it has been observed that the Mendelian inheritance has a major role in PD cases where the disease onset appears in the third or fourth decade of life whereas a polygenic model with a higher environmental participation would account for adult late-onset Parkinson's disease. In this later scenario several genes and their respective polymorphic variations would provide a priori risk contribution. This risk would be posteriorly modulated by acquired environmental circumstances.

Table 25.5 Genetics of Parkinson disease

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
PARK1	4q22.1	168601	*α- Synuclein (SNCA)*	AD	Mild to late adulthood	Cognitive decline, depression, dementia may occur.
PARK2	6q26	602544	*Parkin*	AR	Before 40s	Diurnal fluctuations of symptoms, hyperreflexia may occur.
PARK4	4q22.1	605543	α- synuclein *(SNCA)* duplications	AD	45	Hallucinations, paranoia, dementia.
PARK5	4p13	613643	*UCHL-1*	AD	(49–51)	Resting tremor, rigidity, bradykinesia, postural instability.
PARK6	1p36.12	605909	*PINK-1*	AR	(9–68)	Anxiety, diurnal fluctuation, depression.
PARK7	1p36.23	606324	*DJ-1*	AR	Before 40s	Anxiety, psychotic episodes, blepharospasm may occur.
PARK8	12q12	607060	*LRRK2*	AD	Reduced penetrance (50–65)	Hyposmia, neurofibrillary MAPT (tau)-positive tangles.
PARK9	1p36.13	606693	*ATP13A2*	AR	13	Hallucinations, psychotic episodes, supranuclear gaze palsy, atrophy of pyramids.
PARK13	2p13.1	610297	*HTRA2*	AD	57 (49–77)	Bradykinesia, tremor, muscular rigidity.
PARK14	22q13.1	612953	*PLA2G6*	AR	Young adulthood	Personality changes, eyelid opening apraxia, frontotemporal dementia, variable severity.
PARK15	22q12.3	260300	*FBXO7*	AR	Adolescence or young adulthood	Pyramidal and extrapyramidal signs, spasticity, mainly in the lower limbs.
PARK17	16q11.2	614203	*VPS35*	AD	(50–52)	Motor fluctuation, cramps, akinesia.
PARK18	3q27.1	614251	*EIF4G1*	AD	Late onset (50–80)	Lewy bodies, rigidity.
PARK19	1p31.3	615528	*DNAJC6*	AR	1st decade	Masked facies, mental retardation, seizures.
PARK20	21q22.11	615530	*SYNJ1*	AR	Early twenties	Eyelid apraxia, supranuclear gaze palsy, dysarthria.
PARK21	3q22.1	616361	*DNAJC13*	AD	Late-adult onset	Postural instability, Lewy bodies.
PARK22	7p11.2	616710	*CHCHD2*	AD	56.2 (10–61)	Asymmetry at onset, bradykinesia, rigidity, and gait disturbance.
PARK23	15q22.2	616840	*VPS13C*	AR	Young-adult onset	Incontinence, cognitive decline, axial symptoms.
PARK-RAB39B	Xq28	–	*RAB39B*	X-linked	Early infancy (2–52)	Delayed psychomotor development.

AD Autosomal dominant, *AR* Autosomal recessive

25.5 Inherited Dementias

The term dementia encompasses a group of cognitive, psychological, and memory problems which ultimately render an individual unable to carry-out daily functions involving social interactions, assessment of the environment and consequences of events, reasoning, and problem solving. There are 47.5 million people with dementia worldwide, and 8 million new cases diagnosed every year according to the most recent data published by the World Health Organization [63]. Genetics *per se* contributes to a small proportion of all dementia cases and thus familiar forms are considered rare. Alzheimer's disease (AD) is the most common cause of dementia accounting for 60–80% of all cases, followed by vascular dementia responsible for 25%, Lewy Body dementia (LBD) for 15%, and frontotemporal dementia lobar degeneration forms by less than 5%. Other genetically linked dementia include Niemann-Pick, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler disease (GSD), and Huntington's disease [26]. Most individuals with dementia present the late-onset form starting after the age of 65 making up 90–95% of all cases. Although there are greater numbers of individuals with familial history of early-onset dementia, 95% of all cases are of unknown aetiology. Early-onset AD is 5–10% of all cases of which only 10% is familial [7]. Therefore, most recent efforts in dementia research have focused on finding the genetic factors causing Mendelian inheritance of dementia or can be one of the contributing factors to genetically complex diseases of which dementia forms part of the symptoms (Table 25.6).

25.5.1 Alzheimer's Disease (AD)

The most common symptoms of Alzheimer's disease include difficulty remembering recent events and conversations, often accompanied with apathy and depression followed by poor judgement, personality changes, disorientation, impaired communication, difficulty speaking, swallowing, and walking. AD is currently considered a disease of slow progression starting well before the presentation of symptoms. The major neuropathological hallmarks are the beta-amyloid protein fragment plaques and the tau protein tangles in addition to neuronal damage and loss. Some of the affected individuals express a mutation in one of three genes: the amyloid precursor protein gene (*APP*) and two presenilin genes (*PSEN1* and *PSEN2*). These mutations show dominant inheritance with low prevalence (1 in 1,000 people) and result in early-onset dementia (EOD) with presentation of symptoms as early as the third decade of life. On the other hand, AD presenting after the age of 65 is considered late-onset (LOAD), which is more common than EOAD and exhibits a complex inheritance. No specific gene has been identified to cause LOAD but rather a number of genes increasing the risk. The best known of such risk genes and the one with the highest effect is apolipoprotein E (APOE), found on chromosome 19. Specifically, one of its isoforms, APOE ε4 is present in about 25% of the total

population and is associated with the highest risk for developing AD. Less than 2% of the population carry two copies of the *APOE ε4* which increases their chances tenfold for developing AD, although it does not predict whether they will have AD symptoms in their lifetime. Some of the functions of the proteins encoded by the mutated genes associated with EOAD have been described. APP is known to function as a receptor on the surface of neurons to regulate neurite growth, neuronal adhesion, and axonogenesis. A buildup of amyloid-beta APP fragment has been linked to AD although not exclusively, since elderly people with identified build-up did not exhibit AD symptoms. Both PSEN1 and PSEN2 appear to function as catalytic subunits of gamma-secretase complex responsible for the intramembrane cleavage of the receptors NOTCH and APP. The specific roles of the mutation effects and the risk factors on the pathogenesis are still unclear.

25.5.2 Vascular Dementia

Vascular dementia is the most frequent EOD, being the second most common form of dementia in the general population and younger people [35]. It often results following many small strokes that restrict blood flow to the brain. It is a progressive condition affecting speech, memory, language, and learning. Recent studies support a role for APOE ε4 as a risk factor for vascular dementia, but with much less impact than in AD. Other known risk factors include high cholesterol levels, high blood pressure, and diabetes. In general, genes appear to play a much lesser role in the common forms of vascular dementia compared to familial Alzheimer. However, a rare form of vascular dementia known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is found to be caused by the dominant inheritance of mutations in the notch homolog protein 3 gene (*NOTCH3*). Affected individuals experience migraines and temporary loss of vision and numbness followed by progressive cognitive problems around the age of 50. The *NOTCH3* gene encodes a receptor for membrane-bound ligands, and is mostly expressed in vascular smooth muscle cells regulating cell fate during development. The mutation is thought to alter its ligand-binding site resulting in dysfunction of the vascular muscle.

25.5.3 Dementia with Lewy Bodies (DLB)

Ten percent of individuals with dementia with early-onset have dementia with Lewy body (DLB) also known as Lewy body disease. Some of the clinical symptoms are generally common to other dementias such as difficulty with attention, spatial awareness and memory. In addition, some individuals suffer with hallucinations and movement problems resembling Parkinson's disease (PD). DLB is the second more prevalent form of age related dementia affecting approximately 5% of people over

age 85. The hallmark neuropathological finding of the DLB affected individuals is the presence of diffuse Lewy bodies in the cortical and subcortical regions. Genetic analysis identified a mutation in the alpha-synuclein gene (*SNCA*) that co-segregated with the disease phenotype and two different heterozygous mutations in the beta-synuclein gene (*SNCB*) in unrelated individuals [34]. It has been proposed that the mutations may alter the ability of beta-synuclein to inhibit the toxic alpha-synuclein fibril formation. Moreover, the expression of synuclein specific isoforms are differentially altered in brains of patients with DLB compared to PD [3]. Heterozygous mutations in the glucosylceramidase gene (*GBA*) have also been identified and shown to enhanced susceptibility to the disease. GBA is a lysosomal enzyme involved in glycolipid metabolism. Mutations result in the accumulation of glucocerebrosides in the lysosome leading to cell damage.

25.5.4 Frontotemporal Dementias (FTD)

Frontotemporal dementia (FTD) is a group of neurological disorders caused by damage to the cells of the frontal and temporal lobes of the brain. These disorders are also referred to, by the pathological finding, frontotemporal lobar degeneration diseases (FTLD). The frontal lobe controls the emotions, behaviour, and personality, and is required for language. Most cases occur at ages between 45 and 65 with almost half of the affected individuals having a family history and being caused by a mutation in a single gene [2]. Several subtypes of FTD have been classified by the most prominent clinical symptoms which differ depending on the region of the frontal and temporal lobes affected and mostly restricted by the presence of pathologic inclusions [19]. Clinical symptoms include obsessive, and aggressive behaviours, loss of inhibitions and/or speech difficulties. The FTD subtypes include the behavioural variant (bvFTD), and the language variants primary progressive aphasia (PPA), which include the progressive non-fluent aphasia (PNFA), semantic dementia (SD) and logopenic progressive aphasia (LPA). The most common form is bvFTD. It is characterized by progressive atrophy of the frontal and anterior region of the brain resulting in deficits in complex thinking and planning, and changes in behaviour and personality mostly stemming from behavioural disinhibition, apathy, loss of empathy, and compulsive behaviours. In contrast, the clinical features of PPA include difficulty speaking, word errors, and loss of word retrieval in PNFA, SD, and LPA subtypes respectively. Unlike other types of dementia, memory and executive functions are not affected in the early stages, many times causing patients to become frustrated and depressed as they become aware of their deficits.

The frontotemporal lobar degenerations diseases (FTLD) have been classically grouped by the neuropathological findings after post-mortem examination, mainly the presence of tau-positive inclusions (FTLD-tau) or those with ubiquitin-positive inclusions most of which are also TAR-DNA-binding protein 43 (TDP-43) positive (FTDLD-TDP43) [28]. Other neuropathological subtypes include those with positive inclusions for the RNA-binding protein FUS or for ubiquitinated proteasome

system components [55]. Most recently, the identification of genetic mutations associated with the inheritance of these conditions is helping to link both the pathology and clinical features of these disorders. The most common mutations involve genes encoding for the proteins tau (MAPT), progranulin (*GRN*), and a gene called chromosome 9 open reading frame 72 (*C9orf72*). Less frequent associated mutations include chromatin-modifying protein 2b (*CHMPB2*), TAR-DNA-binding protein (*TARDBP*), the valosin-containing protein (*VCP*) genes, coiled-coil-helix-coiled-coil-helix domain-containing protein 10 (*CHCHD10*), sequestosome 1 (*SQSTM1*), tank-binding kinase 1 (*TBK1*), and fused in sarcoma (*FUS*) genes (Tables 25.6 and 25.7).

The most common clinical subtype bvFTD, with or without motor symptoms resembling Parkinson's disease (PD), is associated with mutations in the tau gene (*MAPT*). More than 50 mutations in tau have been identified associated with hereditary FTD. These mutations can disrupt the function of tau in the maintenance of the neuronal structure and the axonal transport and result in the accumulation and clumping of this protein within neurons. Neuropathological post-mortem findings in these individuals show FTLD-tau positive inclusions. The mutations in the progranulin (*GRN*) gene are responsible for 5–10% of all cases of FTLD and 13–25% of familial cases. *GRN* mutations are associated with bvFTD, PNFA, and rarely with amyotrophic lateral sclerosis (ALS). The missense mutations in *GRN* result in reduced progranulin levels and the formation of TDP-43 and ubiquitin positive inclusions. Likewise, mutations in the *TARDBP* gene encoding the TDP-43 protein have been identified in individuals with sporadic and familial ALS lead to accumulation of ubiquitin and TDP-43 inclusions. Progranulin is involved in cell growth, TDP-43 regulates the protein expression, and ubiquitin helps to clear out the cellular waste products particularly damaged proteins. Mutations in the *C9orf72* gene consisting of a hexanucleotide repeat expansion (GGGGCC) are present in approximately 60% of hereditary FTD with ALS (FTDALS1). Affected individuals show TDP-43 positive inclusions. The protein encoded from the *C9orf72* gene is enriched in neurons and appears to function in membrane trafficking and in the nucleus in RNA homeostasis. The most recent model proposes a role for both, an arginine-rich protein and a repeat-containing RNA in the *C9orf72* mutation induced pathogenesis. Mutations in the *VCP* gene has shown a 100% association with an autosomal dominant condition called inclusion body myopathy associated with Paget disease of bone (PDB) and/or FTD (IBMPFD). *VCP* mutations potentially disrupting the proteins role in the ubiquitin pathway cause the accumulation of inclusions made of ubiquitin rarely TDP-43 or VCP, but not tau. Mutations in the *CHMP2B* gene have only been detected in a single Danish family and lead to ubiquitin, but not TDP-43 positive inclusions in the brain. The protein encoded by the *CHMP2B* gene is involved in the recycling or destroying cell surface proteins or receptors. Because of low casuistic, genetic diagnosis based on mutations in *TARDBP* and *CHMP2B* genes is mostly done on a research basis only. Mutations in *CHCHD10* underlie FTD with ALS (FTDALS2). The *CHCHD10* gene encodes a small mitochondrial protein proposed to be involved in maintaining the morphology of the mitochondrial cristae and in oxidative phosphorylation. Expression of the *CHCHD10*

mutations in cells result in mitochondria fragmentation and dysfunction. The *SQSTM1* gene underlying FTDALS3 encodes a scaffolding protein involved in NFKB signalling and ubiquitin-mediated autophagy. Mutations in the *TBK1* gene are associated with FTDALS4, which encodes a serine/threonine kinase involved in inflammatory responses. The *FUS* gene encodes a nuclear protein involved in DNA and RNA metabolism including repair, transport, as well as transcription. Mutations in this gene are associated in ALS6 with or without FTD.

25.5.5 Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS)

Two movement disorders, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), are also related to FTD and they share some common symptoms. PSP is the second most frequent cause of degenerative Parkinsonism and results in progressive damage to the neurons controlling eye movement. In addition to supranuclear gaze palsy, the clinical symptoms include early postural instability and cognitive decline. The most prominent neuropathological feature is the abundance of neurofibrillary tangles in both neurons and glia in subcortical regions while in Alzheimer's disease these are prominent in the cortex and detected in neurons. Several mutations in the *MAPT* gene, some of which appear to increase tau expression, have been associated with PSP. These mutations often result in particular difficulty with spelling, writing, or math skills. CBS is characterized by progressive neurodegeneration of the cerebral cortex and the basal ganglia beginning in people from 50 to 70 years of age. The prominent symptoms include Parkinsonism, Alien hand syndrome, apraxia, aphasia and cognitive dysfunction. Some individuals are particularly difficult to diagnose since they also experience behavioural and other symptoms resembling Alzheimer's or Parkinson's disease. Recently, two new loss-of-function mutations in the *GRN* gene have been differentially associated with CBS, but not with FTLD diagnosed individuals [56].

25.5.6 Niemann-Pick Disease

Niemann-Pick disease encompasses a group of metabolic disorders characterised by the accumulation of sphingomyelin within lysosomes. Most of the affected individuals are children (70%) and the remainder of individuals having a disease onset during early adolescence (30%). The disease course could be severe, fatal during early childhood or milder resulting in a somewhat normal life span. The most pronounced symptoms result from the organs with the most abnormal accumulation of sphingomyelin such as in the liver, spleen, bone marrow or the nervous system. The later results in ataxia, dysarthria, dysphagia and dystonia, and seizures and

dementia. The symptoms may first present while in early adulthood, at which time the psychiatric illness may appear as schizophrenia or bipolar disorder. Mutations in the *SMPD1* gene produce deficient sphingomyelinase activity and underlie Niemann–Pick disease types A and B (NPCA and NPCB). Mutations in the NPC1 and NPC2 encoding proteins intracellular cholesterol transporter proteins 1 and 2, involved in lipid transport cause Niemann–Pick disease type C (NPC). Type D delineates a common ancestry from Nova Scotia with NPC.

25.5.7 Inherited Prion Diseases

The Creutzfeldt-Jakob disease (CJD) is the most common human form of the rare fatal brain disorders called prion diseases affecting both people and several other mammals. The incidence of all forms of CJD is 0.5–1.5 per million per year of which 15% are familial cases. Unlike the familial CJD, the variant CJD commonly referred to as "mad cow disease" occurs in cattle, and has been transmitted to people mostly through consumption of affected tissue. Likewise, the Gerstmann-Straussler disease (GSD), also known as PRNP-related cerebral amyloid angiopathy, is a prion disease with an autosomal inheritance. GSD is associated with mutations in the prion protein gene (PRNP). It is characterized by memory loss, dementia, ataxia, and pathologic deposition of amyloid-like plaques in the brain. This disease first presents with truncal ataxia, dysarthria, and cognitive decline in the third and fourth decade of life. The fatal familial insomnia (FFI) disorder is another familial disease caused by mutations in the *PRNP* gene. The pathological changes appear localized to the anterior and dorsomedial thalamus. The Asp-178->Asn mutation in the *PRNP* gene (D178N) when the amino acid at position 129 is a methionine, is the only mutation associated with FFI described to date. However, the D178N mutation accompanied by the M129 V mutation in the *PRNP* gene has been shown associated with CJD. GSD is distinguished from CJD and FFI in that it normally has a longer disease course and shows prominent cerebellar ataxia.

25.5.8 Huntington's Disease (HD) and Other Choreas

Huntington's disease (HD), also known as Huntington's chorea, is an inherited autosomal dominant neurodegenerative disease characterised by motor, psychiatric, and cognitive dysfunction. Most commonly, the symptoms first present from the third to the fifth decade. Early symptoms include loss of short-term memory and their planning and organisational skills. The classic signs of the disorder are progressive chorea, rigidity, and dementia accompanied by caudate nucleus atrophy. The clinical features develop progressively with severe increase in choreic

movements and dementia. HD is one of the most common dementia. However, because it can sometimes present without chorea it is difficult to recognize particularly in young patients with dementia. Early onset or juvenile Huntington's disease, typically beginning by 20 years of age, is approximately less than 10% of all HD cases. The genetic cause of HD is an abnormal expansion of a CAG repeat in the *HTT* gene encoding a polyglutamine tract in the N- terminus of huntingtin [27]. The juvenile form is associated with very large number of CAG repeats (more than 60) in the *HTT* gene. It is usually transmitted through an affected father due to the genetic phenomenon of anticipation and male transmission bias. Huntingtin is a ubiquitously expressed protein, which can translocate to the nucleus where it has been shown to regulate transcription. It also has roles in the cytoplasm where its functions include axonal transport [50]. The toxicity of the expanded repeat protein appears to be increased upon cleavage by enhancing the altered conformation and aberrant protein interactions of the mutant protein fragments [47, 49]. A toxic gain-of-function of the mutant protein rather than a loss-of-function mutation has been proposed to be responsible for the pathogenesis in HD.

Some individuals with similar symptoms to HD negative for the *HTT* mutation were further investigated for distinguishing clinical features and potential alternate genetic causes. This led to the description of three Huntington disease-like (HDL1-3) disorders and the categorisation of SCA17 as HDL4. HDL1 presents with chorea, cognitive decline, dementia, ataxia, rigidity, cell loss and gliosis in the basal ganglia, kuru and multicentric plaques in the cerebellar cortex. It is an autosomal dominant disease caused by insertion of 8 additional octapeptide repeats in the prion protein gene (*PRNP*). It distinguishes from other prion disorders by the prominence of psychiatric symptoms and the long progression of the disease course. Huntington disease-like 2 (HDL2) presents chorea and also dementia. It is associated with a heterozygous expanded CAG/CTG repeat in the junctophilin-3 gene (*JPH3*). While normal alleles contain 6–28 repeats, the pathogenic alleles contain over 41 repeats. JPH3 protein mediates the interaction between the endoplasmic reticulum and the plasma membrane thereby mediating the regulation between the cell surface and the intracellular ion channels. It has been proposed that a toxic RNA gain-of-function effect underlies the pathogenesis caused by this mutation since expression of the RNA is sufficient to cause toxicity in cells. Unlike HLD1 and HDL2, HDL3 shows autosomal recessive inheritance which was described in children (onset age 3–4 years old) presenting with Huntington disease-like prominent seizures, rapid course, speech disturbances such as mutism. The identification of the associated mutation is still in progress.

Choreoacanthocytosis (CHAC) and McLeod neuroacantocitosis syndrome are rare movement disorders characterized by progressive basal ganglia neurodegeneration with red cell acanthocytosis, showing variable age of onset typically in the third to fifth decade of life. These are caused by mutations in the *VSP13A* and *XK* genes respectively. The *VSP13A* gene encodes chorein protein while the *XK* gene encodes the membrane transport protein XK, both membrane-bound proteins.

Table 25.6 Genetics of inherited dementias

Name	Locus	OMIM	Gene	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
Alzheimer´s disease						
AD 1	21q21.3	104300	*APP*	AD	Early onset	Presenile and senile dementia, parkinsonism, long tract signs.
AD 2	19q13.32	104310	*APOE*	AD	Late onset	Presenile and senile dementia, parkinsonism, long tract signs.
AD 3	14q24.2	607822	*PSEN1*	AD	20–30	Progressive, memory loss, behavioural and personality changes, gait disturbances, apraxia, extrapyramidal signs.
AD 4	1q42.13	606889	*PSEN2*	AD	35–60	Presenile dementia, sleep-wake cycle disturbance.
Vascular dementia						
CADASIL	19p13.12	125310	*NOTCH3*	AD	3th decade	Vasculopathy, leukoencephalopathy, gait abnormalities.
Dementia with Lewy Bodies						
Dementia with Lewy Bodies	4q22.1	127750	*SNCA*	AD	60–70	Parkinsonism, fluctuations in consciousness, visual hallucinations.
Dementia with Lewy Bodies	5q35.2		*SNCB*			
Dementia with Lewy Bodies	1q22		GBA			
Frontotemporal dementia						
Dementia, familial, nonspecific	3p11.2	600795	*CHMP2B*	AD	57	Mutism, abnormal gait, pyramidal signs, aggressiveness, personality changes.
FTDALS1	9p21.2	105550	*C9orf72*	AD	Adulthood	Muscle atrophy, quadriparesis, parkinsonism, extrapyramidal signs.
FTDALS3	5q35.3	616437	SQSTM1	AD	Late Adulthood	Orofacial apraxia, muscle weakness, mutism.
FTDALS4	12q14.2	616439	*TBK1*	AD	Adulthood	Bulbar weakness, muscle weakness, mutism,
FTD with or without parkinsonism	17q21.31	600274	*MAPT*	AD	45	Frontal lobe dementia, motor symptoms may be present, personality changes.

FTLD with ubiquitin-positive inclusions	17q21.31	607485	*GRN*	AD	62 (45–79)	Dysnomia, mutism, apraxia, personality changes hallucinations.
Inclusion body myopathy with early-onset Paget disease and FTD1	9p13.3	167320	*VCP*	AD	57	Winged scapulae, hip pain, muscle weakness, gait abnormalities.
FTLD, TARDBP-related	1p36.22	612069	*TARDBP*	AD	(25–78)	Tongue hypotrophy, muscle weakness, pyramidal signs, disinhibition.
ALS6, with or without frontotemporal dementia	16p11.2	608030	*FUS*	AD/AR	Adulthood	Bulbar onset, motor neuron loss.
Progressive Supranuclear palsy	17q21.31	601104	*MAPT*	AD	66	Diplopia, Supranuclear gaze palsy, Parkinsonism, Forgetfulness, Dysarthria
Niemann-Pick disease						
Niemann-Pick disease, type A	11p15.4	257200	*SMPD1*	AR	Infancy	Short stature, granular-appearing maculae, xanthomas, Muscle weakness.
Niemann-Pick disease, type B	11p15.4	607616	*SMPD1*	AR	Infancy or Childhood	Dyspnea.
Niemann-Pick disease, type C1	18q11.2	257220	*NPC1*	AR	Early childhood	Vertical supranuclear gaze palsy, hypotonia, developmental delay, ataxia.
Niemann-Pick disease, type C2	14q24.3	607625	*NPC2*	AR	Variable	Vertical supranuclear gaze palsy, hypotonia, developmental delay, ataxia.
Prion Diseases						
Creutzfeldt-Jakob Disease	20p13	123400	*PRNP*	AD	38 – 45	Loss of facial expression, Supranuclear gaze paralysis, Gait ataxia, Hallucinations,
Gerstmann-Straussler disease	20p13	137440	*PRNP*	AD	30s (30–60)	Cerebellar ataxia, parkinsonism, psychosis.
Fatal Familial Insomnia (FFI)	20p13	600072	*PRNP*	AD	18–54	Insomnia, Thalamic, medial dorsal nucleus, neuron loss,
Huntington´s disease	4p16.3	143100	*HTT*	AD	40s (10–70)	Abnormal eye movement, chorea, bradykinesia.

25.6 Motor Neuron Diseases (MND)

Motor neuron diseases (MND) are classified according to whether they are inherited or sporadic, these being the most common, and to whether degeneration affects upper motor neurons (UMNs), lower motor neurons (LMNs), or both. In adults, the most common MND is amyotrophic lateral sclerosis (ALS or Lou Gehri disease), characterised by progressive skeletal muscle weakness, amyotrophy, spasticity, and fasciculations as a result of degeneration of the upper and lower motor neurons, culminating in respiratory paralysis. It has inherited and sporadic forms and can affect the arms, legs, or facial muscles. Most ALS cases are sporadic, and only 5–10% of cases are considered to be familial. Mutations in the *C9orf72* gene are responsible for 30–40% of familial ALS cases in the United States and Europe. Worldwide, approximately 20% of cases of familial ALS are due to a mutation in the Cu/Zn superoxide dismutase–1 gene (*SOD1*). Western Pacific ALS occurs on the islands of Guam (Guam ALS), on the Kii peninsula of Japan, and in Western New Guinea. It is now clear that a subset of ALS cases shows features of frontotemporal lobar degeneration (FTLD) (ie, FTLD-MND/ALS) (Tables 25.6 and 25.7).

Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder that primarily involves the UMNs, resulting in progressive spinobulbar spasticity. Because substantial numbers of cases initially diagnosed as PLS would be reclassified as ALS as the disease progresses, a disease duration of at least 3 years is required to render this diagnosis clinically. There is still debate regarding whether PLS is a distinct pathologic entity or whether it represents one end of a clinical spectrum of ALS.

Progressive bulbar palsy (PBP) is a progressive degenerative disorder of the motor nuclei in the medulla specifically involving the glossopharyngeal, vagus, and hypoglossal nerves, that produces atrophy and fasciculations of the lingual muscles, dysarthria, and dysphagia. In adults, because most of the cases presenting with these pure bulbar symptoms represent so-called bulbar-onset ALS and eventually develop widespread symptoms typically seen in ALS, some authors consider this disorder to be a subset of ALS. Infantile PBP is a rare disorder that occurs in children and presents as the following two phenotypically associated forms: Brown-Vialetto-Van Laere syndrome (pontobulbar palsy with deafness) and Fazio-Londe disease. Brown-Vialetto-Van Laere syndrome is characterised by bilateral sensorineural deafness that is followed by CNs VII, IX, and XII palsies, whereas Fazio-Londe disease causes progressive bulbar palsy without deafness. Both disorders are genetically heterogeneous (Table 25.7).

Table 25.7 Molecular genetics of MNDs

Name	Locus	Gene/Locus	OMIM	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
Amyotrophic lateral sclerosis (ALS)						
ALS1	21q22.11	*SOD1*	105400	AD/AR/SP	Variable	
ALS2	2q33.1	*ALS2*	205100	AR	First decade	ALS2-related disorders.
ALS3	18q21	–	606640	AD		
ALS4	9q34.13	*SETX*	602433	AD	Less than 6 years	UMN and LMN.
ALS5	15q21.1	*SPG11*	602099	AR	Juvenile (<25)	UMN and LMN, slowly progressive.
ALS6	16p11.2	*FUS/TLS*	608030	AD/AR	4th decade	LMN, with or without FTD.
ALS7	20p13	–	608031	AD		
ALS8 (SMAIV or Finkel type SMA)	20q13.32	*VAPB*	608627	AD	31–45 years	Slow progression.
ALS9	14q11.2	*ANG*	611895	AD		UMN and LMN, with or without parkinsonism or FTD.
ALS10	1p36.22	*TARDBP*	612069	AD	Adult onset	With or without FTD.
ALS11	6q21	*FIG4*	612577	AD	Adult onset	Allelic of CMT4J,
ALS12	10p13	*OPTN*	613435	AD/AR	30–60 years	
ALS13	12q24.12	*ATXN2*	183090	AD	Adult	Susceptibility to ALS.
ALS14	9p13.3	*VCP*	613954	AD	37–53 years	UMN, LMN, with or without FTD.
ALS15	Xp11.21	*UBQLN2*	300857	XLD	16–71 years	With or without FTD.
ALS16	9p13.3	*SIGMAR1*	614373	AR	1–2 years	Early lower limb spasticity with hyperreflexia and weakness.
ALS17	3p11.2	*CHMP2B*	614696	AD	Adult	LMN, bulbar signs, respiratory insufficiency.
ALS18	17p13.2	*PFN1*	614808	AD	30s–40s	

(continued)

Table 25.7 (continued)

Name	Locus	Gene/Locus	OMIM	Mode of inheritance	Average onset (range in years)	Distinguishing clinical features
ALS19	2q34	*ERBB4*	615515	AD	60–70	UMN, LMN, no cognitive impairment.
ALS20	12q13.13	*HNRNPA1*	615426	AD	Adult	
ALS21	5q31.2	*MATR3*	606070	AD	30–55 years	UMN, LMN with or without myopathy or dementia.
ALS22	2q35	*TUBA4A*	616208	AD	48–71	With or without FTD.
ALS/FTD	9p21.2	*C9orf72*	105550	AD	40–62 years	With FTD.
ALS/FTD	22q11.23	*CHCHD10*	615911	AD	Adult	With FTD.
ALS/FTD	5q35.3	*SQSTM1*	616437	AD	Adult	UMN, LMN, FTD.
ALS/FTD	12q14.2	*TBK1*	616439	AD	Adult or late	Cognitive impairment, behavioral abnormalities, and speech apraxia and/or UMN and LMN signs.
ALS with dementia	–	–	205200	–	Juvenile	Progressive.
Primary lateral sclerosis (PLS)						
Infantile-onset ascending spastic paralysis	2q33.1	*ALS2*	607225	AR	First years	
Juvenile (PLSJ)	2q33.1	*ALS2*	606353	AR/SP	Infantile/Juvenile	
Adult (PLSA1)	4p16	–	611637	AD/SP	Adult	UPN, corticospinal, corticobulbar.
Progressive bulbar palsy						
Brown-Vialetto-Val Laere Syndrome 1	20p13	*SLC52A3*	211530	AR	Childhood	Progressive bulbar palsy with sensorineural deafness.
Brown-Vialetto-Val Laere Syndrome 2	8q24.3	*SLC52A2*	614707	AR	Childhood	
Fanzio-Londe Disease	20p13	*SLC52A3*	211500	AR	Childhood	Without sensorineural deafness.

Spinal muscular atrophy						
SMA type 1 (Werdnig-Hoffmann disease)	5q13.2	*SMN1*	253300	AR	Childhood	
SMA type 2	5q13.2	*SMN1*	253550	AR	3–15 months	
SMA type 3 (Kugelberg-Welander Syndrome)	5q13.2	*SMN1/2*	253400	AR	2–17 years	
SMA type 4	5q13.2	*SMN1*	271150	AR	20s–40s	
Spinal and bulbar muscular atrophy	Xq12	*AR Receptor*	313200	XLR	3rd–5th decade	Kennedy disease.

LMN lower motor neurons, *UMN* upper motor neurons, *AD* autosomal dominant, *AR* autosomal recessive, *SP* sporadic, *XLD* X-linked dominant, *XLR* X-linked recessive

25.7 Rare Metabolic Neurodegenerative Diseases

Inborn errors of metabolism can be defined as genetic disorders that interfere with chemical reactions that the body uses to maintain life, including energy production. They are an important cause of neurodegenerative processes, and in a recent epidemiological study, they represent up to 60% of progressive neurological deterioration cases, being the most frequent, mitochondrial disorders, mucopolysaccharidosis, and neuronal ceroid lipofuscinosis (NCL) [60]. In this clinical context, they must be considered early in the diagnosis algorithm, as many of them are treatable disorders while in turn a specific diagnosis is crucial for genetic counselling, prenatal diagnosis and assessment of family members.

25.7.1 Classification of Rare Metabolic Neurodegenerative Diseases

According to the mechanisms responsible for their pathophysiology, Saudubray proposed three main groups of metabolic diseases (Table 25.8) [51]:

Group I including those diseases associated with the accumulation of toxic substances because of the defect in the function of an enzyme or transport protein. The main examples are disorders of protein metabolism including aminoacidopathies, organic acidemias and urea cycle disorders. These disorders usually present as an acute encephalopathy and start at young age or even in the neonatal period.

Group II includes diseases where a defect of energy production is implicated in the deficient cellular functioning. The major disorders included in this group are respiratory chain diseases (OXPHOS), beta-oxidation, glycogen storage, and creatine metabolism disorders. They present with either a slowly progressive course and/or intermittent metabolic crises precipitated by stress.

Group III comprises disorders of cellular organelles in which there are storage of large molecules causing progressive dysfunction. Lysosomal storage diseases, peroxisomal disorders, and congenital disorders of glycosylation (CDG) are included among others.

25.7.2 Main Clinical Symptoms

Metabolic diseases are usually multiorganic, albeit in many cases there are predominant features [40]. Global developmental delay can be the main symptom in adenylosuccinate lyase deficiency, lysosomal storage disorders, CDG, but also in

urea cycle disorders, creatine metabolism diseases, mild forms of non-ketotic hyperglycinemia (NKH), homocystinuria, and cerebrotendinous xanthomatosis. Refractory epilepsy starting in the neonatal period or infancy should raise suspicion of possible pyridoxine-dependent seizures, pyridoxamine-5′-phosphate oxidase (PNPO) deficiency, GLUT-1 deficiency syndrome, serine or folate deficiencies, creatine disorders or NKH. Instead, the progressive appearance of pyramidal signs associated sometimes with cognitive decline, movement disorders or ataxia is characteristic of leukodystrophies. Dystonia can be seen in mitochondrial diseases, Segawa disease, late-onset tyrosine hydroxylase deficiency, and in organic acidurias (OAs) like glutaric aciduria type I following episodes of acute decompensation, whereas late forms of GLUT-1 deficiency syndromes can manifest as paroxysmal exercise-induced dyskinesia that improves with rest or administration of sugar. Intermittent ataxia is a main feature in disorders of protein metabolism and mitochondrial disorders, while chronic ataxia appears in mitochondrial disorders (Leigh syndrome, Kearns-Sayre, CoQ10 deficiency), vitamin E deficiency, Refsum disease, CDG, GM2 and Niemann-Pick type C. Finally, autism can be a predominant manifestation of Smith-Lemli-Opitz syndrome, mitochondrial disorders or creatine, folate or biotinidase deficiencies.

25.7.3 Diagnosis

A family history of consanguinity, unexplained hydrops foetalis, sibling deaths or developmental delay must raise the suspicion of a metabolic disease. Similarly, the presence of cerebral palsy of unknown origin or coexistence of neurological and non-neurological features should always raise suspicion of a metabolic disorder. At the neurological level, to differentiate whether the predominant involvement is in the white matter (hypotonia or spasticity and visual impairment) or grey matter (dementia, personality changes, seizures) can be helpful to guide complementary exams. Another important point is to consider treatable disorders first and the most frequent according to the age of onset of symptoms.

Most of neurometabolic disorders are autosomal recessive (Table 25.9), whereas maternal transmission might suggest an X-linked or mitochondrial mode of inheritance. Sporadic cases with de novo mutations are frequent.

In acute metabolic decompensations, studies including lactate/pyruvate ratio, NH3, blood gases, plasma amino acids, urine organic acids, and acylcarnitines are recommended. However, in slowly progressive processes testing for urine glycosaminoglycans, white cell enzymes activity, studies in muscle biopsy, transferrin isoelectric focusing, VLCFA, and 7-dehydrocholesterol may be needed.

In other cases, CSF studies may be undertaken in order to demonstrate high lactate levels in mitochondrial disorders, low glucose CSF/plasma ratio in GLUT1 deficiency and for neurotransmitter analysis [44]. Magnetic resonance imaging (MRI) is important to detect white matter abnormalities, which can have a very characteristic pattern in some leukodystrophy patients, but also signs of cortical or cerebellar atrophy or basal ganglia abnormalities. MR spectroscopy may uncover a low creatine/phosphocreatine ratio, a high lactate peak in mitochondrial disorders, or elevated concentration of N-acetylaspartate in Canavan disease [38].

In recent years, newborn screening (NBS) has been implemented in many countries, allowing early detection of several metabolic disorders before clinical manifestations appear. On the other hand, performance of next generation sequencing (NGS) studies can help in confirmation of molecular basis and guide genetic counselling.

25.7.4 Treatment

In acute metabolic encephalopathies, emergency treatment based on glucose infusions to reverse catabolism and medications or haemofiltration to remove toxins is crucial in order to avoid irreversible brain damage.

In some metabolic disorders there are specific treatment options: enzyme replacement treatment (ERT) have been developed for some lysosomal storage diseases including Gaucher, MPS type I, II, IV, VI, VII, Pompe and Fabry disease; substrate reduction with miglustat has been used in Gaucher disease type 1 and to delay Niemann-Pick C (NPC) progression; ketogenic diet in patients with GLUT1 deficiency syndromes or with refractory epilepsy; and early haematopoietic stem cell transplantation for X-linked adrenoleukodystrophy, Hurler syndrome (MPS I), Maroteaux Lamy (MPS VI) and Sly (MPS VII) syndromes. For most mitochondrial disorders there is no specific treatment, with the exception of coenzyme Q10 and riboflavin responsive complex I deficiency, although some antioxidant molecules have also been used. Creatine deficiency syndromes caused by L-arginine:glycine amidinotransferase (AGAT) or guanidinoacetate methyltransferase (GAMT) enzymatic defects can be successfully treated by creatine and arginine supplements. In the last years, therapy with small molecules chaperones is being investigated in some lysosomal disorders such as Fabry disease, whereas there has been significant progress in the development of gene therapy for several diseases, with currently ongoing clinical trials on Pompe's disease, MLD, and MPS IIIA.

Table 25.8 Classification of the main neurometabolic disorders

Main disorder	Main clinical features	Metabolic tests
Intoxication		
Aminoacidurias	First months (symptom free interval). Metabolic crisis (lethargy, vomiting, seizures, liver failure) precipitated by intercurrent illness or food intake. Chronic (failure to thrive, developmental delay).	Plasma AA, urine OA, acylcarnitine
Organic acidurias		
Urea cycle disorders		Plasma NH3
Metal intoxication (Wilson, Menkes), Fe, Mn	Seizures, movement disorders.	Cu, ceruloplasmin, Fe, Mn.
Neurotransmitter diseases	Dystonia, tremor, parkinsonism, pyramidal signs, autonomic, neuropsychiatric.	CSF neurotransmitters.
Energy deficiency		
Mitochondrial diseases and congenital lactic acidemias (PC, PDH, Alpers, Kearns-Sayre, Leigh, MERRF, MELAS, NARP syndromes), syndromes of mtDNA depletion	Any age. Multisystemic. Global developmental delay, epilepsy, ptosis, external ophthalmoplegia, proximal myopathy, peripheral neuropathy, ataxia, stroke-like episodes, cardiomyopathy, sensorineural hearing loss, retinitis pigmentosa, renal tubular insufficiency, diabetes mellitus, liver dysfunction.	Plasma/CSF lactate and pyruvate, muscle biopsy, molecular studies
Deficiencies creatine metabolism	Intellectual disability, language developmental delay behavioural difficulties and epilepsy.	Creatine/creatinine (u), guanidinoacetate (p,u). MRS creatine peak.
Glycogen storage diseases	Hypoglicemia, hepatomegaly, cardiomegaly, weakness.	Hypoglycemia. Liver or muscle biopsy
Fatty acid oxidation defects	Lethargy and encephalopathy during fasting. Hepatomegaly sometimes.	Hypoglycemia with absent ketosis, liver dysfunction.

(continued)

Table 25.8 (continued)

Main disorder	Main clinical features	Metabolic tests
Complex molecules		
Lysosomal	**MPS**: macrocephaly, developmental delay, dwarfism, bony deformity, organomegaly.	Urinary GAG (MPS). Enzymatic analysis. Molecular studies.
	Tay-Sachs: weakness, startle, seizures, spasticity.	
	Gaucher: anemia, trombocitopenia, HEM, ocular and neuromotor dysfunction**.**	
	Pompe: hypertrophic cardiomyopathy, muscle weakness.	
	Neuronal ceroid lipofuscinosis: seizures, dementia, visual loss, and/or cerebral atrophy.	
Peroxisomal	Hypotonia, skeletal dysplasia, sensory deficits, liver dysfunction.	Plasma VLCFA.
	Zellweger: dysmorphic features, macrocephaly, seizures.	
	X-ALD: leukodystrophy, developmental regression, spasticity, adrenal failure.	
Congenital disorders of glycosylation	Developmental delay, seizures, hypotonia, liver disease, coagulopathy, dystonia.	Sialotransferrin isoelectric focusing.
Disorders of complex lipids metabolism	Spastic paraparesias, neurodegeneration with iron brain accumulation, peripheral neuropathy, muscular/cardiac, ichtyosis, retinal dystrophies, bone dysplasias, segmental overgrowth, liver, renal and immune presentations.	Next generation sequencing. Lipidomics

AA amino acids, *CDG* congenital disorders of glycosylation, *GAG* glycosaminoglycans, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, stroke, *MERRF* myoclonus epilepsy, ragged-red fibers, *OA* organic acids, *PC* pyruvate carboxylase deficiency, *PDH* pyruvate dehydrogenase deficiency, *VLCFA* very-long-chain fatty acids, *X-ALD* X-linked adrenoleukodystrophy

Table 25.9 Genes identified associated with the main neurometabolic conditions

Condition name	Locus	Gene	OMIM
Batten disease/ Neuronal ceroid lipofuscinosis (NCL)	1p34.2	*PPT1*	256730
	11p15.4	*TPP1*	204500
	20q13.33	*DNAJC5*	162350
	13q22.3	*CLN5*	256731
	15q23	*CLN6*	601780
	4q28.2	*MFSD8*	610951
	8p23.3	*CLN8*	600143
	11p15.5	*CTSD*	610127
	17q21.31	*GRN*	614706
	1p36.13	*ATP13A2*	606693
	11q13.2	*CTSF*	615362
	7q11.21	*KCTD7*	611726
Niemann-Pick disease	11p15.4	*SMPD1*	257200 / 607616,
	18q11.2	*NPC1*	257220
	14q24.3	*NPC2*	607625
Pelizaeus-Merzbacher disease	Xq22.2	*PLP1*	312080
Canavan disease	17p13.2	*ASPA*	271900
Fabry disease	Xq22.1	*GLA*	301500
Gaucher disease	1q22	*GBA*	608013, 230800, 230900, 231000, 231005
Hunter syndrome (MPS II)	Xq28	*IDS*	309900
Hurler syndrome (MPS I)	4p16.3	*IDUA*	607014, 607015, 607016
Krabbe disease	14q31.3	*GALC*	245200
Lesch-Nyhan syndrome	Xq26.2-q26.3	*HPRT1*	300323
Menkes and related syndromes	Xq21.1	*ATP7A*	309400
Ornithine transcarbamylase (OTC) deficiency	Xp11.4	*OTC*	311250
Phenylketonuria (PKU)	12q23.2	*PAH*	261600
Sandhoff disease	5q13.3	*HEXB*	268800
Sanfilippo Syndrome (MPS III)	17q25.3	*SGSH*	252900
	17q21.2	*NAGLU*	252920
	8p11.2-p11.1	*HGSNAT*	252930
	12q14.3	*GNS*	252940
Tay-Sachs disease	15q23	*HEXA*	272800
Wilson disease	13q14.3	*ATP7B*	277900
X-linked adrenoleukodistrophy	Xq28	*ABCD1*	300100

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Chapter 26
Immunological Rare Diseases

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Abstract The immune system is delegated to defend the body from attacks from outside or inside. Many diseases can affect immune system reducing its ability to defend self or inducing an abnormal response against external or internal antigens. Rare diseases affecting immune system present some issue in common with other rare diseases and some peculiarities due to the huge variability in the disease's expression. However, a correct estimation of the epidemiology of rare disorders is necessary for evaluating the prognosis and the responses to new therapies, for planning proper public health services, and finally to establish fair and sustainable prices for innovative medicines. Due to the enormous number of different rare immunological diseases, in this chapter we are going to analyse some of them that can be considered paradigmatic of the various expressions of disease.

Keywords Primary immunodeficiency • Common variable immunodeficiency • Systemic vasculitis • Hereditary angioedema • Autoinflammatory diseases • Mediterranean fever • Antiphospolipids syndrome

26.1 What Are Diseases of Immune System

The immune system is delegated to defend the body from attacks that originate outside (infections) or inside (tumours). When responding to attacks from non-self, the immune system uses both non-specific (innate immunity) and highly specific systems (acquired immunity). Innate immunity is activated rapidly, while the acquired immunity takes longer [16].

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Several diseases can affect the immune system. Disorders associated with a reduced response against nonself-antigens are called immunodeficiencies. The most common immunodeficiencies are secondary to (1) infections, such as HIV, (2) chemotherapy or (3) systemic diseases such as diabetes. On the other hand, the primary immunodeficiencies (PIDs) are in most cases rare diseases associated with specific genetic mutations [65]. An excessive response against exogenous antigens is the cause of allergic disorders and hypersensitivity reactions; these are very common disorders, and so we are not addressing them in this chapter [24]. However, some rare conditions associated with deficiency of molecules involved in innate immunity, such as hereditary angioedema due to C1 esterase inhibitor deficiency, have a clinical presentation that may mimic some allergic manifestations [71]. Finally, there is a broad spectrum of diseases characterised by an abnormal response against self-antigens. McDonagle and McDermott proposed in 2006 a classification of this disorders establishing a continuum from diseases affecting mainly the innate immunity (autoinflammatory diseases) to diseases that mostly involve acquired immunity (autoimmune diseases) [50, 60]. Because of the role of innate immunity, most of the autoinflammatory diseases has a systemic involvement. On the other hand, autoimmune diseases may affect a single organ or tissue or the entire body (systemic autoimmune diseases).

Often there is an association between different diseases of the immune system. For example, immunodeficiencies are often associated with autoimmune diseases, such as autoimmune hemolytic anaemia and thrombocytopenia, bowel inflammatory diseases, or systemic sarcoidosis-like manifestations [5, 6, 10]; Job's syndrome is a primitive immunodeficiency presenting with an increased serum level of IgE, susceptibility to bacterial and fungal infections, and manifestations of atopic dermatitis indistinguishable from a hyperreactivity reaction [53]; Churg-Strauss syndrome is an autoimmune, ANCA-associated disseminated necrotizing vasculitis with extravascular granulomas occurring almost exclusively among patients with asthma and tissue eosinophilia [29]; finally many patients with autoimmune diseases have secondary cellular or humoral immunodeficiencies due to the illness or to immunosuppressive therapy [32, 40, 78].

Our data, collected by the Piedmont and Aosta Valley interregional register for rare diseases [3], on a population of over 4,500,000 people in a 10-year span, show that patients with systemic immune system diseases, including immunodeficiencies, vasculitis, and connective tissue diseases account for 15% of reported 17,546 cases. This percentage rises to 18% when considering only the adult age group (2317 of 12,802 cases) (unpublished data). Mazzucato and Colleagues published a similar result (17% above all rare disease cases reported) analysing another population [49]. The importance of immunological disorders in the field of rare diseases is even greater if we take into account autoimmune diseases that affect specific organs or tissues, such as autoimmune bullous dermatosis or autoimmune liver disease [1, 34].

26.2 Rare Diseases Definition

The definition of a rare disease is somewhat vague. A recent survey conducted by ISPOR Rare Disease Special Interest Group identified 296 different definitions related to rare diseases and orphan drugs. The majority of the definition used a prevalence threshold to define rare a diseases. However, the thresholds varied from 1 case/1,000,000 people, adopted in Italy to define ultra-rare disorders to 150 cases/100.000 adopted by a federation of patients in China [74]. Clearly, this variation in the prevalence threshold influence the disorders that can be included among rare diseases.

26.3 Issues in Epidemiological Studies About Rare Immunological Diseases

Epidemiological studies on rare immunological diseases present some issues in common with others rare diseases; these includes the scarcity of patients and the difficulty to reach a diagnosis. However other problems are quite specific; many immunological diseases, especially autoimmune disorders, have a relapsing-remitting nature; furthemore the adoption of different diagnostic and classification criteria throughout the time may partly explain the differences in incidence prevalence, morbidity and mortality observed in various periods. For example, a study conducted in Olmstead County, Minnesota analysed SLE incidence rates in 2 periods; age - and sex-adjusted incidence rate were higher in the latter period (1.5 and 5.6 per 100,000 person-years, respectively, in 1950–1979 and 1980–1992, [87]) probably due to the different and more sensitive diagnostic criteria that were adopted.

Studies based on the use of population registries, potentially allow identifying a greater number of cases [4, 94]. However, often the used diagnostic criteria are not sufficiently controlled. On the other hand, studies carried out by Reference Centers allow a more precise definition of the reported cases but suffer from a selection bias; indeed, often, patients treated at referral centres are affected by more complex and severe diseases and do not represent the full spectrum [59].

Another issue is the potential contribution of undiagnosed disease to the total burden within a population. Johnson and colleagues addressed this issue by a community survey to estimate the prevalence of Systemic Lupus Erythematosus (SLE) among women in Birmingham County (United Kingdom); their study showed that conventional clinical approaches were not able to diagnose 3 out of 4 women affected by SLE [38]. Cunningham-Rundles and colleagues demonstrated a similar underestimation of cases also for PIDs [21].

26.4 Importance of Knowledge About Epidemiology

A proper understanding of the main epidemiological variables of rare immunological diseases is not only an academic exercise. Correct diagnosis and follow-up of all cases, including the milder ones, is essential to evaluate the natural history of the diseases, including mortality and morbidity. This information allows assessing the prognosis of the patient and provide historical data useful to evaluate any innovative therapy [39]. Moreover, a correct estimation of incidence and prevalence of rare diseases is critical for a good planning of the health policies [4]. Finally, information about the prevalence and the natural history of diseases are indispensable for Medical Agencies to negotiate the price of innovative drug [92].

26.5 Examples of Paradigmatic Rare Immunological Diseases

In the following pages, we are going to analyse some specific rare immunological diseases paradigmatic especially because they illustrate the extensive overlapping between various rare diseases of the immune system. This overlap is a challenge both for epidemiological evaluation and for patients care.

26.6 Rare Diseases Mimicking or Complicating Allergies and Hypersensitivity Reactions

26.6.1 Hereditary and Acquired Angioedema

Insufficient levels (type 1) or decreased activity (type 2) of C1 esterase inhibitor, a protease inhibitor controlling classical pathway of complement activation, are the cause of the majority of cases of Hereditary angioedema (HAE) [91]. Due to the impaired function of the complement system, these types of HAE are classified among PIDs [65]. There is also a third form of HAE that is not associate to C1 esterase inhibitor but to the mutation of other proteins, such as the factor XII of coagulation [75]. In a minor proportion of patients deficiency of C1 esterase inhibitor is secondary to haematological disorder of B lymphocytes or plasma cells with the production of autoantibodies directed against the protease inhibitor [89]. In all different forms, the clinical manifestations are due to uncontrolled generation of bradykinin resulting in an increased vascular permeability and severe and potentially fatal attacks of subcutaneous and submucosal edemas of upper airways, facial structures, abdomen, and extremities [17, 95]. The exact prevalence of the different types of bradykinin-induced angioedema is unknown. However, it is estimated that type 1 and type 2 HAE affects between 1 of 10,000 and 1 of 150,000 people without

major sex or ethnic differences [14, 28]. Data from a national registry of Spanish patients with type 1 and 2 HAE report a prevalence of 1.09/100.000 people [76]. Type 1 is estimated to occur in 80–85% of HAE patients and type 2 in the remaining 15–20% [28]. The acquired form of C1 esterase deficiency is even rarer. A national Danish study estimated its prevalence to be about 10% of all the angioedema [13]. HAE provokes a high burden of illness due to the higher rate of hospitalisation among HAE patients and to the high cost of the replacement therapy (estimated up to $96,000 for severe disease) [8, 93].

26.6.2 Eosinophilic Granulomatosis with Polyangiitis (EGPA, Previously Known as Churg-Strauss Syndrome)

Eosinophilic granulomatosis with polyangiitis (EGPA), previously named Churg–Strauss syndrome, is a rare systemic autoimmune small- and medium-sized vessel vasculitis. EGPA is often associated with severe asthma, and blood and tissue eosinophilia; another hallmark of this diseases is the presence of antineutrophil cytoplasm antibodies (ANCA) directed against myeloperoxidase (MPO) in 30–40% of the patients [55].

The epidemiology of eosinophilic granulomatosis with polyangiitis remains unclear because of the uncertainties related to diagnosis [2, 29, 31, 47, 54]. Up to 10% of patients with a major form of vasculitis are recognised to have EGPA. Among the three anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (EGPA, granulomatosis with polyangiitis (Wegener's), and microscopic polyangiitis), EGPA is the least common [43]. Mean age at diagnosis of EGPA is 40 years [20], and it is an uncommon cause of vasculitis in people older than 65 years or in children and adolescents; when it does occur in this age group, it seems to be more aggressive with prominent pulmonary and cardiovascular manifestations. Contrary to what happens in other autoimmune diseases, especially the connective tissue diseases, EGPA does not exhibit a clear gender predominance [96]. A nationwide survey in Japan estimated the prevalence of EGPA at 17.8/1,000,000, with a female predominance (2:1) [77]. The mean age at onset was 55 ± 14 years.

26.7 Rare Primary Immunodeficiencies

26.7.1 Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is a collection of diseases characterised by primary hypogammaglobulinemia. The causes of CVID are extremely heterogeneous and may affect virtually every pathway linked to B cell development and function [5]. The clinical course of this diseases is characterised by the presence

of recurrent infections, chronic lung disease, diffuse granulomatous disease, lymphoproliferation, and autoimmune manifestations [12]. The latter mainly include cytopenias such as immune thrombocytopenic purpura, autoimmune hemolytic anaemia, or both (Evans syndrome), however, also rheumatoid arthritis, SLE, and primary biliary cirrhosis have been reported [90]. The genetic background underlying CVID is relatively unknown indeed, even if many causative and associated genes have been identified, the origins of most cases remain unknown [42]. It is likely that a wider dissemination of next generation sequencing could clarify the genetic origin of many new cases [44].

CVID is the most frequent symptomatic primary immune deficiency condition in adults following only IgA deficiency which however is asymptomatic in most cases [69]. A report from the European Society for Immunodeficiencies registry including 13,708 patients from 41 countries established that CVID is the most common disease representing 21% of all entries [25]. As with many other rare diseases the exact prevalence of CVID is unknown; however, it has been estimated at between 1:100,000 and 1:10,000 of the population [15].

Up to 94% of CVID patients have a history of infections (mainly respiratory and urinary tract infection) [72]. However, the number of infection is decreasing after the adoption of Ig replacement therapy [45]. Chronic lung disease is among the most common complications of CVID, affecting approximately 30–60% of patients [86]; bronchiectasis is the most common chronic lung disease (found in 50% of patients); interstitial lung disease also frequently occurs in CVID and worsens mortality more than bronchiectasis [7]. Autoimmunity occurs in about 25–30% of the patients [11, 26]. A recent study of the Italian Primary Immunodeficiency Network (IPINet) described autoimmunity as one of the presenting manifestations of CVID in 17% of 224 patients; in 2.3% autoimmunity was the only clinical complication at the time of diagnosis of CVID [68]. Due to all these complications, CVID mortality is still higher than that of general population [72].

26.8 Rare Autoimmune and Autoinflammatory Diseases

26.8.1 Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of arterial and/or venous thrombosis, often recurrent, and/or morbidity in pregnancy (recurrent miscarriages, fetal deaths and late pregnancy complications such as preeclampsia and intrauterine growth restriction), in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin (aCL) or anti-β2 glycoprotein-I (anti-β2GPI) antibodies.

In a healthy population, the incidence of aPL ranges from 1 to 5% [63]. It has been observed an increase with age and particularly in coexistence with chronic autoimmune diseases. Among several studies, there is a great dissimilarity in the

incidence of anti-CL antibodies in apparently healthy elderly subjects, ranging from 10 to 60% [73]. The prevalence of anti-β2GPI antibodies is estimated to be as high as 30%. Methodological differences and choice of sample population might explain the differences. In general population, aPL are detected in about one out of five patients who suffered from cerebrovascular events (strokes) under 50 years of age. [79]. The clinical suspicion is clearly enhanced in young patients with additional features of the APS (e.g. livedo reticularis, piastrinopenia). Moreover, aPL can be detected in various conditions including malignancies, infections, vaccination and use of some medications. In these cases, aPL are at low-titre, usually transient, and normally independent of the presence of β2GPI. The prevalence of aPL in healthy obstetric population is difficult to be determined since aPL have been implicated in pregnancy morbidity. However, in two studies involving a large number of healthy pregnant women, aPL were identified in around 3% (0.7–5.3%) [41]. In women with preeclampsia, aPL positivity has been observed in 1 case out of 3 [18]. APS can present in association with other systemic autoimmune conditions, predominantly SLE. About 40% of patients with SLE have aPL, but less than 40% of them will eventually have thrombotic events [9]. Since the first description of APS [33], it has been well documented that thrombotic complications are seen more often in patients with SLE and aPL, as compared to aPL positive patients without an underlying connective tissue diseases [22, 57]. The diagnosis of secondary APS clearly leads to a threefold increase in miscarriages, especially after the 20th week of gestation [19]. aPL have also been detected in other autoimmune diseases, such as rheumatoid arthritis (RA), with a frequency up to 30% [64].

26.8.2 Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is the most frequent monogenic systemic autoinflammatory disease (SAD) [58]. FMF is also the first of these diseases to have been genetically defined [61]. The current classification sets the monogenic SADs, such as FMF, between congenital immunodeficiency [66]. However, FMF and other SAD are characterised by recurrent attacks of fever and polyserositis, often associated with cutaneous rash and abdominal pain [37]. These clinical features of SAD are more reminiscent of autoimmune diseases rather than immunodeficiencies. A severe late complication of some SAD is AA amyloidosis that in some cases can be present even in the absence of fever flairs [51, 56]. Many rare SADs are monogenic diseases due to the mutation of proteins associated with the activity of inflammasome, a cellular machinery that is involved in the development of the inflammatory pathway that ends in the synthesis of IL1[48]. This pathway is activated by several triggers that are related both to innate and acquired immunity [81]. The Classical form of FMF is due to a recessive mutation in MEFV gene that encodes for marenostrin (also called pyrin), a protein involved in the regulation of inflammasome activity [82]; however many patients with symptoms compatible with FMF but only a single MEFV mutation have been described [35, 46]. The therapy of SADs is based

on the use of colchicine (effective mainly in FMF), steroidal and non-steroidal anti-inflammatory drugs, and biological drugs (especially anti IL1 and anti-TNF) [88]; these therapeutic approaches are quite similar to those used in many autoimmune diseases such as rheumatoid arthritis or SLE [80].

FMF prevalence and incidence are higher among population coming from the Mediterranean area, mostly Sephardic Jews, Armenians, Arabs and Turks [83]. Five founder mutations, V726A, M694V, M694I, M680I and E148Q, account for 74% of patients with typical cases from these ethnic groups [85]. M694V is associated with a worst phenotype and a higher risk to develop AA amyloidosis [52, 67]. The presence of atypical cases related to the mutation of a single allele and the different penetrance of heterozygous mutations suggest the presence of modifying genes, or of epigenetic or environmental factors not yet identified [27, 36].

26.9 Conclusion

Rare diseases affecting immune system present some issue in common with other rare diseases and some peculiarities due to the huge variability in the disease's expression and the significant overlapping between different diseases. We could not analyse all the rare diseases of the immune system in this short chapter, nor would have made sense to try to synthesise them in large paragraphs. We have therefore decided to describe few diseases that show the extreme complexity of these diseases and the close links between them. The complex interrelations between the different immunological diseases reflect the extreme complexity of the immune system [23, 62, 84]. Rare diseases, especially, but not only, the monogenic ones, can be considered as a probe that enables us to explore it [11, 30]; this is a hard but exciting task whose goal is not only a better understanding of what happens in our bodies but also a better chance to treat our patients [70].

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Chapter 27
Indigenous Genetics and Rare Diseases: Harmony, Diversity and Equity

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Abstract Advances in our understanding of genetic and rare diseases are changing the face of healthcare. Crucially, the global community must implement these advances equitably to reduce health disparities, including between Indigenous and non-Indigenous peoples. We take an Australian perspective to illustrate some key areas that are fundamental to the equitable translation of new knowledge for the improved diagnosis of genetic and rare diseases for Indigenous people. Specifically, we focus on inequalities in access to clinical genetics services and the lack of genetic and phenomic reference data to inform diagnoses. We provide examples of ways in which these inequities are being addressed through Australian partnerships to support a harmonious and inclusive approach to ensure that benefits from traditional wisdom, community knowledge and shared experiences are interwoven to support and inform implementation of new knowledge from genomics and precision public health. This will serve to deliver benefits to all of our diverse citizens, including Indigenous populations.

Keywords Indigenous • Aboriginal • Genomics • Genetics • Phenotyping • Phenomics • Equity • Innovation • Facial

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Advances in our understanding of genetic and rare diseases, precision medicine [12, 29, 31, 32, 38] and precision public health [18, 39] are changing the face of healthcare. Crucially, the global community must implement these advances equitably to reduce existing and potential health disparities, including between Indigenous and non-Indigenous peoples [5, 25, 35, 36]. In this chapter we take an Australian perspective to illustrate some key areas that will be fundamental to the equitable translation of new knowledge for the improved diagnosis of genetic and rare diseases for Indigenous Australians. Specifically, we focus on existing inequalities in the Australian public health system in relation to Indigenous access to clinical genetics services and the lack of genetic and phenomic reference data to inform diagnoses for Indigenous populations. We provide examples of ways in which these inequities are being addressed in Australia and in doing so we illustrate the imperative to embark on this journey in partnership with Indigenous people and communities.[1] With such an approach, there is the potential to progress in a harmo-

[1] Historic blood samples collected from Indigenous Australians could connect members of the stolen generations to their families and improve healthcare for chronic diseases, but not without confronting a troubled legacy of scientific exploitation and racial classification. About 7000 samples were collected from 43 remote communities in northern Australia in the 1960s and 1970s as part of a range of studies. The samples were used by researchers until ethical concerns about the use of Indigenous DNA prompted a moratorium in the 1990s, and have spent the intervening years preserved in Canberra. They are now collected at the Australian National University's **National Centre for Indigenous Genomics**, which has begun the process of tracking down the donors and their next of kin and getting consent to make sequenced genomes available to researchers. The process has been helped by the possibility the DNA bank could help members of the stolen generation find their lost families "*Because of that it's such a cultural, sensitive, and difficult issue for*

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nious and inclusive way to ensure that benefits from traditional wisdom, community knowledge and shared experiences are interwoven to support and inform implementation of new knowledge from genomics, precision medicine and precision public health. This will serve to deliver benefits to all of our diverse citizens, including Indigenous populations.

Rare diseases (RD) are typically complex, chronic and often multisystem disorders associated with significant rates of morbidity and mortality. Cumulatively they are estimated to affect up to 6–8% of the population [3, 4, 13–15, 33, 34]. In the absence of available data, there is no *a priori* reason to believe that rare diseases are less prevalent in Indigenous populations. In Australia, Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) people, represent 3% of the total population of 24 million [2], suggesting that 43,000–58,000 Indigenous people are living with a rare disease; over a third of which are likely to be children.[2]

Since 80% of rare diseases are genetic in origin, most Indigenous people living with rare diseases would at some time require access to clinical genetic services for

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some of the Indigenous community … so we were driven to create the very best example of Indigenous participation that exists." That includes a world-first "dynamic consent" model which allows the DNA donor to provide or revoke consent for specific projects even after they have consented to their sequenced genome being held on file, Emma Kowal said. Every application to access the data would be decided upon by the Indigenous governance board, which is chaired by the Indigenous human rights commissioner Mick Gooda. Also on the board is Prof Mick Dodson, who was opposed to the genome projects of the 1990s on the grounds that DNA was collective cultural property. https://www.theguardian.com/australia-news/2016/aug/18/indigenous-dna-at-centre-of-ethical-furore-could-help-reconnect-stolen-generations

[2] The Aboriginal and Torres Strait Islander population has a relatively young age structure, in 2011 the median age of the ATSI population was 21.6 years. http://www.abs.gov.au/ausstats/abs@.nsf/Products/C19A0C6E4794A3FACA257CC900143A3D?opendocument

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diagnosis of their condition. However, the nature of clinical genetics practice in Australia suggests that Indigenous people face significant challenges in accessing these services, which creates a disproportionate burden for those with rare diseases [21]. These challenges include referral bias, generally meaning a lack of referral from general practitioners (family physicians) to specialist services, and the fact that many Indigenous people live in remote locations that can be hundreds and thousands of kilometres from where clinical genetics services are based, even with, sometimes geographically broad, outreach services. Around 1 in 5 (21.4%) Indigenous people live in either remote or very remote areas of Australia. This compares with 1.7% of non-Indigenous Australians living in the same areas. Nearly half of Indigenous people (43.8%) live in 'regional Australia' ('regional' being closer to a major city than a remote area) and just over one-third (34.8%) live in a Major City Area, compared to almost three-quarters (71.3%) of the non-Indigenous population [1].

This contributes to Indigenous people being under-represented in patient populations of Australian clinical genetic services, in some jurisdictions by approximately two-thirds in the Northern Territory (personal communication, 2015, Professor Ravi Savarirayan, Consultant Clinical Geneticist, Victorian Clinical Genetic Services and also Director Northern Territory Clinical Genetics Service). This can be especially problematic since some rare diseases in Aboriginal Australians are geographically concentrated in remote areas. An example is the presence of the dominantly inherited Machado-Joseph disease (spinocerebellar ataxia type 3) in Arnhem land, a region of the Northern Territory that is 500 km from the capital city Darwin, where 93 Aboriginal people currently have the disease and 624 Aboriginal people are known to be at risk (personal communication, 2015, Professor Ravi Savarirayan, Consultant Clinical Geneticist, Victorian Clinical Genetic Services and also Director Northern Territory Clinical Genetics Service; and also personal communication Libby Massey, Machado-Joseph Disease Foundation).

A recent study found that nearly one-third (30%) of Australians living with rare diseases wait 5–30 or more years for a diagnosis [26]. In part, this may be a reflection of the relatively uncoordinated approach to rare diseases within the Australian public health system, which is predominantly oriented to address more common chronic conditions. Given that Indigenous people face extra challenges accessing health services in Australia, it could be expected that the diagnostic odyssey is long for an even greater proportion of Indigenous Australians living with rare diseases. This highlights the reality that rare diseases and Indigenous health (including genetic health) have a shared underlying paradigm[3] of inequity, which is greatest at the intersection of the two domains. Lack of access to clinical genetics services will impact on the opportunities for Indigenous people to participate in game changing approaches that are reducing the diagnostic odysseys of individuals living with rare diseases. For example, in Western Australia the implementation of massively parallel sequencing in the statewide clinical genetics service has led to the development of a refined diagnostic

[3] **Human Genetics Society of Australasia (HGSA)**, 39th Annual Scientific Meeting, August 2105, Perth Australia. Rare Diseases and Indigenous Genetics https://www.hgsa.org.au/documents/item/4559 Accessed August 2016.

pipeline which in turn has generated a threefold increase in molecularly confirmed diagnoses [7]. The diagnostic benefits of these new approaches to clinical service delivery are less likely to be experienced by Indigenous people, given that their access to such services is restricted, compared to the general Australian population.

It is important to acknowledge that any activity, whether service delivery or research, associated with the term 'genetics' in Indigenous people has a particular historical resonance, associated with distrust of research in general [37], and of genetic research in particular [22]. Accordingly, even today, there is often a scepticism towards 'genetic' activities, which can only be overcome through a scrupulous regard for ethics, true consultation and joint ownership of both process and outcomes between researchers and Indigenous communities [30]. It is also critical to more completely and rigorously ascertain the levels of use of, and unmet need for, clinical genetic services among Indigenous people across the whole of Australia. Based on current knowledge, it appears there is an urgent need to improve models of care for the equitable delivery of, and access to, such services for Indigenous Australians. In recognition of these issues, two national research organisations recently jointly funded an initiative to support improved clinical genetics service delivery. Firstly, the Lowitja Institute, an Indigenous organisation working for the health and wellbeing of Australia's First Peoples through high impact quality research, knowledge exchange and by supporting a new generation of Indigenous health researchers; and secondly, the National Health and Medical Research Council which is Australia's peak funding body for medical research. The project aims to improve models of care for Indigenous people by using community consultation and participant groups, and patient journey methods, to assess four current models of genetic health care provision in Australia. The aim is to support the ability of clinical genetics services to meet patient and family needs to provide access to, delivery of, and follow up from culturally appropriate genetic health care. It will also build capacity amongst Aboriginal health care workers to collaborate in the provision of genetic health services, such capacity building may help to partly address a number of challenges for rare diseases service provision, including medical staff turnover in remote regions. An enhanced workforce of Aboriginal health care professionals has the potential to increase referrals to genetic services (reducing referral bias) and to ensure greater proliferation and utility of genomics knowledge in a range of settings including remote locations.

In addition to equitable access to clinical genetics services, ascertaining appropriate genomic and phenomic reference data is also critical for enabling the diagnoses of rare and more common diseases for Indigenous Australians. In Australia, as globally, there is a paucity of such reference data for Indigenous populations [6]. This is problematic since the interpretation of results of any genetic or genomic investigation requires an understanding of the range of normal genetic variation and this is partly population specific [17]. Notably, "rare" genetic variants (occurring in less than 5% of the world's population) are disproportionately important [23, 24], most directly as the cause of rare monogenic disease, and also in contributing to the heritability and risk of complex diseases, and for pharmacogenomics.

Rare variations are often population specific, and therefore, reference data from historically geographically isolated and marginalised populations are required to determine pathogenicity [11]. Until recently there has been no publically available Indigenous genomic reference data and that which exists [36] is limited in size and in the proportion of communities that are represented.

The need for Indigenous genomic reference data is well illustrated by a case example of a 10-year diagnostic odyssey in an Aboriginal Australian family. Over an 8 year period, three siblings were seen with a similar phenotype, characterised by various overlapping combinations of macrocephaly, shared facial dysmorphology, small thoraces, connective tissue dysplasia, intellectual disability, seizures, immune dysfunction and intracranial anomalies (megalencephaly and perisylvian polymicrogyria) [6]. The proband was referred for genetic consultation in early childhood and the two siblings were first seen as newborns. Multiple non-informative monogenic tests were performed to ascertain the cause of their condition. Ultimately, based on phenotypic features, massively parallel sequencing targeting interrelated biological pathways was performed. This approach identified a co-segregating variant in the *MTOR* gene. However, the absence of Australian Aboriginal genomic reference data was a challenge to the definitive confirmation of pathogenicity, especially because this was potentially the first reported case of a familial phenotype due to an *MTOR* mutation. Consequently, there was a 2 year delay in diagnosis while functional confirmation was sought and completed. Functional studies showed the expected gain of function and importantly normalisation with the addition of the MTOR inhibitor Rapamycin. These *in vitro* analyses supported the possibility of an unanticipated novel therapeutic intervention through drug repurposing. On the basis of the functional confirmation, a diagnosis of a new disorder was made. This disorder was named the MINDS[4] syndrome (the acronym **M**acrocephaly, **I**ntellectual Disability, **N**euroDevelopmental **D**isorder, **S**mall Thorax), reflecting key phenotypic components and serving as an aide memoire for diagnosis. A new disease code (ORPHA457485) was created for the disorder in the Orphanet database of rare diseases (orpha.net.au) and following publication of the diagnostic findings, other families with an MTOR mutation have been reported [27] and the spectrum of the condition has expanded to include Autism and other more common phenotypes. This case illustrates that Indigenous populations' reference data are necessary to improve our understanding of disease pathogenesis and to support the timely diagnosis of genetic disease among Indigenous populations. These data also have utility for defining a genetic perspective from which to view environmental risk; to facilitate disease risk prediction; and to identify opportunities for drug repurposing, novel therapeutics and pharmacogenomics.

In response to the delayed clinical diagnosis of a rare genetic disease in this Aboriginal family, and similar challenges in interpreting genetic tests in other families that are directly attributable to the lack of a suitable genomic reference, clinical genetics services in Australia have begun to seek ways to improve the availability of

[4] http://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN&diseaseGroup=minds Accessed July 2016.

Indigenous reference data. Fortunately, genome-wide studies, including whole exome sequencing, had been performed in Aboriginal Western Australians on research cohorts unselected for monogenic disease [36]. These studies proceeded with extensive culturally appropriate community engagement and governance [36]. Study participants agreed to the deposition of their genomic data in a public database and application can now be made to the Data Access Committee to obtain allele frequency information to assist clinical diagnostic work in the Australian public health system [36]. This has already been applied to the interpretation of clinical genomic tests in Western Australia [7]. While this is an important first step, critically it must be augmented with additional Indigenous reference data, including for other regions of Australia. Facilitating this, The National Centre for Indigenous Genomics (NCIG), which was established in 2013 by the Australian National University, is establishing protocols for uses of a repository of research biological samples collected in the second half of the twentieth century from approximately 7000 Indigenous people across northern and Western Australia. NCIG is governed by an Indigenous-majority Board and aims to enable appropriate and respectful genetic and genomic research that will benefit Indigenous donors, their communities and descendants, the broader Indigenous community and the general Australian community. In 2014, NCIG commenced a process of consultation with Indigenous communities, families and individuals representing the respective communities. Thereby, NCIG is enabling Indigenous peoples to become involved in genomics in accordance with their desires and cultural and social values. This fusion of the world's oldest culture and new genomic technology is beautifully reflected in an animation video at the NCIGs website.[5]

Ultimately, and complementary to current NCIG initiatives, a prospectively ascertained combination of genomic and phenomic data will be required for maximum clinical utility. Enablers to the collection of phenomic data in a standardised way include precise objective facial assessments, [8–10] and knowledge management platforms that can be aligned to research and clinical processes. For the former, 2-dimensional approaches include the Clinical Phenotype Face Space [16] and the Atlas of Human Malformation Syndromes in Diverse Populations [28]. Furthermore, 3D facial analysis [28] is a data rich approach that provides additional precision, which can be combined with 2D approaches. For the latter, platforms that can text-mine free text and which are adaptable to multiple language formats, such as Patient Archive,[6] are particularly valuable. These platforms standardise the way data is stored and reported, enable cross-cultural interoperability and thereby the sharing of data globally for the purpose of clinical diagnosis. Engaging the Aboriginal community around data sharing will be a key to combined genomic and phenomic initiatives to facilitate the diagnosis of rare diseases, epidemiology and healthcare.

[5] About NCIG: an introduction for donor communities. http://ncig.anu.edu.au/ncig-collection/current-projects/community-engagement/about-ncig-introduction-donor-communities Accessed July 2016.

[6] Patient Archive: Phenotype is fundamentally important to identifying the cause/origin of both rare and complex disorders, and substantially reducing the search-space for genomic variation. http://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/clinical-genomics/about-kccg/teams/phenomics-team#Patient_Archive

To improve access to clinical services and the availability of Indigenous genomic and phenomic reference data demands approaches that are developed in a culturally sensitive manner, requiring continuous open discussion amongst all relevant parties [22]. This highlights the importance of understanding and appropriately using language, which is another way that rare diseases and Indigenous health overlap. The genetic 'language' that is important for rare diseases is written in the four biological letters (A,C,T,G) of our DNA; this language differs in populations around the globe in a way that is poorly understood. We also need to develop the appropriate verbal language to communicate with the Aboriginal and Torres Strait Islander communities about their genetic health care. There is the need for deep community engagement as failure to continuously interact with Aboriginal and Torres Strait Islander Australians in a conversation about genetic health care may contribute to a continuation, or widening, of health disparities [19, 20]. Strategic frameworks relating to Aboriginal Health emphasise it is "everybody's business" to link into a language idiom and community reference used by Aboriginal communities.[7]

In this chapter we have illustrated two areas in which there are opportunities to improve equitable access to the diagnosis and management of rare and genetic diseases for Indigenous people in Australia. Firstly, the ways in which clinical genetics services are organised and delivered require reconsideration to reduce inequities in access experienced by Indigenous people. Secondly, advances in genomic testing and phenomic analyses are increasingly moving towards expanded daily clinical genetic application, providing an increasing requirement to collect and understand data on Indigenous specific variation. To maximise benefit and minimise harm in both of these spheres requires an inclusive approach that is culturally appropriate for the Indigenous community. Reassuringly, there are a number of initiatives that are beginning to address these needs and given that we are still in the early stages of the clinical implementation of genomic knowledge, precision medicine and precision public health, there is an opportunity for Indigenous people to participate, receive benefit and minimise harm at a similar rate to non-Indigenous people. Proceeding in this manner will promote a harmonious and inclusive approach that resonates with the Aboriginal narrative and that acknowledges and benefits from diversity.

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[7] WA Aboriginal Health and Wellbeing Framework 2015–2030 to articulate the commitment and a set of guiding principles, that also articulates the multi-dimensional aspects of health and wellbeing from an Aboriginal perspective and which recognises that Aboriginal people bring a diverse range of skills, including the ability to break down the cultural barriers between our cultures that can prevent best health care for their communities. http://ww2.health.wa.gov.au/Improving-WA-Health/About-Aboriginal-Health/WA-Aboriginal-Health-and-Wellbeing-Framework-2015-2030 Accessed August 2016.

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Chapter 28
Mortality Statistics and their Contribution to Improving the Knowledge of Rare Diseases Epidemiology: The Example of Hereditary Ataxia in Europe

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Abstract Official mortality statistics provide population-based data and serve to improve epidemiological knowledge of rare diseases (RDs), by helping with the description of the natural history of the disease. They are an important complement of registries and estimates of disease burden and costs. At the same time, they heighten both the visibility of these diseases and the interest in their study and the search for treatments that may increase survival. This chapter contains a European analysis of hereditary ataxia mortality, which considers the time trend in different countries and the geographical variability in risk of death. Despite the limitations of applying this data source to RDs, mortality statistics share criteria which facilitate international comparisons and are of great utility for obtaining sufficiently uniform and robust time series for analysis of low-prevalence diseases.

Keywords Mortality rates • Rare diseases • Ataxia • Registry • Epidemiology • Public health indicators

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28.1 Introduction

Mortality is not only an important health indicator, but its reduction is also the goal of any public health intervention policy. Mortality rates are monitored at a local and national level, using standardized specific indicators which measure the health status of each country. Furthermore, mortality data display certain basic characteristics that facilitate comparative studies: (1) they are uniform and follow coding criteria established at a global level, since all diseases are registered in accordance with the International Classification of Diseases (ICD) [55]; (2) these ICD criteria undergo revisions (ICD9, ICD10, etc.) but maintain continuity over time, thanks to the official nexus between versions; (3) their universality enables comparison in different geographical settings; (4) they facilitate the study of diseases through analysis of the underlying cause of death; (5) they are official, accessible population data; and, (6) they enable global population-based data to be compared against analyses of lethality and survival drawn from patient records and case-series studies.

Furthermore, exhaustive analyses of causes of death serve to point out differences in disease distribution and health-care practice, while at the same time enabling possible risk factors of disease or death to be identified [18]. They also facilitate the generation of hypotheses about the etiology of diseases and the development of health-planning policies [3, 49, 50]. In this respect, follow-up of the leading causes of death is a routine and almost standard practice in all countries, including data aggregated at a supranational level, such as those centralized by the World Health Organization (WHO) or EUROSTAT in the case of the EU [7, 10, 56]. However, such surveillance mainly targets common diseases, with the result that the least frequent causes or worst identified diseases in the ICD tend to be overlooked [3, 18]. Although rare diseases (RDs) are an important cause of death [4, 35], the fact that they are not identified as such in government-administered mortality registries means that there is a clear lack of visibility of RDs as a cause of death in national mortality statistics [20, 27].

28.2 Rare Diseases and Registries

The low prevalence of RDs makes for certain difficulties in their epidemiological investigation [16, 27, 35, 47]. The low number of cases, high degree of diagnostic complexity [4, 14], and difficulty of ensuring that RDs are adequately coded and traceable in the ICD [3, 37] are some of the limitations in the process of registering and identifying them in health information systems. Nevertheless, these drawbacks are no bar to having standardized population-based data that are stable and uniform in time and space.

Currently, many countries have succeeded in placing RDs in a prominent position on the health agenda [17, 31] and fostering interest in improving information about them, something that has boosted the emergence of patient records and

databases, albeit with variable coverage [5, 21, 48]. Among other things, the strategies pursued by countries seek to ensure that these records furnish quality information and prove useful for obtaining health indicators in RDs [8, 12, 28, 45, 46]. Using other official population-based data systems to complete the information available in the records will serve to increase the visibility of RDs [40, 49]. In this respect, analysis of national mortality statistics can provide relevant information and thereby become a useful tool and complementary data source, both generally and for the study of low-prevalence diseases. The main limitation of official mortality statistics is the use of coding systems which are adapted to common, higher prevalence diseases rather than RDs [6, 15, 45, 58]. Despite the fact that RDs are poorly represented in the ICD, it is possible to trace some which have specific codes or certain groups in which all the component diseases are rare [3, 37]. Furthermore, the pooling of mortality data from various countries may serve to improve knowledge about certain RDs, inasmuch as this considers series with the highest number of cases [14, 20].

28.3 European Mortality Statistics/Databases

Information on mortality reported by countries to the WHO makes it possible to have epidemiological data based on information systems with uniform criteria, something that facilitates comparability and contributes to better knowledge of the distribution and patterns of some causes of death. Countries report the underlying cause of death by reference to the ICD, be it the 9th or 10th revision. While it is true that the new revisions may not reflect all the changes, countries have been adopting the ICD-10 to remedy the shortcomings of the ICD-9. Without prejudice to other European mortality data sources [7], the data furnished by the WHO-EU [13] are shown below by country, indicating the year in which causes of death began to be reported by reference to the ICD-10 (Table 28.1).

28.4 Rare Diseases Mortality

Since these are infrequent diseases, the study of mortality rates should take into account certain considerations that would ensure the robustness of the results. It is standard practice to make adjustments for age, in order to enhance comparability and prevent time-trend studies from being affected by differences in the demographic structure of the population. When the number of cases is stratified according to this variable, it is likely that few deaths will be found in some age groups, something that improves if the calculation is based on large-sized populations, taking standard error into account. In addition, it is of interest to have a lengthy time series and the minimum number of deaths necessary to monitoring the trend and changes in mortality.

Table 28.1 Respective years in which European countries began to use the ICD-10 to declare cause of death

Country	Start ICD-10
Austria	2002
Belgium	1998
Bulgaria	2005
Croatia	1997
Cyprus	1999
Czech Republic	1997
Denmark	1997
Estonia	1997
Finland	1996
France	2000
Germany	1998
Iceland	1996
Ireland	2007
Italy	2003
Latvia	1996
Lithuania	1998
Luxembourg	1998
Malta	1996
Netherlands	1996
Norway	1996
Poland	1999
Portugal	2002
Republic of Moldova	1996
Romania	1999
Serbia	1998
Slovakia	1996
Slovenia	1997
Spain	1999
Sweden	1997
Switzerland	1996
United Kingdom	2001

Source: WHO-EU

The following section shows the results of analyzing the data furnished by the WHO-EU [13, 56] and applied to a well-identified group of RDs in the ICD-10, namely, hereditary ataxias (HAs). HA-related deaths were selected by reference to the following codes: G11.1, early-onset cerebellar ataxia; G11.2, late-onset cerebellar ataxia; and G11.9, hereditary ataxia, unspecified.

After evaluating all available information, we chose 2000–2012 as the designated study period, as being a time span for which we had complete, consecutive data. The countries included in the example were Germany, Belgium, Croatia,

Denmark, Spain, France, Finland, the Netherlands, Hungary, Lithuania, Luxembourg, Norway, Poland, the Czech Republic, Romania, Sweden and Switzerland. Despite having slightly different time series, the United Kingdom (2001–2013) and Austria (2002–2014) were also included for cartographic representation purposes.

28.5 Time Trends

In the temporal analysis of mortality, we calculated age-adjusted mortality rates that took into account the age structure of the countries analyzed, with the European Standard Population being used for adjustment purposes [1, 34]. Time trends were analyzed using joinpoint regression [22], and the average annual percent change (AAPC) and significant change points in trend were identified using the segmented Poisson regression model. The maximum number of change points was established by reference to the number of years studied, bearing in mind the need to have a minimum of four consecutive years for each change point.

28.6 Geographical Distribution

The Standardized Mortality Ratio (SMR) is a widely used indicator, even in RDs, which enables comparison between deaths observed in a given region and expected deaths according to a reference population. In the example shown in this chapter, the SMR indicates the excess risk or reduced risk of dying due to a specific cause (HA) in a given country vis-à-vis what would be expected for the European population as a whole. The 95% confidence intervals (CIs) of the SMRs were calculated by means of Byar's method [36]. Cartographic representation of SMRs allows for better visualization of results.

28.7 Overview of European Mortality Due to Hereditary Ataxias

HAs are a group of genetic diseases whose clinical course is marked by neurodegenerative disorders which, in general, entail progressive deterioration in gait and permanent disability [2]. Clinical presentation, genetic study and classification are very heterogeneous. There are few population-based studies that report national HA mortality [2, 25, 29] and none to date that do so for Europe as a whole.

Analysis of HA-related mortality in Europe across the period 2000–2012 indicated 2582 deaths, 52% men and 48% women, with age-adjusted mortality rates

of 0.55 (95% CI 0.44–0.68) vs. 0.44 (95% CI 0.34–0.54) per 1,000,000 population, respectively. The average age-adjusted European HA mortality rate for both sexes is 0.50 per 1,000,000 population (95% CI 0.42–0.57). Figure 28.1 shows HA mortality by country in descending order, in relation to the European average. It will be seen that Romania, Hungary, Poland and the Czech Republic registered the lowest mortality rates in Europe.

With respect to different types of HA, 1210 deaths corresponded to the early-onset HA group, 294 to the late-onset HA group, and 1078 to unspecified HA. The age groups in which there were the greatest number of deaths varied according to type of HA, with this being compatible with clinical progress, e.g., early-onset HA accounted for 30% of mortality at ages 45–59 years, late-onset HA accounted for 41% at ages 60–74 years, and unspecified HA accounted for 43% of deaths at ages 65–79 years. Late mortality in the so-called unspecified group would lead one to assume that in this group, the most frequent disease types were mainly late-onset and/or slowly progressive HA.

Insofar as the time trend is concerned, overall HA mortality in Europe has increased by 1.50% p.a. (95% CI 0.60–2.50) in both sexes, going from 0.44 in 2000 to 0.57 per 1,000,000 population in 2012 (Fig. 28.2). In terms of type of HA, this increase was only significant in unspecified HA (5.07% p.a. in both sexes, 3.04% in men and 3.83% in women), whereas early-onset and late-onset HA remained stable. The increase in mortality across the study period may be attributable to a number of reasons, such as: (i) the decision by different European health systems to incorporate genetics into diagnosis, which has therefore improved over the years [41, 43]; (ii) the different strategies adopted by each country to improve records kept on this type of RD, thus allowing for the inclusion of age groups which were not diagnosed in the past but are being diagnosed now [38]; and, (iii) the increase in the diagnosis of some types of HA, particularly those with late onset [19, 51], as well as sporadic cases with no apparent family or medical history of the disease [41, 42] which have become evident with life years gained. Hence, the rising time trend must be assumed to be a reflection, not only of a possible increase in incidence, but also of an increase in prevalence [54], due to longer survival, likely ascribable to improved health care among these patients [9].

In the analysis by country, this global increase in HA mortality was significant solely in Germany, i.e., 1.99% p.a. (95% CI 0.05–3.97) from 2000 to 2012. In the rest of Europe, these figures remained stable. Analysis by type of HA, however, showed an increase in the unspecified-HA mortality rate in Finland (16.20%), France (6.44%), Spain (5.03%) and Germany (3.61%). This growing mortality trend is probably the consequence of improvements in the diagnosis of late-onset HA genotypes [30], due to the investment in health made by these countries [33]. Improvements of the health care could be also contributing to this late mortality because countries situated in the north, west and south of Europe are those with most life years gained in the over-79-year age group [32].

Figure 28.3 shows geographical variability by type of HA. In global HA, Finland, the Netherlands, Switzerland and the United Kingdom had a 1.5–1.9-fold higher risk of death than expected for Europe as a whole. Denmark, Sweden and Spain also

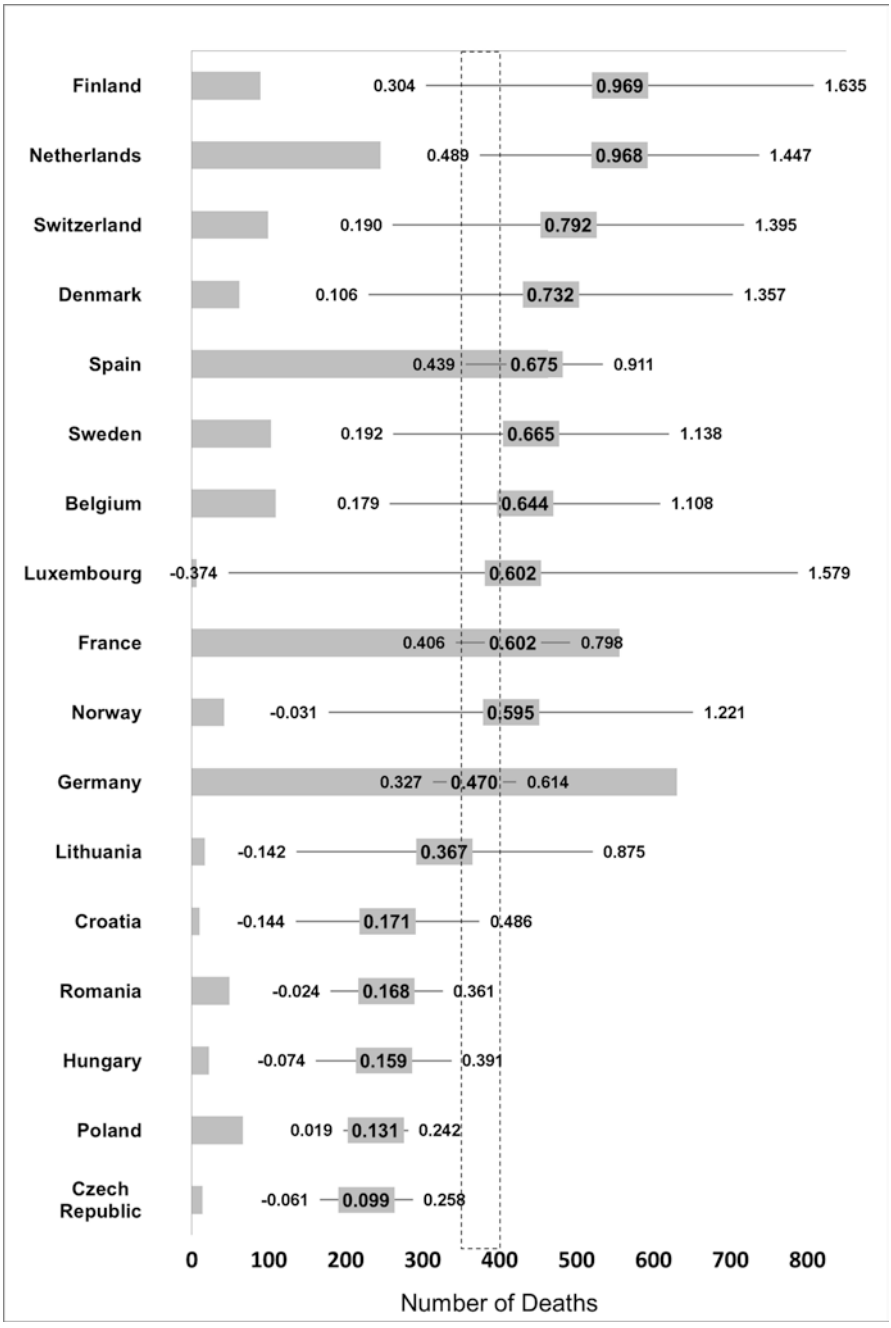

Fig. 28.1 Number of HA-related deaths and age-adjusted mortality rate (95% CI) per 1,000,000 population, according to country (2000–2012). *Dotted* rectangle shows the global European age-adjusted mortality rate

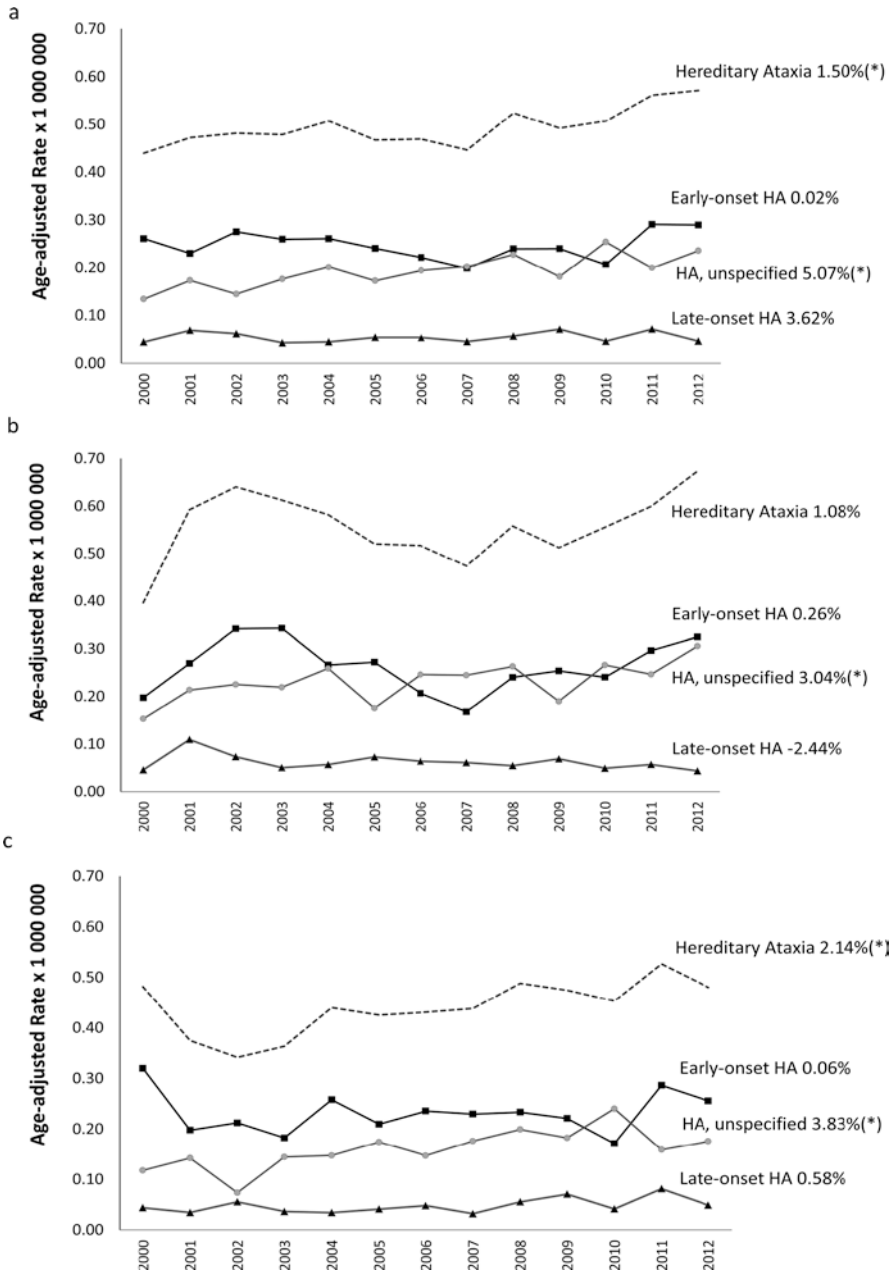

Fig. 28.2 Time trend in the hereditary ataxia age-adjusted mortality rate, and average annual percent change (AAPC) in Europe: (**a**) both sexes; (**b**) males; (**c**) females. (*) Statistically significant AAPC ($p < 0.05$)

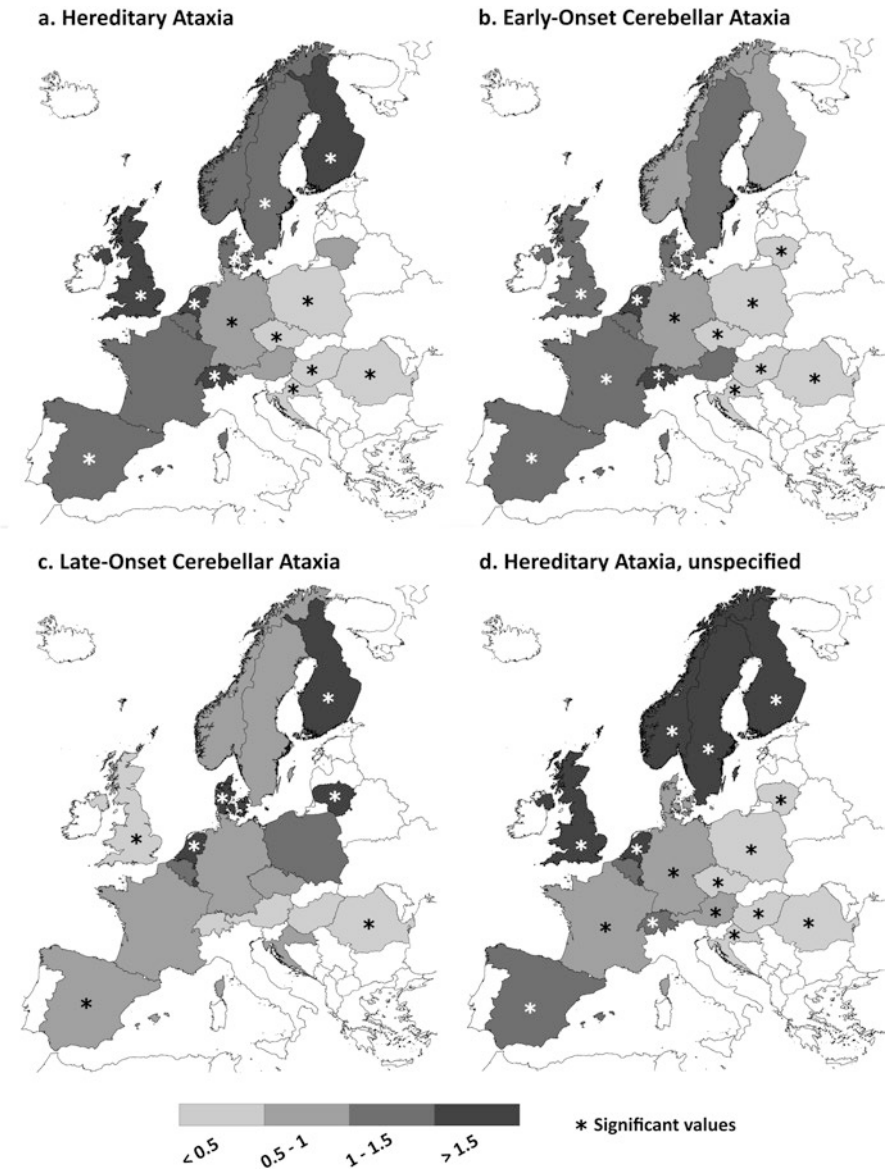

Fig. 28.3 Standardized Mortality Ratio (SMR) in Europe, 2000–2012: (**a**) hereditary ataxias; (**b**) early-onset cerebellar ataxia; (**c**) late-onset cerebellar ataxia; (**d**) hereditary ataxia, unspecified. Note: United Kingdom (2001–2013) and Austria (2002–2014)

registered higher-than-expected risks, though these were less marked (SMRs close to 1.3). The risk of mortality was significantly lower than the European rate in the countries of Eastern Europe (SMRs 0.2–0.3) and Germany (SMR 0.8). Despite the fact that it is not easy to define a geographical pattern, it seems plausible to conclude

that the overall risk of HA-related death tended to increase towards the north and west of Europe, with the exception of Switzerland which also registered a high SMR. A breakdown by type of HA showed that in early-onset HA: significant risks were very high in Switzerland and the Netherlands (SMRs 1.8 and 1.5, respectively); the United Kingdom, France and Spain showed intermediate values (SMRs 1.1–1.3); and risks were lower than expected in Germany and the east (SMRs 0.2–0.8) (Fig. 28.3b). Distribution of late-onset HA was characterized by: very high risks in the north of Europe, i.e., SMRs of 9.8 in Finland, 6.4 in Lithuania, 5.9 in Denmark, and 3.2 in the Netherlands; and risks lower than expected for Europe, in Spain, Romania and the United Kingdom (SMRs 0.5, 0.3 and 0.1, respectively) (Fig. 28.3c). In brief, data aggregated by type of HA showed a different geographical distribution for each group: while early-onset HA followed a rising east-west gradient, late-onset HA failed to display a defined pattern.

Lastly, in unspecified HA (Fig. 28.3d) mortality increased northwards and displayed high risks in Scandinavian countries, the United Kingdom, and the Netherlands (SMRs 1.5–1.9). The risk was intermediate in Spain (1.3) and Switzerland (1.4), and was lower than expected for Europe, in Germany, France and Austria (SMRs 0.6–0.8), and countries to the east (SMRs 0.0–0.2).

It should be said that the risks found might depend, not only on European genetic variability [30], but also on differences when it comes to reporting cases of mortality due to these causes. Similarly, there are other population traits that may determine differences between countries, such as the effect of a founder mutation [11, 23, 44, 53, 57], migratory phenomena [52, 54], cultural patterns [39], and geographic characteristics [24, 26], among others. The influence of these and other factors will have to be analyzed in subsequent studies.

28.8 Limitations and Conclusions

Analysis of mortality at a supranational level has proved useful for obtaining an approximation of the status of the RDs studied. It has made it possible to ascertain both the time-trend changes and the distribution by country of the different types of HA in Europe. The mortality-pattern findings are useful for making inferences about possible related risks, such as environmental factors or genetic variability, and for identifying possible improvements in medical records.

Notwithstanding the fact that having multiple causes of death would enable a higher number of deaths to be identified, analysis of the underlying cause offers an image of mortality directly associated with the disease of interest. Furthermore, the existence of countries which still report mortality as per earlier revisions of the ICD, such as the ICD-9, may hinder comparability of diseases that are inadequately cross-referenced between revisions, with it thus being preferable to exclude them from the analysis. Yet, despite these limitations, mortality statistics share minimum criteria that facilitate comparison among countries and are of great utility when it comes to obtaining sufficiently uniform and robust series for analysis of low-prevalence diseases.

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Chapter 29
Congenital Anomalies: Cluster Detection and Investigation

Eva Bermejo-Sánchez and Manuel Posada de la Paz

Birth defect clusters are incidents that let us turn a challenge into an opportunity for primary prevention

Bermejo and Posada, 2017

Abstract This work summarizes the main aspects to be considered around birth defects (or congenital anomalies) clusters. Most birth defects (BD), considered individually, fall into the definition of rare diseases (RD), according to their low frequency. Likewise, many RD are congenital, because their manifestations are present at birth or can be even evident before the delivery. It has been estimated that overall 7.9 million children are born each year with serious BD of genetic or partially genetic origin, and additional hundreds of thousands more are born with serious BD of post-conception origin.

A "birth defect cluster" can be defined as an unusual aggregation of cases (grouped in place and time) that is suspected to be greater than expected, even though the expected number may not be known. These clusters are incidents or occurrences that let us turn the challenge of identifying the causal agent(s) involved

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in the origin of such clusters, into an opportunity to exert primary prevention, and thus achieve the ultimate goal of enabling infants being born healthy. Therefore, any program or system involved in BD surveillance and research should devote part of its activities to detect and investigate clusters, to ensure that such opportunity for primary prevention will be conveniently leveraged. Regardless the type of cluster, there are several phases that must be undertaken sequentially for proper control and the maximum benefit for the population: cluster detection, evaluation and investigation, management, adoption of preventive measures, and communication of the results to the public or target population.

Keywords Congenital anomalies • Birth defects • Clusters • Cluster detection • Cluster investigation • Prevention

Abbreviations

BD	Birth defects
CDC	Centers for Disease Control
EUROCAT	European surveillance of Congenital Anomalies
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
NBDPN	National Birth Defects Prevention Network
RD	Rare diseases
WHO	World Health Organization

29.1 Introduction

Congenital anomalies are also named as *birth defects*, since there is no general rule to denominate the physical, biochemical or functional defects *that are present at birth*. Both terms, *congenital anomalies* and *birth defects*, are generally used as interchangeable, despite slight nuances. We will opt here for the term *birth defects* because it is commonly better understood.

Most *birth defects (BD)*, considered individually, fall into the definition of *rare diseases (RD)*, according to their low frequency. Likewise, many RD are congenital, because their manifestations are present at birth or can be even evident before the delivery, so they are detected prenatally. Certainly, their presence since birth or earlier implies that they and their consequences have to be faced from that early point, with an overall increased morbidity and a considerable risk for premature death among affected people, as well as for lifelong disabilities and dependence in many

surviving cases. Christianson et al. [13] estimated that overall 7.9 million children are born each year with serious BD of genetic or partially genetic origin, and additional hundreds of thousands more are born with serious BD of post-conception origin. In general, and depending on the population considered, it is estimated that approximately 3–6% of newborn infants worldwide are affected by serious birth defects [11, 18, 55]. Moreover, at least 3.3 million children under 5 years of age die from BD each year and an estimated 3.2 million of those who survive may be disabled for life. These eloquent figures, together with the burden of disease that BD usually cause, and especially the above mentioned fact that they are present since birth, enhance the interest of their study within the field of RD, and make them priority targets for research [5].

Thalidomide's tragedy, in the early 1960s, went down in history and, from that point onwards, it was fully clear that BD surveillance and related pharmacovigilance were essential to try avoiding a similar disaster. The investigation of a cluster of phocomelia was what led to the identification of thalidomide as the causal agent in such cluster [32, 33], although this unfortunately happened after the birth of numerous affected infants. The lesson learnt led to the start-up of programs aimed at the early detection of any unexpected increase in the frequency of BD, in order to investigate its origin and establish the appropriate measures to avoid harmful exposures and prevent the birth of many affected cases. The hypothesis under which such programs work is that any unusual and significant increase of the frequency of BD could be due to the introduction of a new teratogen (any agent that causes an abnormality in the development of the embryo or fetus) in a population, or to the variation of the distribution of a pre-existing teratogen. Therefore, the sooner the increase is detected, the earlier the study will be initiated to identify the causes, what will lead to establish adequate interventions aimed at the **primary prevention of BD** [5]. A detailed review on the recommendations for this kind of BD prevention in national RD plans in Europe can be found in Taruscio et al. [45].

A *birth defect cluster* can be defined as an unusual aggregation (real or perceived) of cases that occurs within a group of people, in a geographic area, over a period of time without regard to whether the number of cases is greater than expected. Even, the expected number may not be known. Most often, they are reported by individuals expressing concern about apparently similar disease manifestations. The widespread sentiment is that environmental (including occupational) causes are responsible and must be investigated.

This concept is slightly different from an *epidemic,* which refers to an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area. *Outbreak* is another related event that carries the same definition of epidemic, but is often used for a more limited group of individuals within a specific period of time. This leads to the consideration that a cluster has *temporal* and *spatial* dimensions. This two-dimensional nature of clusters implies that when studying temporal clusters, the spatial characteristics must be also analysed, and vice versa, it is necessary to evaluate time when scrutinizing spatial clusters. The spatial dimension should be considered broadly, and not as just geographical regarding the residence or the birthplace, to also include under this consideration,

for instance, the place of education, workplace, leisure or any other location where cases could aggregate.

Experience has demonstrated that birth defect clusters are incidents or occurrences that let us turn the challenge of identifying the causal agent(s) involved in the origin of such clusters, into an opportunity to exert primary prevention, and thus achieve the ultimate goal of enabling infants being born healthy. Therefore, any program or system involved in BD surveillance and research should devote part of its activities to detect and investigate clusters, to ensure that such opportunity for primary prevention will be conveniently leveraged. Nevertheless, although this value of clusters is generally recognized and stated in especially relevant publications, by Rothman [40] or Coory and Jordan [14], among many others, it is also true that cluster detection rarely has led to revealing novel epidemiologic insight into unanticipated risk factors [50], and it is rather common that clusters are not finally clearly explained [25]. The rarity of the exposure/risk factor and/or the uncommonness of the effect involved in the cluster can make their causal linking easier, but this clearly is not the general rule.

We will review here the most relevant aspects around BD clusters' detection and investigation, and the actions that should follow those initial steps, although it is clear that almost no general rule can be applied because each BD cluster has its own particularity, so some flexibility must be added to the process.

29.2 Types of Clusters

These are the main types of clusters generally considered, theoretically, according to their more remarkable nature:

- *Temporal clusters*: A higher than expected number of cases is detected for a period of time. Once possible underlying methodological issues have been excluded, any temporal aggregation of cases should be scrutinized in order to confirm a chance occurrence or a specific environmental circumstance that is limited in time. The detection of such clusters is quite common in any BD surveillance system, in the context of the routine analyses of the temporal variations of the frequency, and always requires a careful evaluation of potential causes to try establishing an etiologic linkage to an exposure.
- *Geographical (or spatial) clusters:* Are those for which the apparently higher than expected number of cases is restricted to a delimited area. As commented before, the "spatial" concept can be rather broad, and not limited to the place of birth or residence. Also, geographical clusters can be circumscribed to some specific location, like for instance those identified by Fazzo et al. [24] in the provinces of Naples and Caserta in the neighbourhood of toxic waste dump sites [17]; or alternatively affect a group of locations, like the clusters of limb reduction defects in seashore communities in the UK, that was initially reported by the media [41], and generated considerable anxiety in several countries.

- There is a subtype of *geographical clusters*: the *clusters associated with geographic or cultural isolation, founder effect, and/or parental consanguinity.* This would be the case, for instance, of the aggregates described in South America for oculocutaneous albinism [2, 8, 9, 27], and many other. Nevertheless, although these aggregates have been considered as *clusters* [13], this could be subject to some discussion, since they are rather different from classical clusters, that have a shorter duration, while these can persist for several or many generations, and even result in genetic drift. In fact, these usually have a genetic basis, and gene frequencies of rare single gene defects are greater than expected for the above mentioned reasons [53].
- *Clusters within families:* Like the previous subtype, family clustering is usually associated with consanguinity, and it is particularly frequent in very endogamic communities with a cultural preference for consanguineous marriage [13].

Nevertheless, in fact, the distinction between temporal and geographical clusters is more theoretical than practical, because geographical clusters occur during a period of time, and temporal clusters affect a definite area, that can also change with time. A good and recent example is the initially reported increase in the number of infants with microcephaly in Brazil, first noted in September 2015, after the recognition of Zika virus transmission in the country earlier in the year [28]. In response to the situation, on the 11th of November 2015, the Brazil Ministry of Health [6] declared a national public health emergency. Just few months after (on the 1st of February 2016), WHO declared that the association of Zika infection with clusters of microcephaly and other neurological disorders constituted a Public Health Emergency of International Concern [54].

Regardless the type of cluster, there are several phases that must be undertaken sequentially for proper control:

- Cluster detection
- Evaluation and investigation
- Management and adoption of preventive measures
- Communication

We will now expound on these aspects in more detail.

29.3 BD Cluster Detection

The methods to detect clusters of disease-related events are generally called *event cluster detection methods.* Such methods seek to detect unusual aggregations in space and time, that are above and beyond those explained by local/temporal aggregations of known risk factors [50].

BD clusters, like those for other diseases, can be detected by various agents, at different levels (individual researchers, BD programs, public health authorities, etc.), and by diverse methods. These can have a more systematic and scientific

component, being linked to activities of BD surveillance, public health or research, or alternatively they can have no link with the health systems or with sciences. In this last case, it is not unusual that the community has some concerns (regarding, for instance, specific sites with suspected contaminants, or other) that surface from time to time, specially catalysed by the birth of a case or group of cases with BD. Also, it is not unusual that the press or social media attract attention on apparent clusters of BD. Given the relatively low frequency of the different types of BD, the birth of just an affected child always generates a special attention. Therefore, the coincidence in time or space of two or more affected cases, especially if they apparently share some clinical characteristic(s), shoots up all the alarms and usually gives rise to numerous types of speculations (and even to some well elaborated hypotheses) by lay people, as possible explanations. This sometimes leads to real but unfunded panic around the aforementioned "cause", and regardless the source of the information about the purported cluster, this must be conveniently scrutinised, applying the scientific method, both regarding the available data on the aggregation of cases (to confirm this), as well as in what refers to the search of possible causes. After that process, fortunately, only in very few cases a further public health action is required, but in any case a response or report should be delivered for the society or the media. Sometimes the public is involved in the surveillance process and in generating hypotheses. However, this bears a risk of multiple unjustified alarms, and their required investigation (followed up with dedicated, detailed epidemiologic studies) consumes much of the limited resources generally available for these purposes, what can prevent the allocation of those resources to the systematic surveillance. In fact, it is preferable and more efficient to establish well controlled and more focused systems for BD cluster detection.

For systematic BD cluster detection, it is important to routinely monitor the evolution of the frequency of BD over time, globally in big geographical areas, as well as in detail for each specific sub-area into which a territory can be divided according to different criteria (administrative, orographical, socioeconomical, etc.). It is necessary a good knowledge of the distribution of BD in each location, in order to detect significant deviations from such distribution. It is also important to have an accurate characterization of the population, in what refers to possible confounders, i.e., factors or variables that are associated to BD as well as to other known risk factors. For these purposes, it is essential to have high quality and focused information sources (in which the study population, disease outcomes, exposures and demographic variables are well depicted), like BD and RD registries, with good programs for effective BD surveillance.

Despite the quality of such programs, some false positives are unavoidable, and it has to be assumed that some efforts will be put on apparent clusters that have been detected but do not correspond to real increases of the frequency of BD. Nevertheless, in this context, false positives are preferable to false negatives to ensure safety for the population.

Regarding possible false negatives, it is clear that if the causal agent is rather common, its identification and linking to the increase of the BD frequency will be more difficult than for rare or infrequent factors. Also, if the causal agent (teratogen)

is not very potent, its effect is hardly noticeable. And regarding the observed effect, clusters involving rare BD will be more likely identified and this identification will happen earlier than for more common BD.

It is noticeable that the changes in the frequency can be quite abrupt or more gradual, so the systems must be prepared to detect and interpret either behaviour. Therefore, in order to determine the duration of the cluster, past evolution of the frequency has to be also considered, according to those two possibilities, for more correct interpretation.

Among the most usual problems that the available systems have to face for BD cluster detection, we can highlight that they do not have much power, and are rather slow. Under such conditions, they have to discriminate local collections of cases in time and/or space that are due to chance, from those aggregation patterns unlikely to have arisen casually. Hence, although our aim is not to review in detail the different detection methods for clusters of BD, methods for detecting local spatial clusters typically consist of two interrelated components [36]:

- *Cluster identification:* A geographical search method used to identify local *unusual* concentrations of disease cases to be tested for clustering. For spatial and spatiotemporal cluster detection, multiple methods have been developed. Among the spatial search processes, the most commonly used for BD cluster detection is the *Spatial Scan Statistics* [29], with the assumption that the number of cases in each area follows a Poisson distribution. This procedure, with a scan or "moving window" [37, 49], is used for instance by EUROCAT [19]. It employs a window (circle or ellipse) that varies its radius in space to calculate the maximum excess of cases, and selects those showing statistically significant deviations from the expected values. There are also methods to detect irregularly shaped clusters [44]. The Bayesian models and methods are being applied also to the detection of clusters [34], and for statistical modelling of disease risk [1, 31, 48], having clear applicability in the disease/health context [36].
- *Cluster testing:* A statistical model for determining if the local concentration of disease is unusual (significantly higher than expected). Both frequentist and Bayesian methods have been developed for this. Lawson [31] and Waller and Gotway [51] provided broad overviews of statistical methods and probability models (of "no clustering"), and Tango [43] provided a comprehensive catalogue of statistical hypothesis testing-based approaches. This cluster testing component of the methods for detecting spatial clustering is linked to the following section of this work.

29.4 BD Cluster Evaluation and Investigation

Cluster investigation normally follows four successive phases [15]:

- the generation of one or more etiologic hypotheses,
- the confirmation of the hypotheses,

- an intervention aimed at reducing any dangerous exposure, and
- the evaluation of the effect of the intervention.

Regardless the methodology used to investigate clusters there can be two different *contexts* in which BD cluster investigation can be initiated [21]:

- The starting point is a pre-existing causal hypothesis, and a cluster of BD must be searched for in order to confirm or to rule out that some exposure is linked to BD in an area and/or in a period of time. Here, the *presumed cause* is also what originates further studies.
- Alternatively, a cluster has already been identified or suspected, and a causal hypothesis must be found. Therefore, here the *observed effect* is what catalyses the investigation.

Also, depending on who (and how) established the existence (or suspicion) of a BD cluster or a possibly acting teratogen, the investigation can be carried out with two different approaches:

- *Reactive:* There is some public's concern about a possible cluster of BD (linked or not to some definite exposure or presumed causal agent), or about the risk that some exposure might bear for the prenatal development. In both cases, there is a previous hypothesis, and the investigation will be *reactive* because it starts in response to the media or citizens' concern. Under these circumstances, there can be some pressure on the researchers or public health authorities to find a causal relationship between an agent (possible cause) and BD (presumed effect), what can increase the risk of different biases. An example of a reactive approach is the investigation of the teratogenicity of retinoic acid after the birth of five cases with BD associated to this exposure in utero [39]. The epidemiological studies were performed as a response to the public's concern, just few months after the marketing of the drug in the USA in 1982, and the evidence on its teratogenicity from such studies led to decisions set up by the health authorities [30].
- *Proactive:* A surveillance program has identified a cluster in the routine monitoring of the frequency of BD that usually performs. This *proactive* monitoring approach allows a systematic and well-ordered investigation, with no external pressure, and thus less likely biased. This can also allow the identification of the cluster in its first stages, so in fact is the ideal situation. However, it is not always possible, since it implies that a minimum of the program's resources must be allocated for this purpose. To this respect, it is noticeable that the magnitude of the problem is bigger than what is apparent, since the published clusters represent only a little part of those suspected in the frame of routine surveillance of a population [25]. It seems clear that this type of service to the society falls into what is expected from health systems by the public, addressing their concerns in advance, as a way to ensure a safer and better quality of life.

In general, as we mentioned before, once a cluster has been suspected or detected, it is necessary to perform an initial *evaluation* (before starting the investigation) with at least three aims:

- To evaluate the veracity, precision and quality of the initial data.
- To verify that the cluster is real and not due to any methodological issue, like coding errors, duplicates of cases (in surveillance programs that ascertain cases from multiple sources), or changes in the procedures for ascertainment, diagnosis, hospital referral patterns, or registration procedures, that can lead to apparent clusters.
- To assess the statistical significance of the aggregation of cases. This is sometimes difficult, especially in small areas, in changing populations subject to migratory flows, or when studying very rare BD for which just a small increase in the number of cases (even just one case under some circumstances) can raise the alarm.

For this preliminary investigation of clusters, EUROCAT [22] has its own guidelines, as part of EUROCAT statistical monitoring Protocol [19]. This includes some items for case verification, assessment of diagnostic heterogeneity among the cases involved in the cluster, spatial context and characteristics of the cluster, time dimension, diagnostic and reporting factors, aetiological factors, and local context (regarding concerns and awareness of the public). We want to recognize here the impressive, thoughtful work that EUROCAT has developed about BD clusters and their investigation [23].

In any program, after excluding any methodological problem, with the previous verifications done, the investigation must start quickly to identify the cause(s) of the unusual aggregation of cases, in order to adopt proper preventive measures whenever (and as soon as) possible.

Taking into account all the previous points, the most basic scheme for BD *cluster investigation* can be summarized as follows, based on what was established by the US Department of Health and Human Services [47]:

1. Make a *case definition:* this can be very restrictive or rather broad. Any broad definition will less likely be linked to a unique risk factor or causal agent, due to the heterogeneity of the group of cases. Moreover, when studying BD, it is important to take into account not only the most severe manifestations, but also the mildest ones, and minor expressions of them. Also, the dysmorphic features denoting an adverse outcome must be scrutinized in detail. This type of assessment requires a specific training, long experience and careful evaluation.
2. *Confirm the suspected cases*, and *validate* that the reported ones actually meet the case definition.
3. *Define a "population denominator"* (total births/outcomes in a defined area) and search for additional numerator cases within that population, once the denominator has been established.
4. Based on that denominator, *draw conclusions about the "unusualness"* of the aggregation of cases.
5. *Review the literature* for specific known risk factors and exposure hypotheses, as well as for similar previous BD clusters (or increasing trend in BD frequencies) in the same or different location and, if possible, the result of the investigation of those clusters.

6. Perform an *exposure assessment* (type of exposures, their sources, quantification, biological effects, etc.), and look for commonalities among the cases regarding such exposures. For this purpose, it is necessary to fill in standardized, structured questionnaires including information on medical history, family history, reproductive history, work, hobbies and other activities, lifestyle, local or personal conditions, among others, depending on the analyzed BD. Generally, most BD cluster investigations have to be performed on large populations, in which the different individuals are affected by diverse baseline risk factors, different lifestyles, occupational exposures, and other conditionings, what makes extremely difficult the identification of a common factor that can be linked to the origin of the cluster of cases. A different key issue refers to *dating the exposures*. This obviously can be done according to the date of delivery, but this must be considered as an approximation. In fact, if the date of conception can be estimated, this is a more accurate proxy to establish the timing of the exposures and to correlate them with the embryological or fetal stages of prenatal development.
7. *Generate biologically plausible hypotheses* to explain the cluster. These can result from the analyses of the questionnaires to assess exposures, by comparing the data obtained for cases and for an adequate sample of individuals from the denominator population. The criteria established by Shepard [42] as "proof" of human teratogenicity can guide the assessment of potential teratogens.

A good example in which this scheme was followed for its investigation, was the cluster detected for cyclopia and sirenomelia in Cali (Colombia) [10]. Despite the efforts and rigorous approach of the researchers, supported by part of the team of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) [26], no clear insight regarding potential causal factors apart from a polluting landfield site in the vicinity, could be obtained from the investigation. This situation is quite frequent when studying BD clusters in the frame of surveillance programs.

Table 29.1 depicts a summary of actions in existing protocols, especially applicable to birth defects cluster investigation (based in part on [23]).

For the scrutiny of clusters, it is quite convenient that the statistical monitoring output is assessed by a multidisciplinary committee, with the participation of epidemiologists, clinical geneticists, clinicians and statisticians. Also, for BD cluster investigation, sometimes it is advantageous to see what happens in other places, thus being scrutinized in the context of a bigger scenario. A way to have a wider scope, and even to increase the opportunities to clarify a cluster, is to exchange information and sharing experiences on possible similar clusters in other BD surveillance systems or organizations. In this sense, the participation and collaboration of BD surveillance and research systems in national or international networks provide remarkable opportunities to move forward in BD clusters investigation. Among such existing networks, there are some with long experience, like ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research [26]), EUROCAT (European Surveillance of Congenital Anomalies [22]), and NBDPN (National Birth Defects Prevention Network [38]) in the USA. Moreover, BD clusters investigation

Table 29.1 Summary of actions in existing protocols, especially applicable to birth defects cluster investigation (based in part on [23])

CDC (Centers for Disease Control) [12]	Texas Birth Defects Epidemiology and Surveillance Branch [46]	California Birth Defects Monitoring Programme [7]	Washington State Department of Health [52]	Williams et al. [55]	NBDPN [38]	EUROCAT [19]
Initial contact and response:	*Initial contact and response*:	*Initial report evaluation*:	*Initial stage*:	*Step I*:	*Who should a cluster be reported to?*	*Initial verification*:
Gather identifying information on caller, gather initial data on potential cluster, obtain identifying information on persons affected, discuss initial impressions with the caller, request further information and plan further telephone follow-up, assure that s/he will receive a written response, maintain a log of initial contacts, notify health agency's public health office (or equivalent)	Collect initial data on the cluster (type of defect, number of cases, geographical area, time period, usual number of cases), information on each case (name, birth defect, date of delivery, mothers age at delivery, mothers race, mothers address at delivery), any ideas on what caused the cluster, discuss initial impressions, clarify what caller wants, what they want register to do. Get identifying details from caller, ask how they learned of the cluster, give them your name and phone number.	Details of person reporting, birth defects of concern and how it came to reporters notice, congenital anomalies details: population group, setting, time period, any idea about common cause: characteristics mothers have in common (age rate worksite neighbourhood etc.), with whom concerns have been discussed, whom to contact for more information, index case information for each case (name, address now/at birth, date and hospital of birth, other hospitals of treatment, diagnosis, parental history medical occupational, other family history, other exposure.	Collect initial information and provide education and information to the informant: complete 'new cluster' page (Department of Health intranet): type of illness, number of cases, ages of people affected, time period, location, is there a suspected exposure, have others been contacted about the cluster, organisational affiliation of the caller. Contact local health jurisdiction and others (industry etc), check database for previous cluster of same illness (might be included with this one).	Develop a proactive plan for future birth defects cluster reports. *Step II*: Receive report of a birth defects cluster.	Suspected clusters should be reported to the public health officer in your county health department or the state department of health.	Verify the cases included (correct coding and no hidden duplicates)

(continued)

Table 29.1 (continued)

CDC (Centers for Disease Control) [12]	Texas Birth Defects Epidemiology and Surveillance Branch [46]	California Birth Defects Monitoring Programme [7]	Washington State Department of Health [52]	Williams et al. [54]	NBDPN [38]	EUROCAT [19]
Preliminary evaluation:	*Preliminary evaluation*:	*Index case and exposure verification*:	*Preliminary assessment*:	*Step III*:	*Information that should be included in a cluster report*:	*Methodological scrutiny*:
Geographical area and time period, which cases are included in the analysis, appropriate reference population, calculate rates and asses significance (chi^2, Poisson regression) or clustering statistics	Determine the case definition (geographic area, time period, birth defect diagnosis). Determine the number of live births in the area and time period specified. Find an appropriate reference rate (use published data if possible). Calculate expected cases, do O/E and assess statistical significance.	Visit hospital of birth and review records (using standard procedures), medical records reviewed by specialists to note relevant information on exposures. Environmental health and infectious disease specialists help verify alleged exposures. Review index case and exposure information exclude case if: residence outside geographic boundaries, initial diagnosis ruled out, malformation is part of underlying condition (eg. Down Syndrome), condition cannot be systematically diagnosed (heart murmur), physical findings do not meet specific diagnostic criteria established by geneticist or specialist.	Assess the magnitude of the reported cluster: team from Department of Health assigned to the investigation based on skills, availability etc., local health jurisdiction invited to participate (or take the lead if occupational exposure). Develop case definition, literature review on epidemiology of disease, background rates, common risk factors, confirm cases using readily available data if possible (otherwise assume all real cases), review literature on exposure of concern, calculate preliminary O/E (define geographic and time periods, determine reference population available using pre-existing data).	Verify diagnoses and complete case ascertainment.	In order to evaluate the report, investigators need to know: For each child, the names of the mother and baby, date and hospital of birth, and all the child's diagnoses. Ideas about environmental exposures during early pregnancy. To determine if the cases may have the same cause, investigators need to know what exposures all the mothers have in common.	If the cases are verified, investigate potential changes in diagnostic or ascertainment methods

Case evaluation:	*Case finding and verification*:	*Complete case ascertainment*:	*Next stage*:	*Step IV*:	*Confidentiality of the information provided regarding the cluster*:	*Scrutiny of exposures and risk factors*:
Verify the diagnosis: contact responsible physicians/health event registry, obtain copies of relevant records (e.g. pathology), and obtain case evaluation.	Identify sources to help ascertain other cases (vital records, congenital anomalies registries etc.), for each case ascertain name, diagnosis, date of delivery, gestational age, mothers age/place of residence at delivery, mothers race. Verify defects by referral to congenital anomalies registry or by contacting physician caring for the child, tabulate all verified cases, if necessary form a team to work on cluster. If a specific exposure has been mentioned; review literature for epidemiological and biological plausibility, assess the likelihood that an event-exposure relationship may be established (help from Toxicology and Environmental Epidemiology divisions), determine availability of exposure data in the area of interest. Evaluate the need for environmental monitoring data and gather and analyse data if necessary. Assess community perceptions/reactions/ needs. Re-evaluate the cluster: confirm case definition, re-do O/E (crude and adjusted if necessary eg. for maternal age).	Revise case definition/broaden diagnostic criteria (eg. if Down Syndrome may then include all trisomies). Examine same sources plus birth, death and foetal death records for additional information. Review by epidemiologists, paediatricians and/or geneticist to confirm compliance with case definition. Calculate observed rate in the population and compare with expected rate for a similar population (if available user prior year rates). Plot cases on a map to look at geographical clustering, look at seasonal or other temporal patterns. Is the apparent increase meaningful? Are there known epidemiological patterns which may provide clues for analysis? Are certain agents suspected of contributing to the defects? What is the vulnerable period in embryological development of this defect?	Verify initial assessment: may expand team membership to include Department of Health and local health jurisdiction personnel. Cluster team develops a plan for verification of illness and exposure, refine the geographic area and time period of interest, obtain information on all reported cases to verify diagnosis, time of onset and exposure profile, if necessary refine the case definition. Active case finding: review additional medical records/databases, determine whether there is an excess using standard analytical methods (observed/ expected, comparison of rates ATSDR –Agency for Toxic Substances and Disease Registry– Cluster 3.1 or MMWR describes tests), assess exposure (review of data- not environmental sampling at this stage), review literature on other risk factors.	Compare the observed rate to a reference rate.	State law requires that all identifying information be kept confidential. Only investigating staff have access to this information Public reports are limited to summary data.	Look at the records, looking for exposures and demographic characteristics that might help seek a time-related common cause

(continued)

Table 29.1 (continued)

CDC (Centers for Disease Control) [12]	Texas Birth Defects Epidemiology and Surveillance Branch [46]	California Birth Defects Monitoring Programme [7]	Washington State Department of Health [52]	Williams et al. [54]	NBDPN [38]	EUROCAT [19]
Occurrence evaluation:	*Exposure evaluation and occurrence re-evaluation*	*Next stage*:	*Feasibility study*:	*Step V*:	*Actions that will follow the cluster report*:	*Put the cluster in context*:
Define appropriate geographic (community) boundaries, ascertain all potential cases within space time boundary, identify appropriate database for numerator and denominator data, in depth review of literature, assess likelihood that an event-exposure relationship may be established, assess community perceptions, reactions and needs, complete investigation		Investigation is assigned to a team of epidemiologists who design a study based on current scientific knowledge about the birth defect in question and the alleged exposure.	First check if investigation team needs to be expanded. Then as for CDC guidelines	Ascertain exposures among cases from available records.	Investigators will determine: If all the babies have the same birth defect Whether there are too many babies with the same birth defect—many conditions are more common than people realize If there is a common exposure that may explain the increase. Parents may be asked to provide more information and to give permission for investigators to review their medical records. A written report will be made of the investigation's findings.	Have a wider scope, and consider it as a trend rather than as a cluster (have into account other clusters in the studied period)

Feasibility study:	*Major feasibility study*:			*Step VI*:		*Cluster description*:
Examines the potential for relating the cluster to some exposure: review detailed literature search, consider appropriate study design (including costs and outcomes of alternatives), determine what data should be collected, delineate the logistics of data collection and processing, determine the plan of analysis, assess the current social and political ambience, assess the resource implications and requirements of both the study and the alternatives	Consider the appropriate study design with attendant costs and expected outcomes including: geographical area and time period of concern, case finding, appropriateness of using previously identified cases, confirmation of diagnoses, selection of controls. Determine appropriate plan of analysis. Determine methods for environmental exposure measures if needed, delineate the logistics of data collection and processing, consult with experts and advisory committee, assess resource implications, write report summarizing feasibility study.			Interview case mothers.		If after the preliminary investigation the aggregation of cases remains unusual, then describe the cluster (in relation to spatial aggregation within registry area) to facilitate identifying hypotheses
Aetiological investigation	*Aetiological investigation*:		*Aetiologic investigation*:	*Step VII*:		*Further steps*:
	Protocol develop using feasibility study as a guide.		Standard epidemiological study	Initiate further epidemiologic study–selection of controls.		Recommended further monitoring or moving to a more extensive public health investigation
Risk communication		*Risk communication*		*Step VIII*:		
				Communicate results to the community.		

in the frame of BD surveillance systems can be combined with other activities in the program (like pharmacovigilance [35] or envirovigilance [16], among others, and this will increase their efficacy.

It is important to take into account that *BD are just one type of adverse outcome, but there can be also some other*: infertility, early miscarriages (that occurring in the pre-recognition phase of pregnancy could be "masked" by apparent long menstrual periods), spontaneous abortions, fetal deaths, and even some postnatal effects (like some types of cancer, behavioural problems, or other). All these can be related to the same processes that induce abnormal prenatal development giving rise to BD. Even some early miscarriages and spontaneous abortions can be the direct consequence of some fatal congenital anomalies that affect the embryo or fetus. Therefore, these outcomes should be also considered when evaluating and investigating at least some BD clusters.

29.5 BD Cluster Management

In general, BD cluster management must be guided by a responsibly responsive attitude, with quick and evidence-based responses, being conscious that the precocious identification of the causal agent or factor underlying the cluster, will enable earlier preventive interventions, and this can facilitate the birth of less or no more affected cases. All this can be mostly achieved with the adoption of a protocol for BD cluster management in its different phases, as detailed in Table 29.1.

Needless to say that a responsibly responsive attitude requires that any cluster report must be followed by a response. This means that some agent or agency must be designated in advance to manage BD cluster investigation, to ensure that this essential task will be undertaken. This measure is rather related to policy issues.

It is important that the time spent between the alarm and a final conclusion can be acceptable for the population, and this will depend not only on the existence of an agent specifically designated for BD cluster investigation, but also on the consequences of the BD cluster, and the explanations and the information that can be delivered, mainly by the health authorities. The determination of the duration of the cluster is part of the BD cluster management and investigation. This is an important piece, because even if no clear cause can be elucidated at a specific moment, at least in some cases the health authorities can inform to the public about the cease of the alarm, and this will contribute greatly to the wellbeing of the population.

In general, an early publication of a cluster, at the very preliminary phase of a geographical or temporal feature, has the advantage of alerting other clinicians, public health officers or research workers concerned by the topic, and this can help elucidating the causes of the alleged cluster. However, this can have also an impact on the population's concern, and it should be ideally assessed in advance. Transparency and a balanced provision of information for the population will contribute to the health authorities' trustworthiness, and this reliability will positively affect to the public and interested groups.

It should be considered that the conclusions of a BD cluster investigation may be very different from the ones presumed when the cluster was suspected or detected, and therefore, some reactions can be anticipated. Even if the conclusions are similar to what was initially supposed, this may imply to establish some preventive measures, and all this can have considerable consequences for the community and for individuals. Therefore, before a report is delivered, the program that underwent the investigation may feel a need to consult with a "neutral" body to have a second opinion on the interpretation of a cluster [21]. For this purpose, the EUROCAT Cluster Advisory Working Group developed in 2003 their Cluster Advisory Service.

Regarding the BD cluster management, after completing all the phases of the detection, assessment and investigation, even when a causal agent can be identified and the whole process seems to be concluded, the next step must be continuing the monitoring and performing the follow-up of the cluster.

29.6 Communication Issues Regarding BD Clusters

It is important to recognize the relevant role of concerned communities and the media in cluster management [20]. It has been said that in this context, experts are judged on three characteristics: expertise, credibility and empathy. Transparency must be always a key principle. Nevertheless, when delivering the conclusions of BD cluster investigation, it is important to carefully evaluate, on one hand, the need of the society to be informed, and on the other hand the consequences of providing some pieces of information, in order to avoid unnecessary concerns. As a way to better approach this, it can be useful to get some involvement of the public in BD cluster investigation, although this may depend on the specific circumstances under which a cluster emerged. Williams et al. [55] stated that the purpose of cluster investigations is not only to potentially identify new teratogens but also to respond to the needs of the affected community. It is true that in some cases the conclusion of the investigation of a supposed cluster can be that the cluster is just perceived and not real, but public's concern is a fact, and this requires proportional attention, both to understand the community's alarm, and to respond adequately to alleviate any anxiety or uncertainty. Such discomforts can just be ameliorated by openly explaining the expectations: (a) on the possible outcomes of the investigation (including the possibility of being unable to elucidate what caused the cluster); and (b) on the time needed to scrutiny the cluster (taking into account that for some infrequent exposures or some rare BD, the completion of the study can require even more time than estimated).

When reporting on any cluster and the results of its investigation, there are several questions that should be answered, and these can be summarized as the Six Ws (or Five Ws and one H), as shown in Table 29.2.

The last two questions in Table 29.2 are in fact policy issues, approached in the next section of this work.

Table 29.2 Six questions that should be answered when reporting on a BD cluster

What kind of cluster was detected?
Who is involved?
Where did it take place?
When did it take place?
Why did that happen?
How did it happen?
A seventh question could be added, with two possibilities:
What can be done?
What can be done to prevent new cases?
What can be done to provide the best care and services to the existing cases?

Also, when communicating on a BD cluster, the information provided should follow what could be named the 6 Cs' rule. This means that the information must be: *C*orrect, *C*omplete, *C*lear, *C*oncise, *C*entered and *C*oherent.

29.7 Policy Issues Regarding BD Clusters

The investigation of reported BD clusters is always a major challenge for public health officials, in part because there is no universally accepted standardized protocol to approach such investigation. Therefore, one of the first policy issues must be the establishment of a protocol, by health departments and BD registries, for responding to reports or notifications of supposed BD clusters [55]. This need for specific protocols, taking into account the clinical and epidemiologic concerns related to BD research, has long been known. Based on Williams et al. [55], any protocol for these purposes should basically include the following steps:

- Step I: develop a proactive plan for future birth defects cluster reports
- Step II: receive report of a birth defects cluster
- Step III: verify diagnoses and complete case ascertainment
- Step IV: compare the observed rate to a reference rate
- Step V: ascertain exposures among cases from available records
- Step VI: interview case mothers
- Step VII: initiate further epidemiologic study-selection of controls
- Step VIII: communicate the results to the community. This should not be just the last phase of the investigation. In fact, any result from each of the previous steps can generate useful information that should be conveniently transmitted to the community.

These formulations are rather simple. However, as it has been explained along this document, their put into practice can be quite complex, but it is true that the systematics of a protocol can make things easier.

The interest of BD clusters for *policy makers* is slightly different from the interest that they have for *researchers*, although they are closely related. While for researchers BD clusters represent an opportunity to find clues on the aetiology of BD through the identification of local characteristics that increase the risk for them, for policy makers, clusters provide a prospect to selectively target public health interventions to hotspot areas, thus increasing their effectiveness. A good collaboration between policy makers and researchers will help to achieve the maximum benefit for the population.

Giving an appropriate public health response to clusters is not an easy task (and this can be even more difficult if despite big efforts devoted to their clarification, no indisputable cause can be finally identified, so the best public health response cannot be delineated). Bender [3] called this "the art of always being wrong". Potential policy responses can include:

- More detailed data collection.
- Better characterization of the exposures.
- In-depth investigation of case histories within the cluster.
- More comprehensive study and longer follow up of cases. Also in this sense, it is important that the health departments and BD registries that may receive reports of BD clusters establish specific criteria for continuing or terminating an investigation before receiving cluster reports [55].
- Starting up of a new, more detailed (or on related issues) epidemiological study.
- Information to the population (regarding the identified risk factors and possible control measures).
- Education of the population (on BD in general, on known causes of BD, and known preventive measures).

As we mentioned before, in general, policy issues should be marked by what has been named "the art of being responsibly responsive" [4] to concerns from the public regarding potential local sources of disease risk, in this case for BD. We have already explained some aspects of such responsibly responsive attitude. It does not always require starting an epidemiologic study. Apart from providing proper attention and care to affected individuals, other types of actions can be very effective and needed, like for instance undertaking an educational initiative, by explaining: of course the specific preventive measures for the current BD cluster, but also the known general preventive measures for BD, as well as the importance of pregnancy planning and preconceptional care, the different causes and risk factors for BD (that can affect differently to some individuals), the identification of genetic risks in some specific cases, etc. Other actions (even not knowing the exact causes of the BD cluster) can include a better assessment and control of known risk factors for BD in the population, trying to clarify their possible contribution to the cluster.

All phases of the study and follow up of BD clusters, as well as any measurement or policy issue (aimed to ensure that the specific needs of the affected community are met) must be guided by the most general *ethical rules*. Also, all actors around BD clusters must act *in accordance with the law and regulations* to this respect, with especial attention to *personal data protection*, and the *protection of*

minor individuals' rights (what is very relevant in the field of BD, because a considerable proportion of affected cases are infants of children).

29.8 Conclusions

BD clusters frequently generate more concern and questions than certainties and answers. Concern around this large group of rare diseases constituted by BD is really big among the population, probably because, even not having any knowledge on embryology and developmental biology, individuals perceive (with a kind of instinct, and based on transmitted experience), that the prenatal development can condition a whole life, and BD can produce lifetime disability or even premature death, apart from considerable morbidity.

BD rates normally fluctuate within the populations over time. This means that the establishment and maintenance of good BD or RD registries, and BD surveillance systems, with good information sources (high quality and focused) are needed resources to assess those fluctuations and identify the ones that can be considered as clusters that deserve investigation. For these purposes, it is essential that the study population, disease outcomes, exposures and demographic variables are well depicted. To this respect, the exchange of information, data sharing and sharing experiences, contribute to a good characterization of clusters and to their investigation. The participation and collaboration of BD surveillance systems in national or international networks seem optimal ways to face BD clusters investigation.

For better preparedness, it is necessary to adopt a protocol in advance, considering aspects related to cluster detection, evaluation, investigation, management, the communication around these health events, and policy issues.

There are just few examples of clusters for which their investigation led to the identification of a teratogen. This is the case for congenital cataract and rubella, phocomelia and thalidomide, vaginal adenocarcinome and diethylstilboestrol, and more recently microcephaly and Zika virus. In any case, the analysis of clusters is an essential line of activity for BD surveillance programs. It is noticeable that there are always some claimed clusters for which no statistical evidence is finally found, but even so these deserve some attention from the appropriate bodies, first to be assessed and then to be comprehensibly explained either to the general public, to some target groups or the media.

Finally, just to underline that the analysis of BD clusters must be faced recognizing that such challenge is in fact an opportunity to achieve a better knowledge of causes of BD.

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Part IX
Rare Diseases Policies and Society

Chapter 30
The European Union Policy in the Field of Rare Diseases

Antoni Montserrat Moliner and Jaroslaw Waligora

Abstract Rare diseases, are defined by the European Union as life-threatening or chronically debilitating diseases with low prevalence (less than 5 per 10,000). The specificities of rare diseases – limited number of patients and scarcity of relevant knowledge and expertise – single them out as a unique domain of very high European added-value.

The legal instruments at the disposal of the European Union, in terms of the Article 168 of the Treaties, are very limited. However a combination of instruments using the research and the pharmaceutical legal basis and an intensive and creative use of funding from the Health Programmes has permitted to create a solid basis that Member States have considered enough to put rare diseases in a privileged position in the health agenda.

The adoption of the Commission Communication, in November 2008, and of the Council Recommendation, in June 2009, and in 2011 the adoption of the Directive on Cross-border healthcare., have created an operational framework to act in the field of rare disease with European coordination in several areas (classification and codification, European Reference Networks, orphan medicinal products, the Commission expert group on rare diseases, etc.).

Rare diseases is an area with high and practical potential for the European cooperation.

Keywords European policies • European Union • Commission communication • Rare diseases definition • Council recommendation • European reference networks • Directive on Cross-border healthcare

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30.1 Introduction

Rare diseases are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10,000) that special combined efforts are needed to address them so as to prevent significant morbidity, perinatal or early mortality, a considerable reduction in an individual's quality of life. This definition appeared first in EU legislation in **Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products**.[1] It was extended to the public health field by the **Community action programme on rare diseases including genetic diseases,** 1 January 1999 to 31 December 2003,[2] by the **Commission Communication COMM (2008) 679 final on Rare Diseases: Europe's challenges**[3] of 11 November 2008 and by the **Council Recommendation (2009/C 151/02), on an action in the field of rare diseases** of 8 June 2009.

It is estimated that between 6000 and 8000 distinct rare diseases exist today (currently Orphanet database is covering more than 6800 rare diseases or group of diseases) and could affect in a certain moment of life between 6 and 8% of the European population. In other words, between 27 and 36 million people in the European Union could be affected by a rare disease. The specificities of rare diseases – limited number of patients and scarcity of relevant knowledge and expertise – single them out as a **unique domain of very high European added-value**. There is probably no other area in health where collaboration between 28 different European approaches can be as efficient and effective. Coordination at European Union (EU) level is probably the best way of pooling the very limited resources available.

30.2 The Main Objectives of the EU Policy in the Field of Rare Diseases

The European Union's objective in the field of rare diseases is to bring together the necessary elements for an efficient overall strategy, hence the adoption of **Commission Communication COMM (2008) 679 final** on 11 November 2008, setting out what the European Commission will do in this field, and the **Council**

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=32000R0141&model=guichett)

[2] Decision No 1295/1999/EC of the European Parliament and of the Council of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003). http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf

[3] Communication COM(2008) 679 final from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

Recommendation on an action in the field of rare diseases,[4] of 9 June 2009, advising the Member States on what they should do. The complementarity of objectives in both documents results in a clear strategy for European Union intervention in this field aimed at improving patients' access to appropriate and timely diagnoses, information and care. In this area, European action can be more effective than Member States acting on their own. This involves the following steps:

- **making rare diseases more visible** by developing proper identification and coding of rare diseases, many of which currently go unrecognised, leading to inappropriate treatment for individuals and lack of appropriate resources overall;
- **encouraging Member States to develop national rare diseases plans in their health policies** to ensure equal access to and availability of prevention, diagnosis, treatment and rehabilitation for people with rare diseases. More initiatives in terms of public awareness-raising in the Member States are needed. In addition to targeting public opinion, these efforts should also be directed at healthcare and social services professionals, decision-makers, health and social services managers and the media.
- **providing European support and cooperation**, such as ensuring that **common policy guidelines are developed and shared** everywhere in Europe. There should also be specific actions in areas such as research, centres of expertise, access to information, incentives for the development of orphan drugs and screening. Cooperation between existing European programmes also needs to be improved.

30.3 Rare Diseases also Differ Widely in Severity and in Expression

Rare diseases patients have a significantly lower life expectancy. Many are complex, degenerative and chronically debilitating, whilst others are compatible with a normal life – if diagnosed in time and managed and/or treated properly. They affect physical capabilities, mental abilities, behaviour and sensorial capacities, and generate disabilities. Several disabilities often co-exist, with many functional consequences (defined as polyhandicap or plurihandicap). These disabilities enhance the feeling of isolation and could be a **source of discrimination** and reduce any educational, professional and social opportunities.

[4] Council Recommendation of 8 June 2009 on an action in the field of rare diseases. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

30.3.1 To Develop Equal Rights in Access to Medicinal Products

Under normal market conditions, the pharmaceutical industry is reluctant to invest in medicinal products and devices for rare conditions because of the very limited market for each disease. This explains why Rare Diseases are also called "**orphan diseases**": they are "orphans" of research focus and market interest, as well as of public health policies. The mentioned **Orphan Medicinal Product Regulation** (Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products) establishes criteria for orphan designation in the EU and includes a number of incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) for research into, and the development and marketing of medicines to treat, prevent or diagnose Rare Diseases. Between 2000 and September 2015, the **European Medicines Agency's Committee for Orphan Medicinal Products (COMP),** received **2302 applications for designation**, of which the Commission approved 1544.[5] Of these, 1227 are currently active (some decisions have expired and some products have been withdrawn by the sponsor). After a peak in 2014 the number of applications for orphan designations falls from 329 to 258 in 2015 although this was still higher compared to the years before 2014. EMA fosters the global development of medicines for rare diseases through its collaboration with the US and Japanese regulatory authorities; the parallel submission process helps rationalise and streamline the development of orphan medicines. One in three applications for orphan designation was submitted to EMA and to another regulatory authority in parallel in 2015.

As in previous years, cancer treatment (36%) was the most-represented therapeutic area followed by metabolic diseases (11%). Almost two-thirds of designated orphan medicinal products were for conditions affecting children and the COMP took on average 66 days to evaluate applications (Fig. 30.1).

As of 1 February 2009, designated orphan medicinal products are eligible for reductions for all fees payable under Community rules pursuant to amended Regulation (EEC) 2309/93. The EMA revised the fee reduction policy in April 2011. The revised policy was adopted with an aim to ensuring that incentives for Small and Medium-sized Enterprises (SMEs) developing orphan medicinal products are maintained at the same level as previous years. In order to keep this objective the fee reductions for bigger pharmaceutical companies have been decreased.

After 15 years of implementation of the orphan legislation, the Commission is currently launching initiatives to improve the implementation of the regulatory

[5] COMMISSION STAFF WORKING DOCUMENT Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan mecidinal products – state of play 2015 http://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/orphan_inv_cwd_20160126.pdf

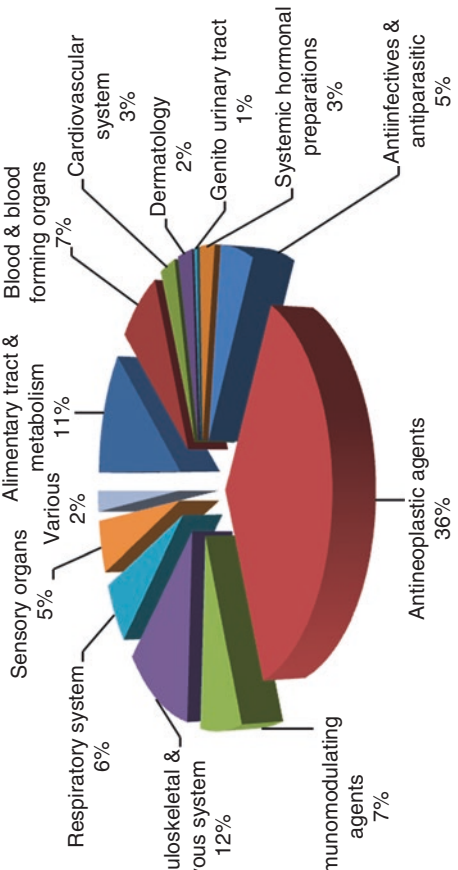

Fig. 30.1 Distribution of orphan designations per therapeutic area

framework with a view to ensure timely access to medicinal products.[6] In this context, the Commission has decided to launch a targeted review of Commission Regulation (EC) No 847/2000 on the concept of similarity. In parallel, the Commission is also finalising the revision of the 2003 Communication on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C 178/02) which will be replaced by a notice.

The cornerstone of the orphan rules is the principle of market exclusivity. When a marketing authorisation for an orphan medicinal products is granted, the Union and the Member States shall not for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product. Article 3 paragraph (3) of Commission Regulation 847/2000 provides a definition of 'similar medicinal products' and a number of examples defining what kind of products are to be regarded as similar for the purposes of the application of the incentives provided under Regulation 141/2000. The definitions of Regulation 847/2000 require adaption to technical progress due to major developments in the field of biological medicines including advanced therapy medicinal products.

The European Medicines Agency is developing a scheme to facilitate development and accelerated assessment of innovative medicines of major public health interest and in particular from the viewpoint of therapeutic innovation to address unmet needs. Additionally he European Medicines Agency ("EMA") has published a **new guidance document for companies that wish to participate in the Adaptive Pathways initiative.** Adaptive Pathways was established as part of the EMA's objective to improve timely access for patients to new medicinal products. Adaptive Pathways applies to medicinal products with the potential to treat serious conditions with an unmet medical need. The concept of Adaptive Pathways is to grant applicants that develop such medicinal products either:

- an initial marketing authorisation with a therapeutic indication in a well-defined patient subgroup. Identification of the initial therapeutic indication could be based on surrogate endpoints. This initial therapeutic indication could be subsequently extended to include a larger patient population based on gradual phases of post-marketing authorisation evidence-gathering, including real world data; or
- an early conditional marketing authorisation.

[6] CONCEPT OF 'SIMILAR MEDICINAL PRODUCT' IN THE CONTEXT OF THE ORPHAN LEGISLATION: ADAPTATION TO TECHNICAL PROGRESS. CONSULTATION DOCUMENT http://ec.europa.eu/health//sites/health/files/files/orphanmp/2016_07_pc_orphan/2016_07_consultation_paper.pdf

30.3.2 Rare Diseases: A Major Objective for Research Policy

Over the last two decades, collaborative and coordinated research projects supported by successive **European Community Framework Programmes for Research and Technological Development have made a substantial contribution to advancing knowledge on rare diseases**. In the different framework programmes rare diseases have been designated a priority for research activities. **Research** on Rare Diseases offers us a much better understanding of the mechanism of common conditions like obesity and diabetes, as they represent a model of dysfunction of a biological pathway. Research on Rare Diseases has been fundamental to identifying most currently-known human genes and a quarter of the innovative medicinal products that have received market approval in the EU (orphan medicinal products). The **FP5 programme** supported 47 research projects on rare diseases (for a total of 64 million euros). There were 59 such projects in the **FP6 programme** (for a total of 230 million euros). The **FP7** devoted over 620 million euros to 120 collaborative research projects on rare diseases giving priority to Europe-wide studies of **natural history**, **pathophysiology** and the development of **preventive, diagnostic and therapeutic interventions**.[7] They covered nearly all fields of medicine, e.g. molecular genetics, metabolic diseases, neurology, neuromuscular and musculoskeletal disorders, cardiovascular, haematological disorders, immunology, cancer, infectious diseases, nephrology, urology, mental health, ophthalmology and dermatology. The EU funding facilitated the formation of multidisciplinary teams from universities, research organisations, SMEs, industry and patient organisations from across Europe and beyond.

With regard to collaborative research, the European Commission will continue the strong commitment to funding excellent research in rare diseases, established through previous framework programmes. The Horizon 2020 Work Programme 2015 for "Health, demographic change and wellbeing" includes an earmarked budget of € 62 million euro for developing new therapies for rare diseases. The Commission will launch in 2017 the initiatives **SC1-PM-03–2017: Diagnostic characterisation of rare diseases** having as scope apply genomics and/or other –omics and/or other high-throughput approaches for molecular characterisation of rare diseases in view of developing molecular diagnoses for a large number of undiagnosed rare diseases. Molecular and/or functional characterisation may be part of the proposal to confirm diagnosis. Promote common standards and terminologies for rare disease classification and support appropriate bioinformatics tools and incentives to facilitate data sharing. Existing resources should be used for depositing data**.** Another initiative **SC1-PM-08–2017: New therapies for rare diseases** will be launched with the scope of Support clinical trials on substances where orphan designation has been given by the EC, where the proposed clinical trial design takes into account recommendations from protocol assistance given by the

[7] Web site of the European Commission on the Seventh Framework Programme (2007–2013) http://ec.europa.eu/research/fp7/

EMA, and where a clear patient recruitment strategy is presented. May include limited elements of late stage preclinical research but centre of gravity must clearly be the clinical trial(s).

Appropriate plans to engage with patient organisations, MS health authorities and considerations of efficacy/potential clinical benefit as well as early indication on health economics should be included.

Other initiatives on Clinical research on regenerative medicine, PCP – eHealth innovation in empowering the patient, In-silico trials for developing and assessing biomedical products, Standardisation of pre-analytical and analytical procedures for in vitro diagnostics in personalised medicine and Supporting innovative SMEs in the healthcare biotechnology sector, will be launched during the duration of the programme.

The Commission is also co-funding **the ERA-NET project E-RARE-3** which will strengthen the collaboration between participating EU countries in funding rare disease research.[8] The ERA-Net "E-Rare" for research programmes on rare diseases has been extended to a third phase "E-Rare-3" (2014–2019) to further help in coordinating the research efforts of European countries in the field of rare diseases and implement the objectives of International Rare Disease Research Consortium (IRDiRC).

However rare diseases are a too big challenge for any country or world region to master alone. **This is why the European Commission, together with European and international partners, initiated the International Rare Diseases Research Consortium (IRDiRC)**.[9] Launched in 2011, it is the biggest collective rare diseases research effort worldwide. **Its key objective is to deliver, by 2020, 200 new therapies for rare diseases and the means to diagnose most of them**.

IRDiRC has currently over 40 member organisations from four continents committed to working together towards the initiative's goals. Members are composed of funding bodies investing a minimum of $US 10 million over 5 years in research projects/programmes contributing towards IRDiRC objectives, and invited advocacy groups. International partners include organisations from Australia, Canada, China, South Korea, Georgia and the USA (Fig. 30.2).

IRDiRC is governed by the Executive Committee, three Scientific Committees and 12 working groups. The three Scientific Committees are for Diagnostics (including sequencing and characterisation), Therapies (including pre-clinical and clinical development) and Interdisciplinary aspects of rare diseases; and Research (including ontologies, natural history, biobanking, registries etc.). Several major policy initiatives were taken during the period 2014–2015:

- The allocation of more funding for Rare Diseases Clinical Research Networks (RDCRN) by the National Institutes of Health (NIH) allowing the establishment of six new consortia;

[8] http://www.erare.eu/project

[9] http://www.irdirc.org/

- The data sharing policy adopted by the NIH applying to all NIH-funded, large-scale human and non-human projects that generate genomic data;
- The institution by the Food and Drug Administration (FDA) of a policy to expedite the review of certain breakthrough therapy-designated applications for the past several months;
- The FDA guidance on ways to use electronic media like interactive websites to help facilitate the informed consent process;
- The FDA new fast track programme to approve high-risk medical devices for diagnosis or treatment of serious diseases for which no technology currently exists;
- The US government investment into the National Institutes of Health Undiagnosed Disease Network (NIH UDN) to address diagnosis of rare and ultra-rare diseases over the next 4 years;
- The adoption by the Commission Expert Group on Rare Diseases (ECEGRD) of a recommendation on codification for rare diseases;
- The EMA and FDA release of a draft joint proposal to facilitate clinical research on new medicines to treat Gaucher disease; and
- The funding by the Canadian Institutes of Health Research (CIHR), in partnership with Genome Canada, of the Canadian Rare Diseases Models and Mechanisms Network to investigate molecular mechanisms of rare diseases.

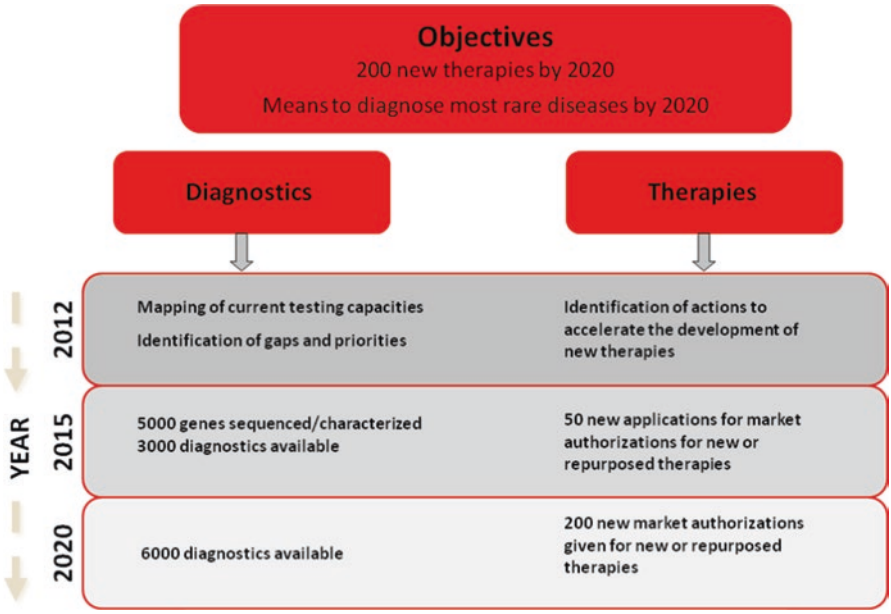

Fig. 30.2 IRDiRC 2020 objectives

30.3.3 The Cross-Border Health Care Approach and the European Reference Networks

In 2005, DG SANCO established the High Level Group on Health Services and Medical Care (HLG) to implement the recommendations of the reflection process on patient mobility and the future adoption of a **Directive on Cross-border healthcare**.[10] One of its working groups has dealt with **reference networks of centres of expertise,** in particular for rare diseases. In the Commission Communication and the Council Recommendation, high importance is given to the creation of **European Reference Networks on Rare Diseases**. Diagnosis of a rare disease is often delayed, and for the majority of rare diseases no appropriate treatment exists. Sometimes, knowledge and appropriate treatment of a disease may exist in another Member State but mobility of information is hampered by inefficiency and fragmentation of the limited resources available.

Rare diseases offer a prime example of the benefits of trans-national coordination. When diseases are rare, expertise is scarce as well. Certain centres have developed expertise which is widely used by other professionals from their country or even internationally. In some countries these centres are officially recognised, but in most they are only established by reputation. The Commission has decided to prioritise cooperation and knowledge sharing between them as the most efficient approach. Certain principles have been developed regarding European Reference Networks (ERN), including their role in tackling rare diseases or other conditions requiring specialised care, patient volumes and other criteria that such centres should fulfil. ERNs should also serve as research and knowledge networks updating and contributing to the latest scientific results, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. ERNs should also reflect the need for services and expertise to be appropriately distributed across the enlarged European Union. The EU rare diseases Task Force 2006 Report ***'Contribution to policy shaping: For a European collaboration on health services and medical rare in the field of rare diseases'***[11] recommends that Member States contribute to the identification of their expert centres and support them financially as much as possible. It also recommends that Member States organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres within the country or from abroad when necessary.

The European Reference Networks will have a strategic role in harmonising **care and improving quality of treatment** for all patients throughout the European

[10] Directive of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare. http://ec.europa.eu/health/ph_overview/co_operation/healthcare/cross-border_healthcare_en.htm

[11] Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force. A technical and scientific report from an expert group of the European Union Rare Diseases Task Force. http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf

Union. Within ERNs, knowledge and expertise will be shared across different Centres. If necessary at specific moments of the development of a disease, it will be considered as "**normal and fair**" **to travel from one Centre to another** within the same network to confirm a diagnosis or seek a second opinion, or for important medical procedures, such as surgical operations, transplantations and other invasive medical interventions. It should not be an administrative, legal and medical battle for a patient to travel abroad for involuntary medical reasons.

The first 24 ERNs were launched in 2017, involving more than 900 highly-specialised healthcare units from over 300 hospitals in 26 Member States. In practice, ERNs will develop new innovative care models, eHealth tools, medical solutions and devices. They will boost research through large clinical studies and contribute to the development of new pharmaceuticals, and they will lead to economies of scale and ensure a more efficient use of costly resources, which will have a positive impact on the sustainability of national healthcare systems, and for tens of thousands of patients in the EU suffering from rare and/or complex diseases and conditions.

The ERNs will be supported by European cross-border telemedicine tools, and can benefit from a range of EU funding mechanisms such as the "Health Programme", the "Connecting Europe Facility" and the EU research programme "Horizon 2020".

30.4 Both Approaches (Transfer of Knowledge and Patient Mobility) Are Useful

A centrifugal approach to transferring knowledge from the central network to a broader periphery allows more local delivery of care/treatment to patients and the dissemination of information. The benefits are care close to the patient's home/environment and dissemination of knowledge to a wide community. This however does not guarantee that the knowledge is in the hands of experts or that the patient will have access to the latest treatment/technology. A centripetal approach favouring the concentration of patients in one expert centre increases the expertise/standard of care of the centre. The benefits are a high quality of care/treatment for the patients, access to the latest technology and the possibility for patients and their families to feel less isolated. However, it keeps the expertise in the expert's hand and requires patients to travel to the centre.

30.5 The Directive 2011/24/EU OF on the Application of Patients' Rights in Cross-Border Healthcare (2011)

The Directive 2011/24/EU OF on the application of patients' rights in cross-border healthcare (2011) was adopted in March 2011 and clarifies patients' rights to access safe and good quality treatment across EU borders, and be reimbursed for it. The Directive will provide a firm basis for increased cooperation between national

health authorities through several actions. Some provisions are addressing the issue of rare diseases.

In particular Article 12 foresees enhanced cooperation of Member States in the area of European reference networks (ERN). It foresees that Commission is going to adopt through legal means (delegated and implementing acts) the criteria and conditions which the ERN and the healthcare providers must fulfil. To prepare these acts, the Commission will carry out appropriate consultations and has set up the Cross-Border Directive expert group which will assist the Commission on this task. In the case of the implementing acts the Commission will be assisted by the Committee on Cross-Border Healthcare composed of Member States representatives created on the 21 June 2011. It further clarifies that ERN could also be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases. The Directive is not aiming to "create" new centres, but to identify already established centres of expertise and to encourage voluntary participation of healthcare providers in the future ERN.

Furthermore, Article 13 requires the Commission to support Member States in making health professionals more aware of diagnostic tools which may help rare disease patients, and in making patients more aware of the possibility of requesting a treatment abroad according and up to the entitlements they have in their Member State of affiliation. Article 8 also encourages Member States to seek the advice of experts when dealing with patients with rare diseases.

The model envisaged by the European Commission includes ERNs by themes composed of designated centers of expertise and associated and collaborative national centers. The horizontal aspects of the networks will be stressed through a dedicated network. Designation at EU level of the centers making up the thematic networks is envisaged: these centers would have to fulfill the criteria provided in the delegated act, and would act as a hub between the national healthcare providers and the ERNs. The national centers in the ERNs will be voluntary members, designated by national authorities, according to national criteria for designation and committed to the general goals and rules of the network: these centers can either be associated (e.g. healthcare provision is their main field of work, they have expertise in the condition/diseases of the ERN, and they provide and coordinate highly specialized healthcare as well as follow-up) or collaborative (e.g. healthcare provision Is not the main field of work, but they have expertise in knowledge dissemination and their main goal is to build and disseminate knowledge and competence). The collaborative centers could be agencies, institutes implicated in training and research etc. Each thematic ERN will have a coordinator and board who will be part of the ERN general board/assembly dealing with horizontal issues.

The European Commission (EC) is supporting Member States into **developing European Reference Networks (ERNs) in an initiative that will link existing highly specialised healthcare providers across the European Union**. Healthcare providers both willing to form a Network and having the endorsement of their Member States, are invited to apply for the call for ERNs. The assessment process for proposing Networks and memberships is based on the regulatory framework of

the **European Commission Delegated Decision (2014/286/EU) and Implementing Decisions (2014/287/EU) of 10 March 2014**.[12] These include compulsory criteria and conditions ERN applicants have to fulfil.

30.6 The 1st Call Has Been Launched in 2016[13]

After consulting the Member States, the Commission shall decide on the appropriate timing for the publication of subsequent calls for interest. The applications will have to pass three steps – the eligibility check by the Commission and the independent assessment bodies, the technical assessment by the independent assessment bodies and the approval by the Board of Member State. For the application, each applicant member will have to secure the endorsement of their Member State. An Assessment Manual and Tool-Kit for applicant members will describe the assessment. To be eligible for application a proposed network has to consist at least of 10 HCP out of 8 member states. The Commission Implementing Decision provides the minimum but not the maximum of possible HCP. This will be agreed by the proposing network along with their considerations of the governance of the network. The possibility to include more than one centre of expertise of a member state by endorsement is in the responsibility of the member state.

2016 is an exciting year for the rare disease community: this is the year which saw the first call for European Reference Networks (ERNs) and the first proposals submitted. (An ERN is -or will be- a network connecting providers of highly specialised healthcare, for the purposes of improving access to diagnosis, treatment and high-quality care for patients with conditions requiring a particular concentration of resources or expertise.) The 5 years since the publication of the Directive on the Application of Patients' rights in cross-border healthcare (Directive 2011/24/EU) have been filled with concerted efforts and hard work by thousands of rare disease stakeholders across Europe, to move the ERN concept into reality. At present, the ERN proposals and the accompanying applications for membership are being reviewed and assessed according to the formal Commission procedure. The successful Networks should be approved by the end of the year 2016.

The ERN deadline coincided with the end of the 1st year of **RD-ACTION, the Joint Action for rare diseases**,[14] a key focus of which has been in fact to support the rare disease field in developing and implementing robust ERN proposals. For instance, the RD-ACTION team at Newcastle University established a 'Matchmaker' resource to support RD experts in organising themselves into collaborative –as

[12] Commission Delegated Decision of 10 March 2014 setting out criteria and conditions that European Reference Networks and healthcare providers wishing to join a European Reference Network must fulfil http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014D0286&from=EN

[13] http://ec.europa.eu/health/ern/implementation/call_en

[14] http://www.rd-action.eu/

opposed to competing- proposals, adhering to the rare disease Groupings recommended by the **Commission Expert Group on Rare Diseases**.[15] The team worked closely with clinical groups and existing networks to develop single, comprehensive proposals in each area. Meanwhile, RD-ACTION partner EURORDIS initiated the European Patient Advisory Groups (ePAGs) to support meaningful patient participation in ERNs.

The EUCERD (European Committee of Experts on Rare Diseases) contributed also to this process adopting two EUCERD Recommendations. One on **Quality criteria for Centres of Expertise for Rare Diseases in Member States** (October 2012)[16] intended to help MS in their reflections or policy developments concerning national plans and strategies for rare diseases when addressing the issue of organisation of healthcare pathways at national and European level. The second on **EUCERD Recommendations to the European Commission and the Member States on European Reference Networks for Rare Diseases** (January 2013)[17] pointing out that it's expertise who travels rather than patients themselves when appropriate through the national healthcare systems there can be very different structures organised by regions, treatments, development and adoption of e-tools for tele-expertise and tele-consultation, and also pointing out that the exchange of data, biological samples, radiological images, other diagnostic procedures and all offers of materials, occurs appropriately when needed to improve diagnosis and care, to improve knowledge and contribute to the development of new therapies.

30.6.1 The Orphanet Database: Access to Information on Rare Diseases

Adequate information on the epidemiology and prevalence of rare diseases is a necessary basis for efficient actions. This type of information is also essential when deciding whether an orphan medicinal product designation is appropriate. The key element for improving diagnosis and care in the field of rare diseases is **to provide and disseminate accurate information** in a format adapted to the needs of professionals, affected persons and their families. Since 2000, the **Orphanet database**,[18] with the support of the Health Programmes and the Framework Programmes for Research, has been providing information about over 6000 diseases in six languages. It provides a comprehensive encyclopaedia of rare diseases; a directory of professional services in 35 countries; a directory of European centres of expertise; a database of orphan drugs providing information on their stage of development and availability in EU countries; and a range of other services for specific categories of

[15] http://ec.europa.eu/health/rare_diseases/expert_group_en

[16] http://www.eucerd.eu/?post_type=document&p=1224

[17] http://www.eucerd.eu/?post_type=document&p=2207

[18] Orphanet. The Portal on Rare Diseases and Orphan Drugs, a project supported by the European Union. http://www.orpha.net/

stakeholders, including a facility to retrieve diagnoses through symptoms and signs and a library of recommendations for emergency situations. **Orphanet** has already established a searchable database of clinical symptoms and provides a valuable resource which constitutes the European and world reference for the identification and epidemiological description of rare diseases.

This project is an evolution of the existing Orphanet website towards a new rare diseases portal. This site is designed to help improve the diagnosis, care and treatment of patients with such diseases, by providing the community at large with comprehensive, user friendly information on rare diseases in six languages.

A Joint Action "**Orphanet Europe**" was selected for funding for the period 2010–2013 under the EU Health Programme. The French INSERM led the Joint Action. As outcome a common European RD portal, providing European citizens with the information they need. The Orphanet dataset will be available for re-use in different formats to ensure dissemination of the Orphanet nomenclature of RD and maximize the use of collected information on expert services. Customized websites at national level in national language(s) will be available in order to disseminate national data at MS level. Orphanet will have the governance needed to ensure its mission at international level.

From 2015 a new **Joint Action RD-Action** is in charge to maintain, update and expand the rare diseases database: the inventory and classification of RD and its alignments with other terminologies (i.e. ICD10, SNOMED CT); links between rare diseases, phenotypes and genes, including cross-references with other resources (i.e. OMIM, HPO); the professional encyclopedia of RD by providing a definition for all RD to be included in the content model of ICD11 and SNOMED CT, as well as in the **Orphanet Rare Diseases Ontology (ORDO)**[19] and by producing new and updated abstracts and disseminating new content produced by others.

This **Joint Action RD-Action** is also the instrument for the European Commission, under the basis of the Commission Expert Group on Rare Diseases "**Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems**"[20] to enable countries to implement coding of rare diseases in a standardized and interoperable way implementing the Orphacodes in their health system. The Orpha codes system is designed based on Orphanet data. **Each of the nearly 6000 rare diseases listed on the Orphanet website has an Orpha code,** meaning a larger number than those rare diseases that have either an ICD or SNOMED CT code. The definition of common guidelines addressing the issues of both quality of codification and coherence of exploitation at the European level is a major ambition of this Joint Action. In a second step the development of a European file holding all necessary Orphacodes to be used for implementation in countries will be developed.

[19] http://www.orphadata.org/cgi-bin/inc/ordo_orphanet.inc.php

[20] http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

Other databases on rare diseases

The Swedish National Board of Health and Welfare is developing a database on rare diseases. Rare diseases are defined as: "diseases or disorders which affect fewer than 100 people per million, and which lead to a marked degree of disability". The aim of the database is to provide up-to-date information on rare diseases and about the support and services required by those affected. To date, close to 300 rare diseases have been described. The database Rarelink aims at establishing contact between persons with rare diagnoses, who are not supported by a patient organization in Denmark, Finland, Norway and Sweden.

Diagnosing Rare Diseases

Rare diseases (RD) are still poorly known both by the general public and by most health professionals. Obtaining an accurate diagnosis is critical for all patients with a rare disorder, but diagnosing these diseases may be difficult.

Some rare diseases are compatible with normal life if diagnosed on time and properly managed. However, the lack of specific health policies for RD and the scarcity of the expertise translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, sometimes birth of affected siblings, inadequate or even harmful treatments and loss of confidence in the health care system. Patients feel isolated when physicians are unable to diagnose their illness correctly or promptly. Physicians, in turn, are often perplexed by the multitude of vague and contradictory symptoms and uncertainty about the characteristics of some diseases.

The national healthcare services for diagnosis, treatment and rehabilitation of people with RD differ significantly with respect to their availability and quality. Citizens from EU countries and/or regions within the countries have unequal access to expert services and to orphan drugs. A few countries have successfully addressed issues raised by the rarity of the diseases, while others have not yet considered possible solutions. Establishing diagnostic criteria to aid clinicians is essential for early recognition and differentiation of many of the rare disorders. This information will assist clinicians in evaluating and managing affected individuals. After obtaining a diagnosis, many patients research on their own information about their disease.

In the EU RAPSODY (Rare Disease Patient Solidarity) project, a Survey of the delay in diagnosis for eight rare diseases in Europe was conducted by Eurordis (European Organisation for Rare Diseases) in collaboration with 67 European rare disease organisations.

The main findings were that 25% of patients had to wait between 5 and 30 years from early symptoms to confirmatory diagnosis of their disease. Before receiving a confirmatory diagnosis, 40% of surveyed patients first received an erroneous diagnosis. 25% of patients had to travel to a different region to obtain the confirmatory diagnosis, and 2% had to travel to a different country. The diagnosis was announced in unsatisfactory terms or conditions in 33% of cases, and in unacceptable ones in 12.5% of cases. The genetic nature of the disease was not communicated to the patient or family in 25% of cases.

Similar results have been reported by the US National Commission on Orphan Diseases: about 50% of the patients reported receiving a diagnosis within a year of their first visit to a doctor. Nearly 30% of patients in the survey reported that as many as five years passed before their disease could be identified; and 15% reported that they were not diagnosed for six or more years.

30.6.2 Classification and Codification of Rare Diseases

The EU should cooperate closely with WHO in revising the existing ICD (International Classification of Diseases) to ensure a **better codification and classification of rare diseases**.[21] All rare diseases should be adequately coded and traceable in all health information systems, thus contributing to adequate recognition of them in national health care and reimbursement systems. Once the ICD-11 becomes available, active cooperation of the EU Statistical Programme will be necessary to ensure that the new version, including new codes for rare diseases, is used in death certificates and hospital discharge tabulation systems in all Member States. Similar efforts should be made to ensure proper coding of rare diseases in the SnowMed and MedDRA coding systems. The ICD is always the basis for the Diagnosis Related Groups used to calculate hospital care disease costs.

WHO has established various Topic Advisory Groups (TAG) to serve as planning and advisory bodies in the update and revision process for specific areas. A Group oversees the overall revision process. A TAG for rare diseases was established in April 2007 as rare diseases should now be traceable in mortality and morbidity information systems. The production of basic information to establish a first draft of the classification of rare diseases has been assigned to Orphanet and will contribute to the whole revision process, as rare diseases involve all areas of medicine. Orphanet has developed a strictly clinical in-house classification to meet the needs of the clinicians serving as basis to build the ICD-11 proposals of revision.

Orphanet was given the task to develop an inventory of rare diseases and a classification system which could serve as a template to update International terminologies. So far 5400 rare diseases listed in the Orphanet database have an endorsed representation in the foundation layer of ICD-11, and are thus provided with a unique identifier in the Beta version of ICD-11, which is ten times more than in ICD10. A rare disease linearization is also planned. The current beta version is open for public consultation and comments, and to be used for field testing. The adoption by the World Health Assembly is planned for 2017.

The overall revision process was carried out with very limited means considering its scope, ambition and strategic significance, and experienced significant hurdles and setbacks. The contrast between the initially declared goals and the currently foreseen final product is disappointing. In the context of uncertainty around the

[21] World Health Organisation (WHO): web site on the International Classification of Diseases. http://www.who.int/classifications/icd/en/index.html

outcome of the field testing and the potential willingness of countries to adopt this new version, the European Commission Expert Group on Rare Diseases adopted in November 2014 a recommendation for health care coding systems to consider using ORPHA codes in addition to ICD10 codes for rare diseases having no specific ICD10 codes. The Orphanet terminology, classifications and mappings with other terminologies are freely available at www.orphadata.org.

To achieve the first year's goal for the **RD-ACTION Joint Action Work Package 5**,[22] a survey has been conducted in several participant countries and has been published. French APHP, German DIMDI and RD Coordinating Centre -Veneto Region worked together to identify key questions that needed to be answered regarding the coding systems in participating countries. A specific coding policy for RD has been set up in five countries, always in the framework of a national programme linked to RD registries or national data repository and two countries started with a pilot project. Half of participants declare a specific coding policy is under discussion. More than half of the respondents do not have a clear knowledge of current RD registries in their country. The harmonisation of diagnosis coding RD in existing registries was poorly rated, so was the prevalence and incidence data value. A third of the participating countries have a national program to integrate registries.

30.6.3 Rare Diseases Registration and Surveillance

Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients.[23]

Because of their low individual prevalence and the scarcity of information about each of them, the benefits of collaboration and maximization of limited resources in establishing patient registries are most obvious for RD, especially for ultra RD for which expertise may only be available in a very small number of European countries. No single institution, and in many cases no single country, has sufficient numbers of patients to conduct generalizable clinical and translational research. Geographic dispersion of RD patients has been a major impediment to patient recruitment into clinical trials.

The document "***RDTF Report on Patient registries the field of rare diseases: Overview of the issues surrounding the establishment, governance and financing of academic registries***" published by the Rare Diseases Task Force in 2008 and

[22] http://www.rd-action.eu/workpackage/workpackage-5/

[23] 2012 Report on the State of the Art of Rare Diseases Activities in Europe - EUCERD Joint Action, July 2012.

updated by Orphanet in January 2016[24] presents a detailed list and overview of the rare diseases registers exiting in Europe. They are **597** presenting the following distribution: 59 European, 40 International, 417 national, 77 regional, 4 undefined. Almost all of these registries concern diseases or groups of diseases for which there is an innovative treatment either in development or already on the market. This is not surprising as registries of patients treated with orphan medicinal products are particularly relevant: they allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing. Most of the registries are established in academic institutions. A minority of them are managed by pharmaceutical or biotech companies, with others being run by patient organisations.

DG SANCO has been financing in the last years, 16 networks of researchers and clinicians on a single or on a group of related rare diseases including registration of RD.[25] The 6th and 7th Framework programmes, managed by DG Research, have funded 18 and 27 projects for rare disease research including registration of RD.[26]

In order to have a better appraisal of the characteristics, expectations and how the funds devoted by the European Commission and other funders to RD registration have been used, the EC selected for funding the **EPIRARE (European Platform for Rare Diseases Registries) Project**[27] to implement a survey addressed to all the RD registers existing in Europe. A questionnaire on the activities and needs of existing RD registries was developed between June and October 2011 and implemented in 2012. A total of 254 registers have accepted to participate to the survey.

Overall, the EPIRARE survey results confirm that the reality of the RD registries currently operating on the European territory is quite complex. The EPIRARE survey provided the possibility for a more in depth analysis. Indeed, as far as governance and financial sustainability are concerned, the survey results show that there are uncertain reference standards to which registries adheres. Naturally, and as tested elsewhere, registries can have very different objectives from one another and this is clearly reflected in the fragmented picture that emerges. Nevertheless, certain weaknesses can be identified that could take advantage of uniform and validated standards assuring a robust and governance transparent governance and a solid financial sustainability of the registry.

Although some replies (no opinion) might suggest some scepticism, the vast majority of the respondents are in favour of a EU portal (73%) and especially of a EU platform (80%). Favourable opinions are lesser (61%) regarding the desirability

[24] **S. Aymé, A. Kole, C. Rodwell** "RDTF Report on Patient registries the field of rare diseases: Overview of the issues surrounding the establishment, governance and financing of academic registries", June 2011. http://www.eucerd.eu/EUCERD/upload/file/RDTFReportRegistriesJuly2011.pdf

[25] http://ec.europa.eu/health/rare_diseases/projects/networks/index_en.htm (accessed on 29/06/2012)

[26] http://e-rare.eu (accessed on 29/06/2012)

[27] http://www.epirare.eu/

of new EU legislation on the matter, and, looking at additional comments received, the doubt was expressed that new legislation could even make registration more difficult and could take too long a time. Expectations regarding public funding to a central registry are positive for about 50% or respondents.

According to the survey results, the main services expected by the registry holders (with a frequency of selection between 39 and 69%) from a EU platform, seem to refer mainly to technological tools (IT tools and networking tools), specific expert advice (legal, quality, privacy, ethics), resources (model documents, quality control systems, access to useful data). The pattern of replies suggests that the registry holders expect from the platform the discharge of those parts of their registry work which is not related to direct scientific interest of their registry, but is a necessary aspect for its success and requires specific competence, continuing attention and resources. These are typical functions offered by a service oriented platform.

In line with this strategy, the Directorate-General Joint Research Centre (JRC), upon request and in close collaboration with the Directorate-General for Health and Consumers (DG SANTE), agreed in December 2013 on the development and maintenance of the **EU Platform on Rare Diseases Registration**.[28] The principal goal of the Platform is to **address the fragmentation** of rare diseases patient data comprised in more than 600 registries across Europe, which severely jeopardises the registries' potential and limits Europe's potential to steer health policy and facilitate research. The main objective is to **maximise access** to patient data in Europe, both within and across many rare diseases in order to achieve a sufficient sample size for epidemiological, clinical, pharmacological, translational studies and research. In this respect the aim is to facilitate planning of clinical trials and to support the enrolment of patients knowing that their geographic dispersion is a major impediment to patient recruitment into clinical trials. The final aim of the Platform is to **maximise the utility of knowledge generated by individual registries** and to address all stakeholders: health professionals, researchers, patients, industry, policy makers, etc. Comparisons across Member States and diseases will be facilitated and valuable support will be given to better plan health and social services for the patients.

The Platform will help to find a consensus mechanism to **agree** procedures for improving the use and quality of registry data including semantic standardization, to stimulate networking and collaboration between registries and the various stakeholders. Based on the benefits of collaboration, of sharing data and expertise and making best use of limited resources, the Platform will promote the **interoperability of existing registries**.

Thus it will implement the **EUCERD Recommendations on rare diseases patient registration and data collection**[29] which state as a very first point: "*Rare diseases registries need to be internationally interoperable as much as possible and the procedures to collect and exchange data need to be harmonised and consistent,*

[28] http://ec.europa.eu/health/rare_diseases/policy/registries_en

[29] http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

to allow pooling of data when it is necessary to reach sufficient statistically significant numbers for clinical research and public health purposes." These **EUCERD Recommendations** are the basis on which the Platform will be established. The Platform will be **as inclusive as possible**. Very important partners for the establishment of the Platform are national, regional, local, hospital, patients' organisations, university-based and other existing registries, including diseases-specific, international registries. All are kindly invited to collaborate and to be part of the Platform. A main objective of the Platform is to **support the creation of new registries** and activities will be developed in close link with other EU and global initiatives in the area, establishing **interaction with international initiatives** involving rare diseases registries -the International RD Research Consortium (IRDiRC), RD-Connect,[30] the Global RD Patient Registry and Data Repository (GRDR),[31] as well as with patients' organisations (EURORDIS),[32] and taking into account outcomes of the projects co-funded by Framework Research Programmes and the Health programme.

Another aspect of the added-value of the Platform resides in the **integration** of RD data into the wider context of health information, stratified medicine, environmental databases, **link** with biobanks and with the European Reference Networks.

The EU Platform on Rare Diseases Registration being developed at the JRC will (a) act as a "hub" improving access to patient registries and data, (b) will help to share knowledge and join competences and (c) will combine resources among RD registries throughout Europe. Its final purpose is to improve knowledge on rare diseases, to support clinical studies, research activities and public health policy in order to improve the quality of care and the quality of life for people living with a rare disease.

30.6.4 Surveillance Networks on Rare Diseases

One of the main solutions provided by the creation of the Platform has been to offer a **sustainable solution** for the two European surveillance networks EUROCAT (**European Surveillance of Congenital Anomalies**)[33] and SCPE (**Surveillance of Cerebral Palsy in Europe**)[34] whose databases and coordinating activities have migrated to the JRC and became part of the Platform.

EUROCAT is a network of population-based registries for the epidemiological surveillance of congenital anomalies, covering 1/3 of the European birth population (more than 1.7 million births/year). Since its establishment in 1979, the EUROCAT central activities including the Central Registry with the central database and the Steering Committee have been funded by the European Commission in the frame of

[30] http://rd-connect.eu/

[31] https://grdr-guid.ncats.nih.gov/portal/jsp/login.jsp

[32] http://www.eurordis.org/

[33] http://www.eurocat-network.eu/

[34] http://www.scpenetwork.eu/

successive projects and health programmes. The EUROCAT central database contains half a million cases of children with congenital anomalies. This data enables provision of prevalence, prenatal diagnosis and perinatal mortality data. The valuable scientific work done over decades made EUROCAT to an EU wide and internationally recognised entity with results highly relevant for European public health. EUROCAT performs annual statistical monitoring to detect new or increasing teratogenic exposures which may require public health action. It develops recommendations considered for primary prevention in the Rare Diseases National Plans for medicinal drugs, food/nutrition, lifestyle, health services, environmental pollution. In order to offer a sustainable solution for the continuation of the EUROCAT activities, to secure the results of former work and to keep the system functioning, it was agreed that EUROCAT becomes part of the European Rare Diseases Platform, since the diseases/conditions they are dealing with belong to the category 'rare'. This is in accordance with the general objective of the Platform to support and coordinate rare diseases registries and networks in view of their sustainability. JRC in close agreement with DG SANCO and in collaboration with EUROCAT representatives conducted extensive negotiations and preparations in view of transferring EUROCAT central structures and coordinating activities to the JRC at the end of the transition period (31.12.2014) corresponding to the operating grant ensured by DG SANTE. EUROCAT Central Registry including the central database were moved to the JRC.

SCPE is a network of population-based registries for the surveillance of cerebral palsy (CP) active since 1998. It has now 31 members in 23 EU/EFTA countries. SCPE promotes quality and harmonization of CP definition/description, develops collaborative epidemiological and clinical research about CP, disseminates knowledge for patients, health care professionals and key stakeholders, develops best practice in monitoring trends in CP and raises standards of equitable care for people with CP. All this improves outcomes for individuals with CP. Dissemination of this evidence-based information to policy makers is helpful to facilitate provision of appropriate, accessible, cost-effective care management programmes aimed to improve the quality of life for children and young people with CP and for their carers. In order to offer a sustainable solution for the continuation of the SCPE activities, to secure the results of former work and to keep the system functioning, it was agreed that SCPE becomes part of the European Rare Diseases Platform being developed at the JRC, since the diseases/conditions the network deals with belong to the category 'rare'. This is in accordance with the general objective of the Platform to support and coordinate rare diseases registries and networks in view of their sustainability. The purpose of this preliminary report prepared for DG SANTE is to document the negotiations and preparations accomplished to date (February 2015) in view of the transfer of the SCPE coordinating activities including the Common Database to the JRC.

30.6.5 Supporting Incorporation of Rare Diseases into Social Services and Policies

Commission Expert Group on Rare Diseases (CEGRD) has recently published **recommendations to support the incorporation of rare diseases into social services and policies**.[35] 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 (RD) specificities into mainstream social and support services, within a holistic and person-centred approach and a human rights perspective.

These recommendations were developed within the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action (N° 20,112,201) and are based on the outputs of several key publications and multi-stakeholder consultations. Leading up to the adoption of the recommendations on social services provision, there was emphasis placed by Officials on the importance of the Expert Group following up on delivery and measuring impact after an appropriate period.

30.6.6 National Plans or Strategies for Rare Diseases

In order to integrate all the necessary initiatives that have to be taken at national and/or regional levels, Member States are invited by the **Council Recommendation on a action in the field of rare diseases** adopted the 9th June 2009 to **establish national or regional action plans or strategies for Rare Diseases before 2013** in order to implement the actions suggested in the Commission Communication and the Council Recommendation. European guidelines for the elaboration of action plans for RD might be useful. In this sense a project **EUROPLAN** (European Project for Rare Diseases National Plans Development)[36] has been selected for funding in 2007 in the Public Health Programme. The project will ensure that common policy guidelines are shared everywhere in Europe and will contribute to the development of national programme for Rare Diseases within Member States linking national efforts with a common strategy at European level. **EUROPLAN** defines a rare diseases plan as *'A national plan/strategy (NP/NS) can be defined as the sum of integrated and comprehensive health policy actions for RD to be developed and implemented at national level. As such a NP/NS should have well specified objectives and actions to be supported by a budget, implemented within a time frame, evaluated with specific indicators'*. Only a limited number of Member States have adopted or will soon adopt a National Plan/Strategy or launch relevant initiatives.[37]

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[35] http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendations_socialservices_policies_en.pdf

[36] http://www.europlanproject.eu/

[37] http://www.europlanproject.eu/NationalPlans?idMap=1

While only **France** has established two comprehensive action plans (2005–2008, 2010–2014 extended for 2 years) and will launch the third Plan in 2017, **Bulgaria** for the period 2009–2013 and **Greece** for the period 2008–2012, other Member States have adopted national strategies not explicitly supported by a budget (**Portugal**, **Spain**, **Czech Republic**) or national policies in a certain number of areas which can be translated in the form of a plan or strategy very soon. The development of health indicators is needed to monitor the situation of affected persons in the EU and its evolution. Compilation of existing sources of data should be encouraged, especially those already funded at EU level.

To ensure a high degree of implementation these National Plans needs to be monitored on the basis of a common set of indicators. The EUCERD (European Union Committee of Experts on Rare Diseases) adopted a set of **Recommendations on Core Indicators for Rare Disease National Plans/Strategies**[38] with the overall objective to capture relevant data and information on the process of planning, implementing and monitoring of these plans and strategies. The Core Indicators are therefore instrumental for the decision-making process related to the adoption, assessment and further development of public policies for rare diseases. EU Member States should use these Core Indicators to collect data on an annual basis.

In September 2014 the Commission adopted the **Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM (2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)**[39] in which the state of play of National Plans was examined. According to this Report **i**n 2009, a focus on rare diseases was relatively new and innovative in most Member States and only a few had national plans in place. These were Bulgaria, France, Portugal and Spain.

Currently by the first half of 2016, 23 **Member States have national plans or strategies in place to address rare diseases**. **Member States with an adopted National plan or strategy for rare diseases:** Belgium, Bulgaria, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Lithuania, Latvia, Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain, United Kingdom. Austria, Croatia, Denmark, Finland, Italy, Ireland.

Countries vary considerably in the level of implementation of their plans. This is partially due to the fact that several countries such as the UK, Germany, the Netherlands and Belgium only recently adopted their plans/strategies. Only one country, France, has already finished implementing the first plan and the second national plan and has announced that a third national plan for rare diseases would soon be launched. Most Member States have no dedicated budget for the implementation of national plans. Funding is usually provided as part of overall health spending. Countries do provide occasional budgets for the implementation of specific projects. Some countries reported that budgets are under additional strain as a result of the economic crisis. Despite their comprehensiveness and inter-sectorial

[38] http://www.europlanproject.eu/Content?folder=3

[39] http://ec.europa.eu/health//sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

approach, all plans were adopted at the level of the Ministry of Health. In the Czech Republic, in addition, the plan was also endorsed by the Prime Minister. The scope of the rare diseases plans differs between countries. For example, while rare cancers are an important part of the rare diseases spectrum, several plans/strategies do not cover this group of diseases. This is true for Germany, France, Belgium, Denmark and Portugal. Denmark does not consider infectious diseases as rare diseases. Fourteen countries have run information campaigns to raise awareness on rare diseases. Germany, Croatia, Cyprus and Latvia are currently preparing their campaigns.

Monitoring and evaluating national plans are important aspects of this initiative and the EU cofounded the EUROPLAN project – and subsequently the EUCERD Joint Action**11** – to provide a framework to support Member States in their efforts to develop and implement their national plans. Other countries with plans in place (Croatia, France, Lithuania, Portugal and Spain) base their monitoring strategy on EUROPLAN indicators. Bulgaria and Slovakia have no monitoring strategy. In the remaining countries monitoring strategies are under development.

30.6.7 Preventing Rare Diseases

Another key element of the Commission Communication (point 5.8) and in the Council Recommendation (point 17 d) is the statement that **neonatal screening** for phenylketonuria and congenital hypothyroidism is current practice in Europe and proved highly efficient in preventing disabilities in affected children. As technology evolves, many tests can now be performed for a wide range of rare diseases, **especially metabolic disorders and genetic conditions** in general. The Council Recommendation refers also to the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences, as a privileged area of cooperation between the Member States.

30.6.8 Best Practices on Rare Diseases

RARE-Bestpractices[40] is a 4-year project (2013–2016) funded by the EC FP7. The project aims at improving clinical management of patients with rare diseases (RD) and at narrowing the existing gap in quality of healthcare among countries. Project expected outputs include: (1) identification of challenges to be considered in deriving high quality standards for CPG on RD; (2) transparent procedures and criteria for the evaluation of CPG and their collection in a publicly searchable database; (3) identification of notation criteria to improve user understandability and implementation of CPG; (4) production of mechanisms to assess RD clinical research needs;

[40] http://www.rarebestpractices.eu

(5) development of training activities targeted to key stakeholders to disseminate process and tools for developing and evaluating CPG; (6) the publication of a new scientific journal (http://rarejournal.org).

30.6.9 Empowerment of Patient's Organisations

Patient organisations play an active and instrumental role in determining rare diseases research policies and projects. Due to the large number of rare diseases, there are over 1700 patients' organisations in Europe. Many of them are organised into national alliances of rare diseases, and/or affiliated to EU disease-specific umbrella organisations, such as the **European Organisation for Rare Diseases (EURORDIS)**. EURORDIS gathers organisations in 33 countries, permitting a direct dialogue between the European Commission, other stakeholders and the patient community of rare diseases. Patient organisations have proven to be invaluable partners, at the Member States and EU level, to increase the visibility of rare diseases, to gather and disseminate the information required for defining a public policy on rare diseases, to improve access to quality information on rare diseases and orphan drugs, to organise workshops at European and national level, as well as to produce guidelines and pedagogical documents.

30.6.10 Governance and European Coordination

The Communication under point 7 states that the Commission should be assisted by an advisory committee on rare diseases. Such a Committee was set up by Commission Decision of 30 November 2009 establishing a European Union Committee of Experts on Rare Diseases (2009/872/EC). The Committee's work resulted in the adoption of five sets of recommendations and an opinion, along with the publication of a bi-monthly newsletter and an annual report on the State of the Art of Rare Diseases Activities in Europe which describes activities at Member State, EU and global levels.

The Committee was replaced in 2013 by the **Commission Expert Group on Rare Diseases** in line with provisions of the Framework for Commission expert groups: horizontal rules and public register. The expert group is composed of Member States' representatives, as well as representatives of patients' organisations, European associations of producers of products or service providers, European professional associations or scientific societies and individual experts. The main task of the expert group is to advise the Commission in the implementation of Union actions on rare diseases including drawing up of legal instruments, policy documents, guidelines and recommendations.

30.7 Some Final Remarks

These specific initiatives described above (orphan medicinal products, codification, European Reference Networks, European Platform for registries, National Plans, research on rare diseases, IRDiRC) aims to improve the chance for patients to get appropriate care and information on rare diseases and to reverse the current situation of uncertainty and invisibility for people suffering from a rare disease. Health professionals and public health authorities have insufficient knowledge of the majority of rare diseases. This lack of knowledge underlies diagnostic error – a great source of suffering for patients and their families – and delayed care provision, which can sometimes be prejudicial. Proposals are still being developed, but are currently structured around **ten specific objectives and actions** in the Commission Communication and in the Council Recommendation on an action in the field of rare diseases:

1. To improve information, identification and knowledge on rare diseases
2. To improve prevention, diagnosis and care of patients with Rare Diseases
3. To develop national/regional centres of reference and establish EU reference networks
4. To help ensure equal access to all EU patients to orphan drugs and compassionate use
5. To help to develop specialised and adapted social services for rare diseases patients
6. To accelerate research and developments in the field of Rare Diseases and Orphan Drugs in order to strength at European level the limited and scattered expertise on rare diseases.
7. To empower patients with Rare Diseases at individual and collective level
8. To support implementation of National Plans for Rare Diseases
9. To develop international cooperation on rare diseases
10. To coordinate relevant policies and initiatives at EU level

Chapter 31
The Role of Solidarity(-ies) in Rare Diseases Research

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Abstract Solidarity plays a relevant role in rare diseases (RDs) research to create and enable research in the field. In Europe RDs are estimated to affect between 27 and 36 million people even though single RDs can count very few patients, making the contribution of everyone essential to reach solid results. Often RD research is initiated by patient groups devoting substantial time and resources to the scientific enterprise. In RD research solidarity is often evocated and expressed, in different ways and on different levels, so that it is possible to talk about "solidarities" played by different stakeholders and sometimes conflicting with each other. In this paper we describe different contexts in which solidarity is expressed and embedded in RD research, in particular the context of tight relationships between individuals and their families or in small communities/ethnic groups; among individuals suffering from different RDs and researchers working on a specific RD or a group of RDs, and within society at large. In all these cases the different types of solidarity should be balanced against each other and also against conflicting values. The request to a patient to share data and samples to increase scientific knowledge on the basis of solidarity values needs to be balanced against the need to protect her privacy and autonomy; the duty for a researcher to allow fair access to RD sample and data collections which were donated in a spirit of solidarity is balanced against the need to be competitive in the research world. In the Report "Solidarity. Reflections on an emerging concept in bioethics", the Nuffield Council of Bioethics defines solidarity as "shared practices reflecting a collective commitment to carry 'costs' (financial, social, emotional or otherwise) to assist others". Therefore, if a solidarity framework

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has to be solid and ethically sound it needs to be framed as a shared value, reflected in the different practices by all the stakeholders and be based on reciprocity (not one sided). The context of solidarity(ies) provides a solid base for framing the research endeavor as collectively valuable, not only for possible results of the research, but as intrinsic valid societal practice. This paper tries to draw the lessons on solidarity that we can derive from the RD world where "solidarities" have been part of the game for long time and are declined on many different levels.

Keywords Solidarity • Reciprocity • International research • Biobanking • Data sharing • Governance • Patient associations

31.1 Solidarity(ies)

Solidarity, considered as "shared practices reflecting a collective commitment to carry 'costs' (financial, social, emotional or otherwise) to assist others" [1], is deeply rooted in human experience and thinking.

According to Emile Durkheim "solidarity is what prevents the breakdown of society" [2] and there is evidence that solidarity and social integration have a role in the preservation of good health and wealth [3]. More in general, it seems then that without solidarity a society's ability to advance the common good, warrant and protect the wellbeing of the worse off might be endangered.

The role of solidarity is crucial for the success of every human enterprise like scientific research, so it is important to analyze the preconditions of it.

One precondition of solidarity, according to Jaeggi, is the realisation that a certain kind of connection relates one's situation to the situation of the others. Therefore, acting out of solidarity means standing up for each other because one recognizes "one's own fate in the fate of the other" [4].

Callahan underlined the importance of common values in maintaining solidarity in a society. According to Callahan the concept of solidarity is based on the idea that members of a group can share a conception of a component of the "good life", and agree upon actions to overcome or lessen common vulnerabilities to make the good life achievable for all members of the group [5].

Solidarity may also derive from the recognition that one's wellbeing depends partly on luck. Acknowledging the arbitrariness of one's fortune creates a sense of solidarity among persons and groups, leading the talented and the most fortunate to give up some advantages to promote the wellbeing of the unfortunate [6, 7].

The concept of solidarity is often related to the concepts of justice and reciprocity [8].

According to the liberal egalitarian political philosophy of John Rawls, justice requires equal distribution of all social primary goods unless unequal distribution of these goods results in an advantage to the least well off [9]. In some way justice is also a prerequisite of solidarity as, to support each other, the members of a society must perceive that the basic arrangements of society are just. This includes

perceptions of fairness, intended as equal opportunity of access and just distribution of the burdens.

Solidarity may thus be thought as a continuum, where the most elementary forms are rooted in the similarity of people's experiences and are oriented towards the goals of a restricted group, and the most diffuse forms are rooted in the sharing of a common sense of human vulnerability and oriented towards the protection of the wider society.

31.2 What Is the Role of Solidarity in RD Research?

In EU countries, any disease affecting fewer than 5 people in 10.000 is considered rare. It is estimated that today in the EU, 5–8000 distinct rare diseases (RDs) affect 6–8% of the population – between 27 and 36 million people [10].

In most cases RDs are life-threatening, chronic and debilitating, requiring long term care. Most rare diseases affect children, and many of young patients die before the age of 5. Most RDs have a genetic origin, thus they are a concern not only for the person affected, but also for the entire family and in certain cases for the wider ethnic group.

The specificities of RDs, including the limited number of patients affected and the scarcity of relevant knowledge, make them less attractive for the drug industry which is not interested in reaching small populations, and difficulties in situating them in healthcare policies and plans. The limited expertise and resources available require RD patients, associations, researchers and governments to join their efforts and share knowledge, experiences and resources in order to achieve common goals [11].

So we could argue that solidarity in the RD world is a necessity coming from need. But we also saw examples of societies moving towards solidarity approaches (orphan drugs regimes), that are divergent from the classic cost/benefit approach and that did create virtuous cycles for research and patients.

Solidarity is essential in the care and research on RDs and RDs offer a nice perspective to disentangle the many ways solidarity is active in societies.

In RD research different types of solidarities are active involving respectively persons suffering from the same RD and their families, restricted communities or ethnic groups sharing a similar genetic background; persons suffering from different RDs; researchers working on a specific RD or a group of RDs and society at large. The different types of solidarity that are active in RD research need to be balanced against each other and against conflicting values (Table 31.1).

The strength of solidarity among RD patients, rooted in the common need to deal with the same practical difficulties (i.e. lack of interest by the industry, lack of epidemiological data to be considered in healthcare planning, etc.) and the positive outcomes it carries to RD research, together with a policy of incentives for orphan drug development in many industrialized countries (i.e. in Europe the Regulation (EC) No 141/2000 on orphan medicinal products passed in 1999 [12]) is making RD research very appealing for the drug industry, getting the RD sector out of the niche.

Table 31.1 Type of solidarities in RD research

Name	Roots	Actors	Actions	Interests to be balanced
Solidarity among the same RD group	Same illness experience	Patients	Informational, psychological and practical support	Costs in terms of time and resources
	Same genotype or phenotype	Families	Funding and fundraising activities	Possible competition with other RD groups
		Ethnics groups	Donation of samples and data	Respect for patient autonomy
			Agreement to data sharing and matchmaking	Protection of confidentiality
			Participation to clinical trials	Risks in early phase trials
Solidarity among different RD patients	"Being rare" same practical difficulties (access to information, services, lack of knowledge, etc.)	RD patients associations	Informational and practical support	Costs in terms of time and resources
			Training and patient empowerment	Equally involve RD patients
			Lobbying activities to increase visibility of RDs as a whole and drive public investment in RD research	Equally distribute funds for research on different RDs
				Possible competition with other research fields (i.e. common diseases)
Solidarity from researchers to patients: reciprocity	Reciprocity with RD patients	RD researchers	Identify the lines of research that are most promising for patients but may not be "the most competitive"	Competitiveness in science
			Share results with patients	
			Share knowledge and optimize access to resources in order to obtain better results for patients	Recognition in research
			Collaborate with patients to identify their real needs	
			Acknowledge patients expertise	

Collaborative solidarity with other researchers	Same practical difficulties (lack of expertise, lack of data and samples)		Provide fair access to data and samples	Maintain competitiveness
				Respect for patient autonomy
			Share knowledge	Protect confidentiality
			Acknowledge databases and biobanks in publications	(Modest) costs in terms of time
Broad/ social solidarity	Vulnerability of all members of society to illness, disease and disability	Payers, funders, society at large	Regulate research in order to allow better outputs	Ensure equal funding for research on different RDs
			Enhance policies for "shared" knowledge and non competitive acknowledgment	Keep the research environment competitive
			Fund RD research by general contribution	Maintain high research quality and research freedom
			Fund research infrastructures	Ensure funding for both clinical and translational research
			Fund care and treatments for RDs	Fund care and treatment for all diseases and welfare in general

This is resulting in an ever growing number of applications for marketing authorizations of orphan medicinal products which are then reimbursed by the general contribution following negotiations among national welfare systems and the industry, with increased scrutiny on sustainability [13]. Thus, the results achieved in RD research, also thanks to solidarity(ies) among RD patients and researchers, are creating new solidarity needs at the institutional level. In order to ensure RD patients proper access to orphan drugs we can observe a social level of solidarity in different countries where a joint effort is required to negotiate the price of orphan drugs with pharmaceutical companies. The involvement of all partners that collaborate to RD research and orphan drug development, including RD patients, clinicians, charities and public funders, will help keeping a right perception of fairness and preserve society's willingness to invest on RD research.

31.3 Solidarity Among Patients Suffering from the Same RD

Solidarity among persons suffering from the same RD is rooted in the common phenomenological experience of "illness" of RD patients, intended as the ill health the person identifies herself with, based on the perception of physical or mental symptoms [14].

The experience of illness carries a need to understand, control and manage physical, psychological and behavioral symptoms and to deal with the possible psychological and social consequences of such symptoms (i.e. not being trusted by others in the absence of clear signs, dealing with social stigma when signs are too evident, etc.).

Living with a rare disease is a very stressing and perturbing experience and the rarity of a condition is accompanied by a sense of loneliness and social isolation which leads RD patients to look for each other on the web or in existing patient associations to find emotional, informational and material support [15–17].

Solidarity inside the same RD group is based on a sense of similarity, equality and reciprocity among patients. The special solidarity that ties up persons suffering from the same RD and disabilities may help them to turn vulnerability into strength and join efforts to set up RD patient associations where they can share experiences, knowledge and information and organize common actions as well. In a context of human isolation, RD patients and their families are particularly active and keen to devolve substantial time, financial and other material resources to increase knowledge on their condition, and they are usually very favorable to donate biomaterials and collect and share registry data to promote research activities in their RD of interest [18–20]. Without this close solidarity among "same RD" patients research on RDs would not be made possible [21].

In genetic diseases solidarity may be strengthened by familiar and community ties. Moreover, persons affected by genetic diseases share not only common experiences and feelings but a common genetic setting. Solidarity with one's own genetic group carries a strong moral effect in encouraging people to participate in research.

This is particularly clear for very rare monogenic disorders where the number of patients and families may be very small even at the global level. If the persons who have the affected gene do not want to participate in research, the medical situation for the group with the same gene could hardly be improved or improvement may be slowed down. Thus some argue that possessing a gene that is known to cause a RD carries a responsibility to make one's biological material available for research in the hope of obtaining better health outcomes in the future for one's group.

According to Harris [22] the argument concerning the duty to participate in research should be compelling for anyone who believes there is a moral obligation to help others. Also, the obligation derives from an appeal to the unfairness of being a "free rider", enjoying the benefits of scientific research without having contributed to it.

This includes minimally invasive and minimally risky procedures such as participation in registries and biobanks, provided that strong safeguards against wrongful use are in place [23] and that proper procedures for involving patients in the decision making process are taken [24, 25].

We agree that participation holds moral value, but transforming it from a moral duty into an obligation to participate overrules some relevant individual rights that we believe should not be challenged such as the right to individual integrity and autonomy. There is a moral duty to help children in need in the world, to end famine, but this is not translated into individual's obligation. Obligation holds negative aspects that also imply that society would/could not contribute otherwise and that on a societal level the benefits are so great and fundamental (as it happens with emergencies, epidemics etc.) that we can overrule individual rights. It also should imply that society is ready to respond to the threats posed by such a practice (abolishing consent). We can identify a double standard, or at least an incongruence in Harry's theory that calls for scientific freedom as a high value against individual freedom. In fact if the "social fundamental need of research" was true and comparable with an emergency situations where individual rights are overruled, then also scientific freedom would fall into the emergency be pushed into a "result for society driven" policy, "highly regulated and controlled" in order to get most of the social benefits out of it.

With this paper we would like to showcase that RD research is a clear example where solidarity and partnership can play a highly positive role without imposition that is built on a culture of trust that enhances participation in a democratic and participative pathway, that benefits patients as well as research.

RD research provides many examples in which it is clear that partnership with patients and providing an active role for them in designing research together is a key element for enhancing participation and support for research, not only on the individual project level, but also on a political one [25].

With respect to genetic diseases, the basis for a principle of solidarity is particularly strong, provided that adequate protection against discrimination is in place. Individuals need to be protected and respected, and there needs to be adequate data protection to safeguard against misuse, discrimination and stigmatization.

One risk of this "same RD" solidarity is that it may be too narrow and not be a drive for common actions in the field. A gap can be identified where the interests

and needs of patients within one group have to be balanced with the needs of other patients, for example to gather the attention of the drug industry to fund research on a RD, or of public health authorities to reimburse medicines to treat a specific rare condition [26].

In communities where a genetic disease is prevalent there is the risk that the majority decides to fund one specific treatment by denying similar coverage for a similar condition or by denying coverage treatment for more common conditions. This danger exists whenever a single ethnic group dominates the state and considers treatment for a disease that solely affects its own welfare [27]. Also, this danger may be exacerbated when the costs of orphan drugs are too high.

Joint patients endeavor such as EURORDIS [28], Telethon [29] and other joint efforts show that this can be overcome through clear policies and transparency in the utility of a broader approach.

31.4 Solidarity with Other Patients

Persons suffering from different RDs are linked to each other even though they do not share the same "RD specific" illness experiences and they have partially competing interests. What all RD patients are sharing is the experience of 'being rare' which is a key feature of the category of rare diseases [30].

Different RD patients and their families are confronted with the same wide range of difficulties going from lack of access to correct diagnosis, lack of information about the disease itself and about where to obtain help, lack of scientific knowledge on the disease, social consequences of the disease like stigmatisation, discrimination and isolation, lack of appropriate quality health-care, high cost of the few existing drugs and care and inequities in availability of treatment and care [21]. Due to their rarity, patients with RD have always been convinced that numbers means power [31].

Actually in the USA, more than 1200 patients' organisations active in one or more RDs are linked to one of the major networks such as the National Organization for Rare Disorders (NORD) [32] and the Genetic Alliance [33]. Also in Europe a similar number of organisations are federated by the European Organisation for Rare Diseases (EURORDIS) [28], set up in 1997.

These organisations contribute at all levels to RD research, from funding research to dealing with regulatory aspects of the orphan-drug market, to producing educational information and organising training activities for RD patients, to help designing public policy and study projects.

Thanks to their work many industrialised countries have passed specific legislation defining epidemiological or/and economic criteria for designation of orphan status and consequent incentives to counteract the neglect of orphan diseases in industrial research.[1]

[1] US (1983), Japan (1993), Taiwan and Australia (1997), European Union (EU) (2000) and Canada (2008).

The laws and regulations passed in recent years to provide incentives for orphan drug research could be interpreted as attempts of democratic society to pursue the principle of non abandonment and to counteract distributive injustice caused by market incentives [34, 35].

Without the coordinated efforts of federated associations like NORD, Genetic Alliance and EURORDIS many achievements of the RD community would have not been possible, also in the field of RD research.

Under their impulse, and following empowering initiatives carried by umbrella organisations, RD patients are contributing to research in many ways. Besides supporting financially RD research projects, collecting registry data and donating tissues, blood, or other specimens, they are taking a more active role in the search for a cure for their disease and there is growing worldwide recognition of their role as active study collaborators.

The collaborative partnership that exists among RD groups and the scientists involved in RD research is unparalleled in other areas of medical research and product development [18, 25, 36].

31.5 Solidarity by RD Researchers: About Reciprocity

Solidarity is also a concern for RD researchers.

Up to now, research into RDs has typically been fragmented and organised in silos, where different kind of data for different RDs are kept separately and are not collected in interoperable format.

Research is increasingly based on data and the need to collect and share data is critical especially in RD studies, where few patients and data may be dispersed in different countries and institutions [37].

As in other research field, in RD research there is a strong call to making data more Findable, Accessible, Interoperable and Reusable (FAIR) [38].

Independently of their fields of expertise, RD researchers encounter similar problems in their activity, like the scarcity of knowledge and expertise and the rarity and unease accessibility of RD data and samples. Moreover, besides the scarcity of resources there are barriers to their use, due to ethical and legal constraints (privacy barrier) and to cultural and motivational barriers of researchers as well [39, 40].

While solidarity is a strong moral framework for patients, this framework has rarely been applied on the research side. Is there a duty to solidarity for researchers? If sharing has been defined as compelling in order to get good results, then this puts this practice into a solidarity approach to patients, even if it may be difficult to balance with the framework of competitiveness that is dominant in science. Creating a solidarity approach in research may give strength to the idea of reciprocity to patients and contribute to mitigate the role of competition.

Also the apparent return of data sharing practices in terms of saving lives (i.e. in epidemics outbreaks) and accelerating scientific discoveries is increasingly supporting the view that researchers and institutions have a moral duty to make data avail-

able [41] and that data sharing has become an "ethical and scientific imperative" [42] even though there is controversy about which data should be shared, with whom, and how quickly.

In RD research there are different aspects that make collecting and sharing data and samples morally desirable, all related to reciprocity to patients and solidarity with colleagues as well:

- enhance efficacy and data completeness: research on a specific RD or group of RDs requires the systematic collection of data possibly from all known patients (data completeness), especially when the disease is ultra rare and causative genes for the conditions have not been found (i.e. in undiagnosed diseases). Sometimes the matching of just two cases that share a suspicious variant and a similar phenotype provides sufficient evidence to causally implicate the gene [43]. Thus, physicians should be encouraged to propose matchmaking or participation in registries to RD patients that they encounter in clinical practice and, if patients agree, to report them to the relevant RD registry or matchmaking databases.
- Solidarity in providing data that may improve the study of other diseases and contribute to science: data sharing may equally benefit research on different RDs and common diseases sharing common features (genes, phenotype traits, pathways, etc.).
- Enhanced possibility to feed back results to patients: Sharing information on many levels provides higher chances to get results. Even though data and biomaterials are usually donated by patients in a spirit of solidarity, there is still e hope of getting advantages in terms of either information (in case of undiagnosed diseases) or therapies and more information for individuals in the family or for the disease group; so researchers have a moral duty of reciprocity towards their patients, associated with the duty to share samples and data in a fair manner to provide better chances for them to get results [44];
- Social interest in the investment: RD registries and biobanks are often set up thanks to the financial support of patients and patient organizations, short-term research grants, private donations, membership fees, or fees for service [45]. Thus, as for public (co)funding, researchers must ensure that the data and samples are used as much as possible to ensure returns from public and private investment, and that best use is made of them, according to the values and preferences of donors and to the expectations of funders as well [46].

While data sharing aims to benefit RD patients and the research community as a whole, it may place large costs on the researchers attempting to share their data and as a result scientists are still not very keen to share data, especially in research on human subjects, were probably the impact of sharing would be higher [40, 47].

Researchers and institutions still tend to behave on the assumption that there is no operating duty to share their data, and that free and unconditioned accessibility is not the best option [48–50].

To promote data sharing there is a need for more reciprocity, removal of obstacles and incentives from other researchers and society.

In this regard solidarity needs to be expressed by society on a regulatory level in order to maximize outputs of research and change or remove obstacles to perform research and to return results to patients.

Incentives may consist in clear guidance on data citation [51, 52] and recognition and, independently of the publications, if a dataset is made publicly available it would be useful to track the number of access from the source.

This is what happens for instance in data repositories curated by the National Center for Biotechnology Information (NCBI) and the European Bioinformatics Institute (EBI) where data producers and annotators are uniquely identified along with their data and accession numbers to database entries are routinely used for data retrieval. Tagging a database as "highly accessed" may be used to accrue credit for their authors in a systematic process of microattribution [53].

Researchers should be offered the possibility to keep control over the data throughout priority right for publications [54], participation in federated systems of data sharing where the data are released after proper evaluation of requests by a data access committee involving the RD researcher in the evaluation.

Data sharing should facilitate new collaborations with other RD researchers, also following the assumption that a researcher's willingness to share research data is related to the quality of his work [55].

Rewards would also come from a data sharing culture [56, 57] that in RD community is being promoted by different initiatives [58] and international research consortia like the International Rare Diseases Research Consortium (IRDiRC) [59] and The Global Alliance for Genomics and Health [60].

31.6 Broad Solidarity: Social Support and Policy

The extent of solidarity in RD research and its positive outcomes in terms of political and legal achievements and support for research infrastructures is making the RD field become attractive for public and private investments. The development of new treatments for rare diseases is being fostered by the legislation passed in different countries to encourage the drug industry to invest in the development of orphan drugs (i.e. in Europe the Regulation (EC) No 141/2000 on orphan medicinal products passed in 1999 [12]) including incentives such as protocol assistance for clinical trials, scientific advice from EMA before the submission for marketing authorization and market exclusivity of 10 years once the medicine is marketed.

Only in Europe by the end of 2015, 89 different orphan medicinal products had received authorization to enter the market from the EMA's Committee for Medicinal Products for Human Use, and an increasing number of applications for orphan designation are submitted to EMA each year [61].

If the therapeutic benefits of orphan drugs have been substantial in some cases this success is counterbalanced by the very high costs of available treatments which also accumulate with time being most RD congenital or requiring long term care [62–64]. The high costs of orphan drugs present difficult dilemmas for public health

officials as from an ethical standpoint a patient cannot be denied effective orphan drugs on an economic ground [65].

However, access cannot be separated from pricing and responsibility to afford access to the orphan drug for a RD patient cannot rely only on Governments purchasing capacity, also pharmaceutical companies have an implicit obligation to put patient wellbeing and resource utilization on equal footing with return on investment [35, 66].

Strategies to moderate the prices of orphan drugs on the part of public health services have been proposed, and include: (a) rigorous adherence to clinical indications for therapy and request to validate the prescription by a designated centre of expertise; (b) set up of diagnosis-based, regularly updated registries with high-quality data to assess the safety and efficacy of the drug in a real life setting; (c) systematic negotiation of the prices of orphan drugs taking into account the documented costs of drug development; the estimate number of eligible patients; and a reasonable margin of profit should be allowed [64].

There are successful experiences in Europe based on broad institutional solidarity approaches among the welfare states of three countries: Belgium, Luxembourg and the Netherlands, which are aimed at ensuring sustainability for orphan drugs. From 2015, the three states have adopted a common strategy on negotiations about the pricing of orphan drugs which is putting the health ministers in a better position to negotiate favourable pricing for the orphan drugs. By their side, pharmaceutical companies also benefit from this strategy as by combining the population of more countries they increase their market size, for which they only have to submit one reimbursement dossier [67].

Following these experiences a wider international collaboration among public health authorities in different countries would help improve the process of negotiation of pricing preserving the social perception of fairness and society's willingness to invest on RD research.

Negotiation should involve all the partners that, besides pharmaceutical companies, collaborate to RD research and orphan drug development, including RD patients who invest their time and resources in all phases of research and assume the risks of participating in clinical trials, physicians who collaborate in clinical trials on behalf of their patients, and the scientific community that develops the basic mechanistic understanding of a disease.

Significant collaborative efforts are still required among all these partners to meet the unmet diagnostic and treatment needs for patients affected by RDs worldwide [68]. Solidarity plays a relevant role in RD research, and informed lots of the practices in science introducing unprecedented models of collaboration on all levels. RD research can provide some good hints to rethink the framework in which medical research is performed. Where patients are partners everyone plays her role and solidarity becomes a shared and reciprocal framework.

31.7 Conclusions

In this paper we suggest that different levels of solidarity are playing a role in RD research. Recognizing the interplay among them may help in shaping fair policies where the role of the different players is equally recognized and enhanced by proper participatory mechanisms on the political table. Recognizing the role of patients and of society in building the research world that leads to results may put an emphasis on the fact that experts are not the sole players and that more reciprocity mechanisms should be promoted in order to keep this virtuous mechanism working [69].

We argue that RD research provides a valuable model for identifying the solidarity mechanisms that could be used to frame other types of patient/researchers relationships. Gaps in the solidarity model can be identified on the reciprocity level and on the broader societal support. Solidarity has been often invoked in relation to patients in order to create policies in which they could collaborate more to research. This type of solidarity is given for granted, since patients are theoretically the one that ultimately would benefit from research [23].

Solidarity has been used less referred to the research level where higher standards of collaboration (overcome models based purely on competition), sharing resources (sharing existing data and results) and societal inputs (ad hoc regulations and policies to increase and praise collaborative results) could really provide inputs to run "the extra mile" or simply to optimize resources allocated often thanks to patient's commitment and solidarity.

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Chapter 32
Bridging the Gap between Health and Social Care for Rare Diseases: Key Issues and Innovative Solutions

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Abstract Bridging the gaps between health and social care for rare diseases is not only necessary but crucial to increase the life expectancy, quality of life and autonomy of people living with a rare disease, supporting them in the full realisation of their fundamental human rights.

The complexity of rare diseases, their strong relation to disability and the current unmet social and daily life needs of people living with a rare disease must not be underestimated and require urgent attention from all stakeholders involved in care provision, from healthcare to social and community services.

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The Commission Expert Group Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies, adopted unanimously in April 2016, by the representatives of European Member States and the other rare disease stakeholders, clearly set the tone for the need to promote measures that facilitate multidisciplinary, holistic, continuous, person-centred and participative care provision to people living with rare diseases.

These recommendations, sided by other recent policy developments at European and national levels, represent an important policy step into approaching rare diseases' complex challenges in regards to holistic care provision.

Innovative approaches aiming at bridging the gap between health, social and community service and support providers are currently being developed and tested in different European countries: standards of care, networks of expertise, case management services, one-stop-shop services, amongst others.

These ongoing pilot approaches, presented in this chapter, have the power to inspire future policies and the effective and efficient implementation of holistic care pathways for people living with a rare disease, bringing about significant changes for patients, carers, care providers, competent authorities and the society at large.

Nonetheless, the challenges to fully address this issue remain numerous and other key issues will also need to be taken into account when moving forward with the implementation of measures that aim at bridging the gaps between care providers and providing holistic care to people living with a rare disease.

Keywords Integrated care • Holistic • Clinical pathway • Disability • Social services • Case management

32.1 Introduction

Rare diseases are heterogeneous in terms of prevalence, age of onset, clinical severity and outcome. However, they share various common features: they are often serious, chronic, progressive, degenerative and associated with co-morbidities [1].

The rarity and complexity of rare diseases highly condition the availability of knowledge about their impact on patients' and families' life expectancy, daily life and autonomy. On one hand, patients affected by a particular rare disease are few and spread geographically; on the other hand, information and expertise on specific rare diseases are often scarce and scattered.

If providing holistic support to any given patient is certainly a challenge, doing so for a person affected by a rare disease implies facing the added challenges posed by rarity and high complexity.

This chapter will both highlight the results of recent studies on the relation between rare diseases and disability and provide an insight in regards to the impact of rare diseases on the daily life of people living with a rare disease and their families.

The challenges faced when attempting to provide holistic care to people living with a rare disease and the current European policy scenario will also be presented, as essential elements to support the development of innovative care pathways and integrated care solutions.

Lastly, this chapter will present recent innovative approaches aimed at reducing the gaps between health, social and community services to improve holistic care for people living with a rare disease and their families.

32.2 Rare Diseases and Disability

> *«When you have a rare disease it feels like you are so alone and no one cares»,* Janet, mid 50s, living with Alkaptonuria [2].

In recent years, several initiatives and studies have focused on bringing to light the relation between rare diseases and disability.

In 2008, the European Rare Disease Task Force put the spotlight on the significant impact of rare diseases, on patients' life expectancy and disability. The task force concluded that rare diseases substantially affect patients' life expectancy and altogether account for a considerable rate of the early-life deaths and life-long disabilities in the European population [3].

Data from a survey conducted in Italy with 516 families, involving parents of patients with a rare disease, has shown that nearly 70% of patients had a disability: 49.2% of patients were affected by a motor disability, 33.3% by an intellectual disability and 22.4% by both motor and intellectual disabilities [4].

In a study involving 46 Australian families living with various rare diseases, 63% of respondents were found to have some level of disability and 13% had a severe disability [5].

An analysis of a local registry including 1739 children with severe impairments conducted in France has shown that rare diseases often lead to various types of disability, with different severity levels: 3.3% of severe psychiatric disorders, 16.0% of intellectual impairments, 37.2% of hearing impairments, 41.2% of neuromuscular, skeletal, movement impairments and 81.1% of visual impairments identified in the study resulted from a rare disease. The study has also concluded that a rare disease was at the origin of 26% of the cases of severe impairment [6].

These figures highlight the important and significant relation between rare diseases and disability, demonstrating that rare diseases are the cause of various severe impairments in the general population, and this is specially the case for most severe disabilities. Moreover, a high percentage of people with a rare disease is affected by motor or intellectual impairments, which can occur simultaneously.

Although more therapies are becoming available, there is currently no treatment for 4000 to 5000 rare diseases [1] and when treatments are available, they are not always able to minimise the complex impairments generated by the disease. Additionally, as a consequence of improved diagnosis, research, care and treatment, more children with a rare disease now reach adulthood. However, their disability frequently worsens over time and leads to a considerable loss of autonomy [7, 8].

Little is known on the level of visibility and recognition of the consequences of rare diseases within the national systems responsible for assessing functionality and for providing corresponding compensating measures.

A recent study conducted in the Spanish region of Murcia, by the Information System on Rare Diseases of the Region of Murcia (SIERrm), has revealed that one in every three persons with a rare disease in the region have obtained the official recognition of their disability (34.0% in the case of women, 33.5% in the case of men). 47% of these have classified by the assessment system as having a grade 3 disability (33–64%), 29% as having a grade 4 disability (65–74%) and one in every four individuals were placed into the maximum grade of disability (equal to or above 75%) [9].

This data, although giving a snapshot of the recognition of disability of people living with a rare disease in the region, has not been cross-referenced with patients' perspectives on whether they consider that the assessment of functionality is able to take into account their specific impairments, the accumulation of their various impairments and other important factors such as degeneration and acute disease periods.

The collection of data and knowledge on the impact of rare diseases on patients' functionality remains a challenge. Furthermore the recognition and adequate compensation of the disabilities of people living with a rare disease by competent authorities at national level is an even greater challenge which, if not addressed, adds to the social and economic vulnerability of people living with a rare disease and their families.[1]

32.3 Unmet Needs of People Living With a Rare Disease

> *«MP has so many medical appointments, and therapy sessions that I had to stop working. I have only 4 hours free to come back home, do the cleaning, cook, go to supermarket, deal with the infinite bureaucratic processes to get a special school, special social wealth assistance and ask for budget support. Then, I pick him up, come back home and accompany him in all the exercises his therapist has given him. I go to bed exhausted and I don't get a lot of help at home. I loved my work and I miss it a lot! At this moment, it is impossible for me to find a job»,* Sandra, mother of MP, living with Congenital Disorder of Glycosylation [2].

Rare diseases and disabilities have cumulative effects in terms of social exclusion [9]. The social challenges faced by people living with a rare disease are numerous and seriously affect their dignity, autonomy and other fundamental human rights expressed in the Universal Declaration of Human Rights and in the United Nations Convention on the Rights of Persons with Disabilities [10].

[1] Orphanet, the reference portal for information on rare diseases and orphan drugs, is currently working on describing the functional consequences of each rare disease, having developed the Orphanet Functioning Thesaurus, derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007). More information is available here: http://www.orpha.net/consor/cgi-bin/Disease_Disability.php?lng=EN.

People living with a rare disease face challenges with, for instance, access to school and education [11], employment, leisure, transport, adapted housing and bank credit.

In regards to employment, the EURORDISCare Survey programme conducted with over 12,000 patients in 23 countries (2002–2008), has demonstrated that patients and families often have to reduce or stop professional activity as a consequence of a rare disease: 1/3 of the respondents reported that a patient in their family had to reduce or stop professional activities due to the disease and an additional 1/3 of the respondents reported that one member in the family had to reduce or stop professional activities to take care of a relative with a rare disease [12].

With the reduction of professional activity, families are forced to cope with a significant loss of income and find themselves in financial difficulties [13]. And compared to people living with more common diseases, people living with a rare disease are more often facing financial and housing difficulties [14].

In a study conducted by the National Organisation for Rare Diseases in the United States of America (NORD) among 138 parents of children with rare diseases, 77% of respondents reported that living with a rare disease had led to a financial burden for the patient or his/her family; 32% of these reported to face an "extreme" burden [15].

Patients enquired in the 'Study on the Situation of Social-sanitary Needs of People with Rare Diseases in Spain ENSERIO (750 patients) also reported on some specific financial investments that they were forced to make as a consequence of their disease: 27% of the respondents spent income in adapted transport, 23% in personal assistance and 9% in adapting their house [16].

Moreover, many people with a rare disease need to relocate to another home adapted to their health needs or situated closer to the health or social services, which affects both their financial capacity and their social integration: 1/5 of the respondents of the EURORDISCare Survey programme reported that they had to move to another home [12].

Numerous people living with a rare disease also have important needs in terms of assistance and social support. According to the Spanish study ENSERIO, people living with a rare disease generally need support for the following activities: domestic life (46%), transport/mobility (42%), personal mobility/posture (40%), leisure activities (37%), educational or professional activities (39%) and self-care (32%). Only 1 in 10 patients interviewed in this survey has stated to not need any sort of assistance in daily life [16].

As a consequence of these various health, social, economic and daily life challenges, patients and families frequently need support from a social worker: 1/3 of the respondents of the EURORDISCare Survey required assistance from a social worker in the 12 months preceding the survey. Out of those, 1/3 indicated that they actually met the social worker with difficulties or did not meet one at all [12].

On top of those challenges, people living with a rare disease feel that they face discrimination: in the ENSERIO study, patients have reported to feel discriminated in: leisure activities (32%), education (30%) and daily activities (29%). 32% of

patients also felt discriminated in the labour market, either when searching for a job (17%) or at their current job (15%) [16].

The particular context of rare diseases, including the challenges in regards to diagnosis, feelings of exclusion and lack of treatment generate a considerable moral suffering [8] and burn out situations are frequent among patients and family members.

Rare diseases therefore pose a considerable burden on patients and families and according to a survey to 20,500 patients with chronic diseases, 8,2% of which were rare diseases, the experience of people living with rare diseases is worse than the experience of other chronic patients, in terms of loss of social and economic activities, as well as medical care [14].

32.4 Specific Challenges of Social Care Provision to People Living with a Rare Disease

> *«Only the strong survive»,* mother of rare disease patient while navigating the welfare system [5].
>
> *«It is not possible to get a 'check list' of all the people you need to talk with. Also, service providers differ in the amount of interest they show»,* Denis Ryan, husband of Anne, living with Huntington Disease [2].
>
> *«If anyone would coordinate my daughter's care it would be wonderful as I've been doing it for years», parent of patient with 1q21.1 micro deletion* [17].

The particular features of rare diseases create huge obstacles to the provision of holistic, integrated care, leaving many health and social needs unmet [10]. A patient with a rare disease is seldom a standard beneficiary, due to the combination of rarity, complexity and lack of treatment [18].

The experience of the healthcare system is worse among patients with rare diseases than among patients with more common chronic disorders like cardiovascular diseases, respiratory diseases and diabetes. Additionally, bottlenecks in care for rare diseases have been mentioned as an important factor adding burden to patients' and families' daily life [14].

Various hurdles in care provision for people living with rare diseases have been identified through the work of the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action (2012–2015)[2] Work Package 6 on 'Provision of Specialised social services and Integration of Rare Diseases into Social Policies and Services',[3] via literature reviews and through the organisation of a multi-stakeholder

[2] The EUCERD Joint Action: Working for Rare Diseases, co-funded by the EC, supported the activities and mandate of the EUCERD until the end of 2013 and the activities of the CEGRD, from 2014. More information available at: http://www.eucerd.eu/?page_id=54.

[3] More information available at http://www.eucerd.eu/?page_id=304.

workshop dedicated to "Guiding Principles for Social Care in Rare Diseases" (2014)[4]:

- Scarcity of information on rare diseases and their consequences [19];
- Lack of knowledge on rare diseases by the various professionals involved in care provision, leading to lack of understanding, inadequate care and reluctance to treat patients [12];
- Patients' and families' need multidisciplinary, continuous support from a range of care providers across sectors managed by different competent authorities and civil society organisations and funded by different financial models [18]. Looking at health services alone, the average patient requires more than nine different health services over a two-year period [12];
- Lack of communication and coordination within and between health, social and local services [20];
- Care systems design is usually focused on common diseases and mainstream services are not flexible enough to take into consideration the specific needs of people living with a rare disease [12];
- Care pathways are fragmented and extremely difficult to navigate for patients and families [18];
- In most cases, the management and coordination of care has to be done by patients and families, generating a considerable burden for patients and families [21].

These difficulties in accessing appropriate care are of particular importance to people living with a rare disease and their families, as they perceive that their quality of life is more closely linked to the quality of care provided than to the severity of their illness, or the degree of the associated disabilities [12].

To overcome these obstacles and challenges, the provision of care to people living with a rare disease should be holistic, multidisciplinary and tailored to each person's unique needs [13].

Coordination of care is therefore critical for people living with a rare disease as they often need care and support from different health professionals, social workers and other social and local service providers [12]. This implies the provision of a set of health, social and community services, including rehabilitation, day-care, home care, personal assistants, respite services, adapted schools and work place, psychological support and social prescribing, amongst others [18].

For this reason, the provision of holistic and integrated care to people living with a rare disease requires the involvement of all stakeholders.

[4] More information available at http://www.eucerd.eu/?page_id=3449.

32.5 Current Policy Scenario in Europe

European Member States and the European Commission recognise the necessity of coordinating care provided to people living with a rare disease, nationally and internationally.

Back in 2008, the European Commission adopted the Communication "Rare Diseases: Europe's Challenges"[5] along with a proposal for a European Council Recommendation. The "Council Recommendation on an action in the field of rare diseases"[6] [22], was adopted on 8 June 2009, and recommended that Member States:

- Establish and implement plans or strategies for rare disease in order to aim to ensure that patients with rare diseases have access to high-quality care, within the framework of their health and social systems;
- Organise healthcare pathways for people living with a rare disease through the establishment of cooperation with relevant experts, and exchange of professionals and expertise within the country or from abroad when necessary;
- Encourage Centres of Expertise[7] to be based on a multidisciplinary approach to care when addressing rare diseases;
- Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: (a) the sharing of best practices on diagnostic tools and medical care as well as education and social care in the field of rare diseases.

As a consequence, the development of National Plans[8] for rare diseases has been encouraged over recent years, alongside the organisation of national care pathways - embedded into the health system, including Centres of Expertise and national networks for rare diseases – and the development of European Reference Networks for Rare Diseases.[9]

Currently, 20 EU Member States have developed and adopted a national plan or strategy for rare diseases, while four Member States are discussing a second national plan for rare diseases and France is moving with the elaboration of the third national plan.

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[5] The European Commission Communication can be consulted at: http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf.

[6] The Council Recommendation can be consulted at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF.

[7] Centres of Expertise are physical expert structures for the management and care of RD patients. Each CE is specialised in a single RD or group of RDs and share the mission of providing patients with the highest standards of care to deliver timely diagnosis, appropriate treatments and follow up. More information available at http://www.eurordis.org/sites/default/files/publications/fact-sheet_Centres_Expertise.pdf

[8] More information available at: http://www.europlanproject.eu/Content?folder=1.

[9] Further information on European Reference Networks for Rare Diseases available at http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm.

The national alliances of rare disease patient organisations across Europe had a crucial role in promoting these national strategies by organising conferences[10] to bring stakeholders together in shaping national policies for rare diseases. These national conferences have been organised in conjunction with EURORDIS who coordinated the entire process to ensure a common approach through European funded projects:

- EUROPLAN Project (2008–2011): 15 national conferences organised;
- EUCERD Joint Action (2012–2015): 25 national conferences organised;
- RD-ACTION (2015–2018): 22 national alliances of rare disease patient organisations have expressed interest in regards to organising a national workshop focused on national plans for rare diseases. Various of these workshops will focus on moving towards the implementation of measures in specific thematic areas of the adopted national plans/strategies, including social services and policies.

The EUROPLAN final report (2010–2011) [23], recommended taking into account the need for social inclusion, psychological and educational development for people living with rare, chronic and debilitating diseases. The report also recognised the instrumental role of social services to the empowerment, the wellbeing and health of people living with a rare disease.

Several adopted national plans include specific measures to facilitate coordination between health and social and support services. And various countries have already started to implement some of these approaches.

The second French National Plan for rare diseases (2010–2014)[11] [24], for example, promotes the development of links between care providers, namely by the promotion of "the use of complex case managers and "insertion technicians" (*techniciens d'insertion*). This plan also recommends the reinforcement the knowledge on rare diseases amongst health and social professionals.

The UK Strategy for Rare Diseases (2013)[12] [25], on the other hand, proposes that patients should have an overall care plan to manage coordination of care between health and social services. This care plan should involve the extended family of the patient.

According to the National Rare Disease Plan for Ireland (2014–2018) [26], due to the complexity of the various rare diseases and in order to provide efficient formal guidance and support to care coordinators, it is recommended that a rare disease care pathway be developed to provide for high-quality care, to assist in guiding patients through care and social services, increase efficiency of state resources and reduce waiting times for accessing support and social services.

[10] The EUROPLAN National Conferences are aimed at fostering the development of comprehensive National Plans or Strategies for Rare Diseases addressing the unmet needs of patients living with a rare disease and integrating current European policies and recommendations in this field.

[11] Available here: http://www.orpha.net/actor/Orphanews/2011/doc/Plan_national_maladies_rares.pdf

[12] Available here: http://health.gov.ie/wp-content/uploads/2014/07/EditedFile.pdf.

Various sets of recommendations of the European Union Committee of Experts on Rare Diseases (EUCERD)[13] to the European Commission (EC) and Member States have been adopted over the last years, focused on promoting a set of important measures and quality criteria,[14] supporting the development of multidisciplinary healthcare pathways at national level as well as of European networks.

The EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases[15] [27] highlight the key role of health expert services in facilitating integrated care provision, recommending that Centres of Expertise:

- Bring together, or coordinate, within the specialised healthcare sector multidisciplinary competences/skills, including paramedical skills and social services;
- Provide education and training to (…) non-healthcare professionals (such as school teachers, personal/homecare facilitators);
- Contribute to and provide accessible information adapted to the specific needs of patients and their families, of health and social professionals.

On the other hand, the EUCERD recommendations on European Reference Networks for Rare Diseases[16] [28] state that these European Reference Networks should:

- Collaborate with each other, with patient groups, health and social care providers;
- Follow a multi-disciplinary approach;
- Function as a platform to share experiences and promote cooperation between Member States, to develop precise descriptions of the services required and elaborate common guidelines.

More recently, the unanimously adopted Commission Expert Group on Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Policies and Services state that Member States should ensure that people living with a rare disease are afforded the same standards of care and support as the ones available to other citizens with similar requirements, and should recognise the particular challenges posed by rare and complex conditions [10].

The recommendations promote the development of holistic and integrated care pathways for rare diseases affirming that integration of care and services, including health, social and support services as well as the community at large, are essential

[13] The EUCERD was charged with aiding the EC with the preparation and implementation of Community activities in the field of RDs, in cooperation and consultation with the specialised bodies in MS, the relevant European authorities and other relevant stakeholders. In 2014, the EUCERD was replaced by the European Commission Expert Group on Rare Diseases. More information available at: http://www.eucerd.eu/.

[14] EUCERD recommendations available at: http://www.eucerd.eu/?page_id=13.

[15] Recommendations available at http://ec.europa.eu/health/rare_diseases/docs/eucerd_centresexpertise_en.pdf

[16] Recommendations available at http://www.eucerd.eu/?post_type=document&p=2207.

to ensure appropriate care to people living with rare diseases[17] and Member States should include specific measures in this respect in their national plans and strategies for rare diseases (Box 32.1).

Box 32.1: European Commission Expert Group on Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies (April 2016) [10]

Recommendation 4: Member States should promote measures that facilitate multidisciplinary, holistic, continuous, person-centred and participative care provision to people living with rare diseases, supporting them in the full realisation of their fundamental human rights. In particular:

- Ensure that people living with a rare disease are afforded the same standards of care and support as the ones available to other citizens with similar requirements;
- Recognise the particular challenges posed by rare and complex conditions.

Recommendation 6: Transfer of information between care providers, within the limits of data protection legal frameworks, should be promoted to support holistic care provision.

Recommendation 7: Member States should promote coordination and networking between all parties involved in the care provision of persons affected by rare diseases, including public, private and civil society organisations as well as between providers and patient/disability organisations.

32.6 Bridging the Gaps Between Health and Social Care: Innovative Approaches

The challenge of providing holistic care to people living with a rare disease is huge and requires multidisciplinary teams, involvement of all stakeholders as well as change of perspectives, of care provision concepts and of services. The organisation of holistic care pathways at national level is essential to overcome this challenge.

Care pathways usually define best practices or essential care components for a group of persons with a given diagnosis or health condition and they determine locally-agreed-upon, multidisciplinary practices [29]. The term “care pathway” makes reference to how national systems seek to provide seamless care and treatment to patients, from the moment of detection and diagnosis [30].

[17] More information available at: http://ec.europa.eu/health/rare_diseases/docs/recommendations_socialservices_policies_en.pdf.

Despite the recent advances in policy, care pathways for rare diseases remain very complex in most Member States [31]. Different innovative solutions can be implemented in order to support the building of this integrated care pathway and to ensure that people living with a rare disease are cared for in a way that is adapted to their needs.

32.6.1 Quality Standards: Guidelines and Standards of Care

For those rare diseases for which there is a quality standard, mostly some kind of guideline - good practice, clinical practice or emergency – those standards often do not provide answers on the many issues regarding organisation of care. The standards of care in the Netherlands do describe the care needed and the organisation of it, for the entire health continuum of any specific chronic disease: early recognition and prevention, diagnostics, treatment options and monitoring, relapse-prevention, revalidation and reintegration [32, 33] (Box 32.2).

Box 32.2: Innovative Solution: Develop Modules of Quality Standards
The Dutch standards of care are based on the Chronic-Care model [34] and are norms, describing the minimal requirements of the care and its quality and organisation for a specific chronic disease, rare or not, from the patients' perspective [35]. The standards are written with care professionals and patient organisations and are authorised by a selected group of national medical societies and associations.

These standards of care can be viewed as multidisciplinary care management tools which define the different tasks to be undertaken by professionals involved in patient care and are essential to ensure equality in the level of care and services provided to people with a rare disease. They can be used to develop holistic health-care pathways for the disease in question. Each standard of care includes a general follow-up and monitoring scheme, that can be used by hospitals to develop their own healthcare pathway for a group of people with the disease in question. Such pathway is not limited to hospital care and comprises all required healthcare and social.

Between 2011 and 2015, the Dutch Genetic alliance has developed 16 standards of care for different rare diseases [36]. Several of these are now being implemented. The Dutch Genetic Alliance has been an important stakeholder in this process and keeps developing standards of care and other quality standards, according to a new national guideline [37]. This new national guideline makes it possible to develop only parts of a quality standard (called modules), that aim at answering questions that are based on bottlenecks that patients and professional caregivers face in daily life practice. As standards of care are expensive to be developed, this new way of "modular' development of a quality standard allows to develop many more organizational quality standard modules for many more rare diseases.

Several Member States are currently developing care pathways for rare diseases using quality standards. For example, France and the Netherlands are establishing standards of care, in which the organisation of care within the national health network is described for a certain rare disease (Box 32.3).

Box 32.3: Innovative Solution: Use a Simplified Method for the Development of Quality Standards

In France, by April 2016, 65 national good practice guidelines for diagnosis, treatment and follow-up of patients with rare diseases had been developed by expert health centres with the support of the French National Authority for Health (HAS). These include recommendations on social care (notably in the annexes of the document). In 2012, the HAS published a new simplified method to develop these guideline, aiming to boost the production up to 200 protocols in 4 years [38].

In 2015, this methodology and the validation procedure were simplified again which boosted the production of national guidelines. The production of these good practice guidelines is one of the main missions of the National Health Networks for Rare Diseases (*Filière de Santé Maladies Rares)*, in an pluridisciplinary approach and with an implication of patient organisations in the process.

In addition to that, Orphanet has developed since 2013 a series of "disability factsheets" (Orphanet Disability Encyclopedia - *Encyclopédie Orphanet du handicap)* that include a description of disabilities associated with a rare disease and some recommendations for social care. 36 of these factsheets had been published by May 2016 [39]. Orphanet also shares information or recommendations on social care established by other organisations in France or abroad.

32.6.2 National Networks of Expertise

In the national plans for rare diseases, national centers of expertise play an important role: these centers are the core of good health provision for people with certain (groups of) rare disease(s). Centers of expertise are responsible for gathering and coordinating knowledge and care within the MS and as such are key players when it comes to cooperation with other care providers.

Certainly, national centers of expertise need to cooperate with other medical and social services. Such a cooperation can be well defined and organised in Member States through the development of national networks of expertise for a certain (group of) rare disease(s) (Boxes 32.4 and 32.5).

Box 32.4: Innovative Solution: National Networks for Rare Diseases
In France, 23 National Health Networks for Rare Diseases (*Filière de Santé Maladies Rares – FSMR*) have been created by the Ministry of Health to coordinate actions between different stakeholders involved in care provision to people living with rare diseases.

Each network of expertise brings together: national centres of expertise (*Centres de Référence Maladies Rares*); regional centres of expertise that are attached to these national centres (*Centres de Compétence Maladies Rares)*; local healthcare structures working with the centres of expertise; laboratories and diagnosis platforms; professionals and structures from the social sector; fundamental, clinical and translational research teams; learned societies; and patient organisations.

The mission of these Health Networks for Rare Diseases consists of: reducing the diagnosis and therapeutic wavering; facilitate the entry and orientation in the care pathway; reinforcing the connection between care providers, innovation in diagnosis and therapies, research and social care.

The Health Networks implement actions in the social field, targeted at improving social care and allocation of disability compensatory benefits. These actions are implemented in collaboration with the CNSA (National Solidarity Fund for Autonomy), to whom the Ministry of Health has delegated the coordination of activities in the social field. Specific actions are defined according to needs of the diseases covered by the network and inter-networks actions are also developed.

As an example, a working group has been set up to improve education, pathway at school and care taking at school for children living with a rare disease, in link with the Ministry of Education. Another working group, including representatives of several Health Networks for Rare Diseases, the local social services providers (*Maisons Départementales des Personnes Handicapées*) and the regional teams for rare and complex disabilities (*Equipes Relais Handicap Rares*), aims at integrating rare diseases into the national disability assessment system (creation of a complementary tool, specific to rare diseases) and at improving relations, contacts and exchange of information.

Box 32.5: Innovative Solution: Bottom-up Approach and Consensus Driven Formation of a Network

In the Netherlands a pilot project is aiming at developing the first Neurofibromatosis type1 (NF1) national network of expertise. There is one official national centre of expertise. People with NF1 are however visiting regular hospitals and other specific intervention centres, because they either live far from the centre of expertise or do not need top-level healthcare, since they have a mild form of the disease. Regular hospitals and intervention centres often lack the knowledge on NF1 and may miss signs of possible complications.

The Dutch Neurofibromatosis organisation has therefore initiated a project establishing a national network of expertise, together with the national centre of expertise, based on the different types of healthcare services described in the standard of care for NF1: at least one national centre of expertise and several regional centres of competence; centres for symptom-specific interventions may also join the network; collaboration with the general practitioner and all other paramedical and social services is guaranteed and coordinated either by the centre of expertise or by one of the regional centres of competence.

Together with the Dutch Genetic Alliance, this project has reached several milestones. All national hospitals and intervention centres taking care of a sufficient number of patients with NF1 have been invited to join the network, resulting in participation of all eight university medical centres as well as several intervention centres. Quality criteria have also been developed for NF1 centre of competence and NF1 intervention centres.

A true network is being formed in which partners commit to exchange data and to work together with all other local care providers. There are two key contacts for the patient in such a network: firstly, the patient's physician-manager, who is responsible for the multidisciplinary medical care provided as described by the standard of care; secondly, the nurse-practitioner, who is responsible for the coordination of care and logistics within and outside the hospital, providing information about and referring to support services upon needs. These services report back to the monitoring hospital and exchange relevant information with each other.

32.6.3 Perspectives on Upcoming Integrated Care Approaches: Case Management

A case manager is a form of integrated service at the level of the individual [40]. For instance, in a multidisciplinary team, one team member could act as the case manager and ensure the coordination between the team members and the user. More integrated approaches rely on an intensive case management where the case manager coordinates the services for the user, especially for users facing complex and long-term needs such as people living with rare diseases [41].

Case managers have an instrumental role in adapting the existing care system to patients' individual needs and in supporting holistic and continuous care by establishing networks of care providers, providing information and support to local professionals, patients and families coordinating individual care plans and providing information on cross border care when needed.

Case management programmes, when implemented effectively, can improve the care of patients. To do so, key factors lie in the design of these programmes, in the training of professionals and in the implementation of a wider system of integrated and co-ordinated care. One particular factor of success is the integration of case management in a wider strategy or programme for the management of a specific population [42].

Because of the complex needs of people living with rare diseases and the challenges to provide health and social care to this group, there is a need for a case manager reaching out to local professionals, in order to complete the line of care from the central to the local level, to delineate a personalised pathway for each patient and to create effective changes in patients' autonomy and daily lives.

In most rare disease cases, the role of the case manager is assumed by patients or family members, without having sufficient information regarding care, the health and social system and relevant contacts. This situation is very burdensome for people living with a rare disease and their families. Family members – often the main carers – frequently find themselves in burn out situations, unable to cope physically and psychologically with the situation [11]. Therefore, case managers also have an important role in relieving the care burden of people living with a rare disease and their families.

A new EU-funded project called INNOVCare[18] [43] will test use of case managers in the context of rare diseases, and should bring to light more information on the impact of this type of service on care provision and on the quality of life of patients and families (Box 32.6).

[18] More information at: www.innovcare.eu.

Box 32.6: Case Manager Experiences in Rare Diseases

Case managers are defined in the French National Plan for Rare Diseases (2011–2016) as the element that can ensure that there is a better coordination in the care pathway of people living with a rare disease, functioning as a link between the health and the social needs of the patient, particularly in very complex situations, due to the course of care and the need for the intervention of multiple structures and professionals.

A pilot implemented in France, PRIOR-RH, shows how case management can be organised by a regional centre of expertise for rare diseases. PRIOR-RH employs a multidisciplinary mobile team - health manager, genetic counsellor, social worker, psychologist, occupational therapist – which undertakes the role of case management for people living with rare diseases in the region, thus improving their care pathways.

PRIOR-RH has built a regional network of competence both in health and social care involving 23 partners. Additionally, PRIOR-RH provides information on rare diseases, draws-up an inventory of regional expertise, directs patients towards social and healthcare services, provides social follow up to support patients in their life course, and organises stakeholders meetings.[19]

In The Netherlands, case management for an individual with a rare disease is often divided into organisational and medical components.

People with rare diseases need help regarding the organisational aspects of care such and their questions related to these can be answered by a nurse-practitioner who is in close contact with the responsible clinician.

The latter is – in case of many rare diseases – the so-called physician-manager for the patient in question. A physician-manager is thus a case manager, responsible for medical issues only. Having an overview of all recent medical examinations the patients has underwent, the physician-manager coordinates the multidisciplinary care and is the immediate contact for medical questions. The physician-manager can refer the patient to other professional care-givers within the network of expertise or outside of it for paramedical care or other types of services. The physician-manager has a broad overview of the disease and its health impact, but also on the possible psychosocial impact of the disease and on the patient's capacity to practice self-management.

According to the European Commission [44], the outreach, and the thus the coverage, of social services could be increased through the use and training of high quality case managers, able to assess and provide individualised guidance to people's needs.

[19] More information at: http://download.eurordis.org.s3.amazonaws.com/emm2015/ws4/5.DOMINIQUE_FRANCE_Prior%20Eurordis%20Madrid.pdf.

32.6.4 Perspectives on Upcoming Integrated Care Approaches: One-Stop-Shop Services

Participants in a study performed by RehabCare, in Ireland, reported that services for rare diseases were too scattered and they felt that a one-stop shop approach to social support and therapy provision was needed. Participants also felt that they had to constantly chase up services and experienced frustration at the fragmentation of services. The large number of people involved in the process of acquiring a service was also frustrating [13].

One-stop-shop services are an advanced form of integration which comprises multi-service delivery in a single location. This form of integration can include a stronger coordination between services but it can also lead to the creation of a single body with a more or less autonomous decision making authority which implies more deep structural changes. The integration of social services through setting up one-stop-shop services has the potential to generate cost efficiency, effectiveness of the delivery and capacity to tackle complex and multiple problems while also ensuring take-up and coverage [44].

Resource Centres for rare diseases are one-stop-shop services, specifically designed for people living with a rare disease, often functioning in partnership with Centres of Expertise. Resource centres undertake an essential role in integrated care provision to people living with a rare disease, commonly create a bridge between patients/families and various stakeholders involved in patient care [45], such as health services, rehabilitation and therapeutic services, social and support services, education professionals and other professionals directly working with people living with a rare disease. Resource Centres can coordinate with regional or local case managers.[20]

Resource Centres empower patients, families, carers and professionals at various levels. Their services include information and guidance, training courses, respite care, therapeutic education, information on social benefits and research. Sometimes daily therapies, medical/psychological consultations and therapeutic recreation are also provided [18].

The EUCERD Joint Action (2012–2015) mapped existing Resource Centres for rare diseases, identifying 21 services in 12 European countries[21] [46, 47]. Among these are NoRo (Romania), Frambu (Norway) and Ågrenska (Sweden) (Box 32.7).

[20] More information at:http://www.eurordis.org/sites/default/files/publications/fact-sheet-resource-centres.pdf.

[21] Map and list of services available at: http://www.eurordis.org/specialised-social-services.

Box 32.7: Case Studies: Resource Centres for Rare Diseases

The NoRo Pilot Reference Centre for Rare Diseases is a Resource Centre accredited both as a social service and a medical service which provides holistic care based on a multidisciplinary and complementary approach and on the individual assessment of patients' needs. The centre ensures continuity of care through collaboration with other services in the community and by establishing networks with medical universities. NoRo runs a help line for rare diseases, organises training for patients, volunteers and professionals,[22] support groups, therapeutic weekends for families and therapeutic camps for children.

Frambu's multidisciplinary team provides services to people affected by over 120 different rare diseases as well as to carers and service providers. The centre complements the services provided by the Norwegian health system and works in connection with university hospitals. Frambu is a meeting place for families and professionals providing competence, knowledge, documentation and guidance and organising residential courses, summer camps, research projects and outreach activities in local communities.

Ågrenska's main objective is to gather, develop and spread knowledge on rare diseases and their consequences. The centre provides family programmes, adult programmes, respite care services, summer camps, a family support unit, courses for professionals and social research. The centre aims at supporting and empowering people to cope with everyday life and to be as independent as possible.[23]

32.7 Conclusion and Outlook

The rarity, complexity and lack of treatment of rare diseases lead to significant unmet health and social needs and create particular obstacles to the provision of holistic integrated care to people living with a rare disease and their families.

Bridging the between health and social care for rare diseases is not only necessary but crucial to increase the life expectancy, quality of life and autonomy of people living with a rare disease, supporting them in the full realisation of their fundamental human rights.

The provision of integrated care will ensure the transfer of the scarce expertise and information, support the coordination and communication between care providers, support the integration of rare disease specificities into mainstream services, improve care and care pathways, optimise resources, lead to efficiency gains, and reduce the burden of the disease on patients and families.

[22] More information at: www.edubolirare.ro.

[23] More information available at: http://download.eurordis.org/documents/pdf/sss/3-RCS-Agrenska-Gunilla-Jaeger.pdf.

The Commission Expert Group Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies (2016) encourages European Member States to promote measures that facilitate multidisciplinary, holistic, continuous, person-centred and participative care provision to people living with rare diseases.

Various methods are currently being used to promote integrated care for rare diseases including those presented in this chapter: standards of care, national networks of expertise, case management services and one-stop-shop services. Nonetheless, the challenges to fully address this issue remain numerous.

In order to inform future policies addressing integrated care for rare diseases, it is necessary:

- To consolidate information on the impact of these ongoing experiments and to ensure that their impact is assessed using a suitable comprehensive set of outcome indicators that take into account both the evaluation of impact of healthcare and social services' interventions as well as the personal outcomes for patients, their families and carers.
- To involve patients and families directly in the design and implementation of these innovative solutions, in a participative, co-productive and co-responsible manner.
- To encourage research on economic evaluation of the integrated care, considering the economic long term impact beyond the healthcare and service provision onto a society level: taking into account the consequences of the impact of integrated care provision on patients' and carers' health, wellbeing, autonomy and financial burden.
- To understand how these solutions, relate to the overall implementation of ongoing integrated care programmes within health systems at large and whether the solutions used to stratify health populations accessing these programmes properly recognise the specific needs of people living with a rare disease.

The INNOVCare project (2015–2018),[24] co-funded by the EU, addresses the issue of integrated care for people affected by rare diseases by developing, testing and promoting a holistic, personalised care pathway, using regional case managers connected to a resource centre (one-stop-shop service) for rare diseases.

The project will conduct a pilot in Romania (2017) and will collect important data on the social and economic impact of the innovative care pathway. Additionally, INNOVCare will develop roadmaps to support the up-scaling of the pilot model to other European Member States. The up-scaling road maps will be developed with input from the project Advisory Group, composed of over 20 representatives of national competent authorities from across Europe.

The data provide by INNOVCare and other ongoing projects will be essential to support informed policy decisions on integrated care for people living with a rare disease.

[24] More information at: www.innovcare.eu.

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Chapter 33
Health Systems Sustainability and Rare Diseases

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Abstract The paper is addressing aspects of health system sustainability for rare diseases in relation to the current economic crisis and equity concerns. It takes into account the results of the narrative review carried out in the framework of the Joint Action for Rare Diseases (Joint RD-Action) "Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases", that identified networks as key factors for health systems sustainability for rare diseases. The legal framework of European Reference Networks and their added value is also presented. Networks play a relevant role for health systems sustainability, since they are based upon, pay special attention to and can intervene on health systems knowledge development, partnership, organizational structure, resources, leadership and governance. Moreover, sustainability of health systems can not be separated from the analysis of the context and the action on it, including fiscal equity. As a result of the financial crisis of 2008, cuts of public health-care budgets jeopardized health equity, since the least wealthy suffered from the greatest health effects. Moreover, austerity policies affected economic growth much more adversely than previously believed. Therefore, reducing public health expenditure not only is going to jeopardise citizens' health, but also to hamper fair and sustainable development.

Keywords Health system sustainability • Health equity • Fiscal equity • Austerity • Resilience • European Reference Networks

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33.1 Health Systems Sustainability in a Context of Rampant Inequity

Sustainability is the capacity to endure and can also be defined as a process characterized by the pursuit of a common ideal [1]. Pursuing health protection is the ideal inspiring health systems. Nowadays, sustainability of health systems is being challenged by many factors. Social and demographic pressures increase demand for health care: the aging population carries an increased burden of non communicable diseases; citizens' expectations claim a major their role and participation in decision making, factors that can increase compliance clinical path. On the other side, technological and scientific advances continue to raise costs. In addition to these dynamics, the global financial crisis posed major threats to healthcare sustainability. Governments' response to the crisis was cutting public health-care budgets, and transferring healthcare costs to individuals and families through out-of-pocket payments.

The scientific literature highlights the negative impacts of austerity on citizens' health status: mental health has been most sensitive to economic changes so far. There has been a notable increase in suicides in some EU countries, often reversing a steady downward trend, and some evidence of an increase in the prevalence of mental disorders [2]. The same Authors underline that vulnerable people may be more negatively affected than the population in general, and that these people tend to be hidden in aggregate data. Moreover, the full scale of the effects of the crisis on health may not be apparent for years and there are likely to be further adverse effects on health due to increases in household financial insecurity, inadequate and delayed access to health services and breakdowns in the management of chronic disease. These effects may not manifest themselves for some time. Failure to monitor and act will be costly in both human and economic terms.

In Europe, some health systems were better prepared than others to cope with severe fiscal pressure. Factors that helped to build resilience included countercyclical fiscal policies; adequate levels of public spending on health; no major gaps in health coverage; relatively low levels of out-of-pocket payments; a good understanding of areas in need of reform; information about the cost–effectiveness of different services and interventions; clear priorities; and political will to tackle inefficiencies and to mobilize revenue for the health sector. These factors made it easier for countries to respond effectively to the crisis. In contrast, weak governance and poor health system performance undermined resilience [2].

As a result of the financial crisis, cuts of public health-care budgets jeopardized health equity, since the least wealthy suffered from the greatest health effects. Moreover, austerity policies affected economic growth much more adversely than previously believed. Neoliberal policies imposed structural adjustments in the 1980 and 1990: the World Bank published in 1993 a World Development Report that stated "do not rely on public financing for health care" [3] and the International Monetary Fund was applauding to inequality as a stimulus for economic growth. On the contrary, instead of delivering growth, neoliberal policies have increased

inequality and have not performed as expected. The same IMF recognizes that the costs in terms of increased inequality are prominent and such costs epitomize the trade-off between the growth and equity effects of the neoliberal agenda [4, 5]. Also the Organisation for Economic Co-operation and Development (OECD) recognizes that growth has disproportionally benefited higher income groups while lower income households have been left behind. This long-run increase in income inequality not only raises social and political concerns, but also economic ones. It tends to drag down the growth of the Gross Development Product (GDP), due to the rising distance of the lower 40% from the rest of society. Lower income people have been prevented from realising their human capital potential, which is bad for the economy as a whole [6]. At the moment, the same international institutions imposing austerity policies are now advocating public investments to overcome economic stagnation [4, 6].

As a matter of fact, the wealth of the world is divided in two: almost half going to the richest 1%; the other half to the remaining 99% of the population. The mechanisms that allow concentrating richness in the hands the few are not the result of individuals' good performance, but the result of political and economic decisions taken by the society, inspired by the neoliberist model. Health determinants are largely conditioned and constrained by economic practices, and by government legislation that regulates such practices or seeks to mitigate inequalities that arise from them. Currently, the ability of national governments to intervene in economic practices has been reduced by the dominance of a neoliberal economic orthodoxy, which emphasizes free (unregulated) markets and a 'minimal' welfare state, and the growth in regional and global free trade and investment agreements. Regressive taxes and deep spending cuts, particularly to public services such as education, healthcare and social security, dismantle the mechanisms that reduce inequality and enable equitable growth. Moreover, other mechanisms intervene magnifying the problem, such as lobbying by global corporations that use their influence to secure generous subsidies and tax avoidance schemes; fiscal evasion and/or elusion, with fiscal heavens that allow hiding fortunes through shell companies established in foreign countries, making it easy to evade taxes; corruption. The recent Panama Papers data leak brought to the light how shell corporations were used for illegal purposes, including fraud, kleptocracy, tax evasion, and evading international sanction [7].

The World Economic Forum has identified inequality as a major risk to human progress. Extreme economic inequality and political capture are too often interdependent. Left unchecked, political institutions become undermined and governments overwhelmingly serve the interests of economic elites to the detriment of ordinary people [8].

Given this situation, is it fair to continue advocating public spending reduction and limits for the role of the State in defining redistribution policies?

According to the International organization Oxfam, several countries have successfully reduced economic inequality by means of cracking down on financial secrecy and tax dodging; redistributive transfers; and strengthening of social protection schemes; investment in universal access to healthcare and education; progressive taxation; strengthening wage floors and worker rights [8].

Oxfam calls on governments to use their tax revenue to provide universal healthcare, education and social protection for citizens [8]. Moreover, it has recommended policies in multiple contexts to strengthen the political representation of citizens to achieve greater equity, underlining the importance of citizens' active participation in the mechanisms of resilience. These policies include:

- A global goal to end extreme economic inequality in every country. This should be a major element of the post-2015 framework, including consistent monitoring in every country of the share of wealth going to the richest 1%.
- Stronger regulation of markets to promote sustainable and equitable growth; and
- Curbing the power of the rich to influence political processes and policies that best suit their interests.

In order to address fiscal pressure in future, international and national policymakers should aim to [2]:

- Develop better **information systems**, in order to get timely and relevant data to monitor health effects of economic shock
- Strengthen **health financing policy design**: public spending on health is more explicitly linked to population health needs; the public revenue base is not overly reliant on employment; and tax subsidies do not foster inequalities in paying for and accessing health services.
- Invest in measures to promote **efficiency**.
- **Foster governance** and **leadership** at international and national levels.

33.2 Health Systems Sustainability for Rare Diseases (RDs)

Sustainability of health systems for RDs shares both similarities and additional challenges to those faced by healthcare systems. Affordability and financial sustainability are the biggest issues confronting healthcare providers. Across Europe, notwithstanding the complexity and differences in how healthcare is funded and organised, the countries face the same challenges: how to continue to provide high quality and universally accessible health services in a financially sustainable way. Healthcare expenditure is too often seen in a narrow context, purely as an economic cost. However, even at economic level, health expenditure properly organised and delivered will reduce other welfare costs, and generally improve productivity. Evidence demonstrates that significant savings can be created by investment in prevention [9, 10] and early intervention. Investment in prevention and early intervention is essential for healthcare sustainability and socioeconomic development and stability.

In spite of the importance of health and healthcare for citizens' and society wellbeing, the voices of key stakeholders, the health policy community, health-care managers and leaders, national governments, and politicians at both a national and a European level have not been as influential as they should be. Few studies are

carried out on health policy research, on design of funding systems and their effect on financial performance, on health-care quality, and health status [11].

Groups concerned with biomedicine, pharmaceuticals, and medical technologies are driving the process for setting health research priorities, and government ministries of science have coordinated them nationally with little input from Ministries of Health. Research budget at EU level is dominated by biomedical topics: only 4% of the €642 million EU cooperation programme for health research in 2011 was allocated to health systems, public health, or health policy research [12]. A report recommended that 25% of health research budgets should be spent on public health, health systems, and health policy research [12]. Horizon 2020, the biggest EU Research and Innovation programme, dedicates 38.53% of its total budget to Societal Challenges. Yet this issue concerns several fields: health, demographic change and wellbeing; food security, sustainable agriculture and forestry, marine and maritime and inland water research; Bioeconomy; Secure, clean and efficient energy; Smart, green and integrated transport; Climate action, environment, resource efficiency and raw materials; inclusive, innovative and reflective societies; security of Europe and its citizen. Horizon 2020 narrows the interpretation of health and wealth agenda, regarding health research as a lever for economic growth through exploitable intellectual property [13].

In the framework of the Joint Action for Rare Diseases (Joint RD-Action) "Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases", a narrative literature review was carried out in order to identify and understand mechanisms that influence the sustainability and resilience of health systems for rare diseases.

The narrative review identified networks as important sustainability and resilience mechanisms. Moreover it hypothised possible leverages for intervention, that are shown in Table 33.1.

The following section of the paper is addressing the legal framework of European Reference Networks and their added value for health systems sustainability.

Table 33.1 Possible intervention leverages for health system sustainability for rare diseases

Organizational structure	Infrastructural ability of the system to contribute to goals to healthcare systems for RDs
Resources	Allocation and provision of human and financial resources to healthcare systems for RDs
Partnership	Collaboration between organizations for effective practice
Workforce	Qualified human resources with adequate skills and knowledge
Knowledge development	Knowledge base that provides information on the health status and supports evidence-based health policy and interventions at all levels
Leadership and governance	Ability and willingness of governments to improve public health by developing and implementing effective health policies and by expressing qualities in leadership and strategic thinking
Country specific context with relevance for RDs	The political context and other characteristics of a country that may have an influence on health policies and capacity building efforts

Modified from Aluttis et al. [35]

33.3 European Reference Networks: The Legal Framework

The definition of European Reference Network (ERN) is "a network connecting health care providers and centres of expertise of highly specialised healthcare, for the purpose of improving access to diagnosis, treatment and the provision of high-quality healthcare for patients with conditions requiring a particular concentration of resources or expertise no matter where they are in Europe. Clinicians network already widely: for them ERNs will represent the formalisation of their networking structures/practices in highly specialized healthcare. For those without specialist networking communities at present, ERNs will promote expertise and support health care providers in order to bring local, regional and national provision of healthcare closer to the patients (http://ec.europa.eu/health/ern/implementation/faq_en.htm).

Three documents form the basis of the European Reference Networks:

- the Directive 2011/24/EU on patients' rights in cross-border healthcare [14];
- the Commission delegated decision listing the criteria and conditions that health-care providers and the ERNs should fulfil [15];
- the Commission implementing decision containing criteria for establishing and evaluating ERNs, including the exchange and dissemination of information about the ERNs [16].

Indeed, already a number of years ago public health experts recommended "a system whereby the Commission might seek to encourage identification of Centres of Expertise (CEs) on rare diseases (RDs) and support the establishment of networks for the development of research in appropriate fields. *[…]* focal points (CEs on RD and networks with a central secretariat) should be identified and the existing structures concerned with RDs within the MSs should form the backbone of the focal points" (Birth CA, 1997; Commission Communication, 1993).

Thereafter, several EU documents and projects bring out the need for the development of CEs and ERNs [14, 17–30].

The process for becoming an ERN is complex. The EU Commission gives the following suggestions before setting up an ERN (http://ec.europa.eu/health/ern/implementation/faq_en.htm):

- To review the information on the Commission webpage which includes the current framework, the legislative proposal and a many frequently asked questions (FAQ);
- To contact the national representatives in the ERN Board of MS, in order to have more specific information on the national endorsement process;
- To conceive a one page document with the network proposal and share it with the national and European medical societies as well as the national representatives;
- To address a wide scope in the network proposal referring to thematic groups (providing also examples of possible groupings [31].

In this process, an important element is the "Assessment Manual and Toolbox", based on the criteria established in the Commission Delegated Decision on ERN. It is available on the EC website (http://ec.europa.eu/health/ern/implementation/call/more_info_en.htm) and includes a list of useful documents:

- Description and procedures
- Toolbox (applications, checklist, etc.)
- Operational criteria for Networks
- Operational Criteria for Healthcare providers
- Application Form for Networks
- Application Form for Healthcare Providers
- Self-assessment for Networks
- Self-assessment for Healthcare providers
- Sample Letter of National Endorsement for Healthcare Providers

The EU Commission provides also information on the process for becoming a member of an ERN (http://ec.europa.eu/health/ern/implementation/faq_en.htm). This is clearly defined in the Implementing Acts. A healthcare provider (HCP) wishing to become a member of an ERN will have to pass an assessment process based on the criteria in Delegated Decision (2014/286/EU) Annex II and on the Implementing Decision (2014/287/EU). This assessment will be composed of several steps:

- the formal support/endorsement by the Member State in which the HCP is based (for further information an interested HCP should approach the relevant MS representative on the Board of Members States of ERNs and ensure they understand and abide by the agreed national process for endorsing HCPs (More information Choose translations of the previous link).
- After passing an eligibility check a technical assessment composed of documentation review, teleconferences and on-site visits will follow.
- The final approval of the proposed ERN will take place by the Board of Member States.

The process includes the establishment of a Board of Member States, as laid out in the Commission Implementing decision. It was set up on February 2014, with the following main tasks:

- Approval of Networks proposals and healthcare provider's membership applications included in a Network proposal
- Approval of healthcare providers wishing to join an existing Network
- Termination of a Network (evaluation)
- Decision on loss of membership

In the EC website, further information on its functioning, meetings and outcomes, as well as policies and activities related with the implementation of ERNs is available (http://ec.europa.eu/health/ern/board_member_states/index_en.htm).

A public call for the Networks proposals, in two stages, has been launched by EC (DG Health and Food Safety) on March 2016 for applying for ERN and grant, on

June 2016 for ERN without funding (http://ec.europa.eu/health/ern/implementation/call/index_en.htm).

The technical assessment of ERN proposals will be carried out by contracted institutions or entities with a solid background and experience in the field of accreditation/certification.

33.4 European Reference Networks: A Paradigm Shift in RD Health Care Systems

> Europe [is] a giant "natural laboratory" for health systems, with enormous potential for countries to learn from each other. European cross-border healthcare is the key to unlocking that potential…" (Nick Fahy, Luxembourg, September 2010).

An higher healthcare expenditure does not necessarily mean better health, but timely and smart investment today will reap benefits tomorrow. With this belief, the EC is seeking alternative and economically sustainable approaches in healthcare field that take into account of the cultural and economic differences of the EU MS. Among these, the cross-border and cross-sector collaboration have been promoted for many years and tested in several instances; yet the Directive on patients' rights in cross-border healthcare (2011/24/EU) represents a ground-breaking development in the field of healthcare cooperation and is widely seen as the beginning of a new era for European action in health services. Its ambitious aim is to design a real "legal status of the European patient", ensuring the effective implementation of freedom of movement of persons [32]. This has led to explore some opportunities related to the concept of European Centres of Expertise (CoE) and, especially, European Reference Networks (ERNs) aimed at pooling resources in specialized healthcare and improving access to and provision of high-quality specialized care especially in the area of rare diseases (Art. 12, OJ, 2011). However, as the Member States are at different stages in defining and monitoring reference centres nationally, the directive has focused on networks rather than centres, since this helps to avoid the different national centres taking part in networks having to compete against each other. Yet certain actors can function as benchmarks for others within the same network. Member States remain primarily responsible for the organisation and delivery of their healthcare; national participation in ERNs is therefore voluntary. When a healthcare centre does not have the required level of expertise to be part of an ERN as a centre of expertise it can participate as an associated or collaborative centre. In any case, health, equity and financial objectives seem to encapsulate the basic rationales for implementation of reference networks: to improve quality and safety of care, to ensure equitable access to high quality care for all EU citiziens and to save costs by maximizing the cost–effective use of resources or realizing economies of scale. Besides creating a clear governance structure for knowledge sharing and care coordination among EU countries, the innovative character of ERNs can also lead to long-term economic benefits for MS, reducing costs while improving health outcomes and patient access to healthcare (overcoming the barriers of distance) and

ensuring the equity principle. This is particularly relevant for small countries with limited capacity and resources to provide comprehensive highly specialized services, because it can improve access to treatment for their citizens (Rare Diseases Task Force 2006).

However, the incentives for Member States to participate in reference networks could be very diverse. Not just smaller countries but countries with less financial capacity may prefer not to invest in their own responses but to look to access (reference) centres abroad; other countries will want to share expertise around very complicated diseases or cost-intensive interventions.

Dissemination of knowledge through ERNs could also help to establish shared information databases and in turn support the development of best practice protocols. This could contribute to the 'levelling up' of the expertise of healthcare professionals, who can benefit from the experience of their counterparts in other EU Member States. "These information databases could also be used to further research in rare diseases. Despite some short-term administrative burdens, in the long-term ERNs have the potential to reduce costs due to centralization of resources and economies of scale, while ensuring Europe-wide access to high quality healthcare. The sustainability of ERNs will also depend on the funding for these networks. This is possibly the most serious threat to the project, as there is presently no secure sustainable form of funding available at European level. The stringent budgetary frameworks being applied to health systems at national levels indicate that Member States will find it difficult to spare funds for the maintenance of ERNs" [33]. Although alternative sources of funding are being explored, public funding is of crucial importance, if ERNs are to work independently. A possible solution to be discussed is a limited participation of the industry in the work of ERNs where appropriate, without any involvement in the development of clinical guidelines and protocols, such as care pathways, treatment guidelines and diagnostic strategies, nor in the steering committee or board of trustees of ERNs [34]. On the other hand, many healthcare professionals have relationships with industry, which supports patient organizations in disease awareness activities, diagnostic recommendations and management guidelines [34].

It is commonly believed that the centered-patient strategy is a key element for a long-term efficient health system, economic growth and social welfare. In several MS, patient organizations are increasingly involved in developing care pathways and research and, although patient representatives are not legally required to participate in the governance and evaluation, however ERNs are required to demonstrate patient centric care and patient empowerment. Indeed, it is important that patient representatives and clinicians collaborate jointly in the new system of ERNs. On the other hand, patient groups (particularly in RD field) have been very active in promoting the development of ERNs, since patients will obviously be the beneficiaries of the improved treatments the networks will bring. For this reason, EURORDIS is developing a European Patient Advocacy Group (ePAG – http://www.eurordis.org/content/epags) for each ERN rare disease grouping, in order to ensure a democratic process of patient representation throughout the ERN development process. Membership of ePAGs is open to all rare disease patient organizations (EURORDIS

members and non-members based in the European Union). ePAG patient representatives have an official permanent mandate to represent EURORDIS and the affiliated patient organizations. Their role and function will be agreed with the ERN Network Coordinating Lead. In brief, their task is to:

– represent the perspective and interests of rare disease patients;
– ensure that health care is patient-centred and respects patients' rights and choice;
– ensure the application of personal data rules, compliance of information consent and management of complaints.

33.5 Conclusions

Sustainability of health systems can not be separated from the analysis of the context and the action on it, including fiscal equity. Sustainability of health systems for RDs shares both similarities and additional challenges to those faced by healthcare systems. Networks play a relevant role for health systems sustainability, since they are based upon, pay special attention to and can intervene on health systems knowledge development, partnership, organizational structure, resources, leadership and governance.

Resilience is an inner mechanism of communities and organizations to counterface hardship. However, it is not meant to substitute governments' responsibility to promote and protect citizens' health. Reducing public health expenditure is going to jeopardise citizens' health, with consequences also on fair and sustainable economic development.

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Chapter 34
Preparing for the Future of Rare Diseases

Stephen C. Groft and Manuel Posada de la Paz

Abstract Members of the rare disease community have devoted significant financial and personnel resources to address the numerous issues surrounding rare diseases. The past has been devoted to developing an emphasis on rare diseases including an emphasis on research studies or locating information on rare diseases and the requirements and limitations of conducting clinical trials with small patient populations. The expanded role of patient advocacy organizations and patient engagement in all aspects of clinical research continues to gain acceptance within the research community. The future will require a greater understanding and interpretation of available information from multiple sources including electronic health records and big data sources. The pipeline of potential orphan products continues to grow significantly and holds great promise for novel interventions due to advances in clinical trial design and data analyses. Expanding diagnostic procedures with improved sequencing methods will speed up the diagnosis or rare diseases. Accepting agreed upon nomenclature and codification of rare diseases will assist in differentiating diseases and identifying selected sub-populations of rare diseases. Improvements in patient recruitment and increased flexibility in the product review and approval procedures by regulatory agencies will facilitate product approvals. Children particularly will need help and assistance dealing with feelings of isolation from their peers due to their rare disease. During the transition from childhood to adolescence to adult, difficulties of fitting in with peers and not wanting to be different are a major concern. In response to increasing costs of treatments, Value-Based Care is gaining greater acceptance by the reimbursement and the payer community as a basis for payment for interventions. Mobile Health (M-health) Technologies have the potential to revolutionize how clinical research is conducted in the future. Wearable devices, remote sensors, and the development of mobile device applications (apps) will all assist in constant monitoring of patients for safety and efficacy

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of approved and investigational compounds. Tele Health and Tele Medicine may provide the necessary access to expert clinicians with a better understanding of individual rare diseases. The future promises great advances and even greater personalized treatments with the introduction of novel treatments and approaches to care.

Keywords Rare diseases • Orphan products • Patient-centric research • Transitional care • Mobile health technologies • Telehealth • Telemedicine • Value-based care

34.1 Introduction

For many years, members of the rare disease community have devoted significant financial and personnel resources to address the numerous issues surrounding rare diseases. The past has been devoted to developing an emphasis on rare diseases including an emphasis on research studies or locating information on rare diseases as well as the requirements and limitations of conducting clinical trials with small patient populations. The future will require a greater understanding and interpretation of available information from multiple sources including electronic health records and big data sources. These sources of information will include extensive clinical information and outcomes of treatments. They provide a picture of the natural history of the disease in many patients including a significant percentage who have rare diseases. Information gained from exquisite or exceptional responders, partial responders and non-responders will guide product development and will require even closer observations of individual genetic variability, environmental exposures, patient behaviors and lifestyles as co-factors determining the onset of a disease across the lifespan. These co-factors are expected to affect outcomes of clinical trials. Results from "N of 1" studies will suggest patient recruitment and study design for larger populations with similar phenotype and genotype description of diseases. We are seeing this specificity for many clinical trials investigations and treatments with different cancers and selected rare diseases. Examples include product approvals for selected sub-populations for lumacaftor and ivacaftor which have been granted for patients with cystic fibrosis who are homozygous for F508del mutation in the CFTR gene. Another product, eliglustat has been approved for Type 1 Gaucher disease patients who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs). Eteplirsen is now available for treatment of Duchenne muscular dystrophy (DMD) patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

The pipeline of potential orphan products continues to grow significantly and holds greater promise for novel interventions. Advances in clinical trial design and data analyses, continuously expanding diagnostic procedures including newborn screening, correlating the phenotype and genotype information with whole genome

and exome sequencing methods to respond to undiagnosed diseases, rare diseases information development and dissemination, agreed upon nomenclature and codification of rare diseases, increased flexibility in the product review and approval procedures by regulatory agencies, the expanded role of patient advocacy organizations, and improvements in patient recruitment. These advances are all leading to a greater understanding of rare diseases and conditions. An emphasis on patient registries and natural history studies of rare diseases can now differentiate effects of interventions from the natural course of the disease. All of these areas will continue to gain emphasis along with the continued need to understand the basic underlying pathophysiology of diseases at the molecular and cellular levels. We, as a community, must continue to evolve and devote additional resources to novel approaches to meet the needs of patients and families with rare diseases, health care providers, research investigators, the biopharmaceutical and medical devices industries, and government research, regulatory, and health services agencies,

34.2 Patient Centric Research

Patient engagement in all aspects of clinical trial planning and study design continues to gain acceptance within the research community. Patient led innovation has been used extensively by many Patient Advocacy Groups (PAGs). Several steps have been taken to foster this active engagement. PAGs are now recognized as key stakeholders in this research process. They provide valuable insights and services under the concept of "Patients as Partners" to gain acceptance of patient-centered indicators of response to therapies and shared decision-making with patients and families. It is essential to provide useful and reliable information and education resources about the rare disease and the clinical trial to patients, their families and caregivers. It is also helpful to provide opportunities for the patient to take a more active role in the management of their disease under the direction of the treating physician. The expanded use and increased acceptance of patient registries utilizing patient entered-data as a source of reliable information is encouraging to continue to gain the patient perspective [1, 5]. To many, patient-centric research is a novel approach to planning and conducting clinical research studies of rare diseases. To many others who have adopted this approach, this concept is essential if advances are to be realized with rare diseases. To be successful, patient-centric research must be implemented and accepted at all levels of an organization in both the public and private sectors.

Improvements in health literacy for the entire population, including a clearer understanding of genetics, will become an even greater need to improve the understanding of risks and benefits of treatments and the numerous aspects of the heritability of rare genetic diseases. It is essential that information developed for public use is easily understood by patients and their families.

34.3 Clinical Trial Access and Participation

Clinical trials are vital to medical advances because they test new and existing health-related interventions to determine whether they are safe and effective in humans when used as intended. Clinical trials provide information about use in selected sub-populations of rare diseases. Lack of ready access for the entire global populations to planned or ongoing clinical trials is of great concern. Selected populations in developing nations and in geographical sections of many other countries without access to major clinical trial sites needs to be addressed and resolved. Novel approaches to the recruitment of patients and expanding access to clinical trials at non-traditional research sites is crucial.

Expanding the registration information in ClinicalTrials.gov improves people's ability to find clinical trials in which they may be able to participate and gain better access to investigational therapies. More information about the scientific results of trials, whether positive or negative, may help inform healthcare providers and patients regarding medical decisions. Additional information will help researchers avoid unnecessary duplication of studies, focus on areas in need of study and improve study designs, ultimately advancing the development of clinical interventions. Treatment Outcomes information from clinical trials will become more readily available to patients and families and continuing the theme from previous statements, will require greater efforts to educate the public and patients about interpretation of data from multiple sources. A question we ask "Are patients prepared adequately to evaluate outcome data and to have this information guide their decision making?" One can anticipate an even greater role for the patient advocacy group to provide extensive interpretation of results from clinical trials.

34.4 Transitional Care and Adherence to Treatment and Transitional Care

As more treatments become available for pediatric population, the transition of patients from pediatric to adult clinics is of growing concern. The American College of Physicians has made available a pediatric to adult care transition Tool Kit [6]. Success is dependent upon the readiness of the youth to manage their disease. It is important to assess self-care knowledge and skills in this population. It is also important to provide for the transfer of the pediatric patient and their medical history to the adult clinics. With increased access to interventions and the increased number of products available for treatment, similar problems of lack of adherence to treatment are expected to occur as with other diseases and treatments. The reported rates of adherence to medication treatments suggest a range between 58 and 65%. Lack of adherence to treatment can become a major problem if patients begin to feel well on treatment and then elect to discontinue treatment due to accompanying side effects of a product or the high cost of drug product. This could be a

major concern as children move away from home. They may also question the value of continuing the product after responding to medication and may feel like they have been cured and no longer need the medication.

Children particularly will need help and assistance dealing with feelings of isolation from their peers due to their rare disease. During the transition from childhood to adolescence to adult, difficulties of fitting in with peers and not wanting to be different are a major concern. Social media platforms and PAGs can provide this assistance to emphasize adherence to treatments throughout the lifespan. It remains important to continue to work with biopharmaceutical industry, families, and PAGs to develop materials for distribution via e-mail, text messages, social media networks, and web sites [4]. It is always useful to develop information in consultation with the intended patient population and their families to gain their insights and identify critical information for their specific use. Continued emotional support may be required for patients as they move from children to adults. Discussions and guidance on psycho-social aspects of transitioning to adult life are extremely important as dating and other relationship, increased social interactions, educational and training possibilities, and employment opportunities.

34.5 Valued-Based Care and Costs of Orphan Products

In response to increasing costs of treatments, Value-Based Care is gaining greater acceptance by the reimbursement and the payer community as a basis for payment for interventions. More new products are arriving on the market with considerable anticipation and expectations of access to an effective product. Assessments of Value-Based Care are becoming a normal response to the introductions of new treatments pre- and post-marketing approval decisions. One aspect of introducing a new product to the marketplace includes an assessment of the innovation and the value of a new drug when compared to existing treatments. More and more products are now expected to demonstrate clinical and economic superiority over an existing approved product before reimbursement is approved. The end results will require the rare diseases community and all stakeholders to achieve Value-Based Care and guarantee patient access to innovative compounds. As novel gene therapies continue to be tested and shown to be effective, similar data will be needed to justify the estimated cost of $1 million USD per treatment [2, 3].

Value-Based Care is receiving greater consideration in the reimbursement process. The terms financial toxicity and financial distress have been used to describe the situations when patients have been unable to afford their treatments. These high costs sometimes lead to non-compliance with prescribed treatments due to reduced dosage or discontinuation of treatment. The community will continue to increase their voice to gain access to products at costs that do not cause significant financial distress or toxicity [8, 9]. To assist in this determination, accepted standards of care for most rare diseases need considerable emphasis. Development of standards of

care can be a lengthy and difficult process with or without an active treatment but need to be developed to optimize treatment and care of patients with rare diseases.

34.6 Telemedicine and Telehealth to Aid in Precision and Personalized Medicine

Several novel approaches are expanding in mainstream medicine and at research sites. The future suggests a greater reliance on precision medicine and use of validated biomarkers as part of clinical trial assessments. Use of appropriate biomarkers and precision medicine approaches are directly applicable to rare diseases in all segments of the population in all locations. More widespread utilization of Telemedicine or Tele-Health or could revolutionize patient access to medical specialists from around the world. We often think these applications would only be used in rural or in developing countries without ready access to expert physicians. Residents of urban and rural locations in both developed and developing countries would benefit from this ready access. Health care professional licensing agencies in various states and nations are addressing this issue. The bioinformatics and information technology capabilities are readily available and suggest this access can be readily obtained if organizational and societal commitments are made to provide these services with adequate reimbursement for the practitioners and their institutions. The goal remains to provide the best possible care for all patients regardless of their economic status or geographic location.

34.7 Mobile Health (M-Health) Technologies

Mobile Health (M-health) Technologies have the potential to revolutionize how clinical research is conducted in the future. Wearable devices, remote sensors, and the development of mobile device applications (apps) will all assist in constant monitoring of patients for safety and efficacy of approved and investigational compounds. M-health offers the potential to provide a better 24 hours a day and 7 days a week understanding of rare diseases and the responses to treatment on an ongoing and more objective with less subjective variability in the evaluation phase. However, there are concerns with m-health products and applications including the privacy of patient data collected, remote interruption of reporting operations, the reliability of captured data potential from big data sources and reduced efficiency, effectiveness and degradation of remote sensors over extended periods of time. These concerns are being addressed in both public and private sector research and regulatory organizations. Developers of these novel technologies are encouraged to always consider applications to rare diseases.

34.8 Continuous Evolution of Rare Diseases Initiatives by National Plans and Legislative Mandates

The tendency is to maintain the status quo of existing legislation, national plans and implemented policies and programs. However, we recognize the needs of the patients, while basically the same today as in the 1970s when legislation related to rare diseases and orphan products was being created, there are now available resources that can be utilized and shared at a global level by everyone involved in rare diseases programs and initiatives. Sharing of information and data from successful and unsuccessful preclinical and clinical trials, chemical libraries, and patient derived information is essential to develop essential interventions for the prevention, diagnosis, and treatment of rare diseases and conditions. In the United States of America, the twenty-first Century Cures Act, various new programs at government agencies have been mandated by the legislative process and signed by the President and is now Public Law 114-255 [7]. The legislation addresses many issues including Research and Development, the Opioid Epidemic, FDA drug approval process, informed consent, medical research, behavioral health and healthcare access and quality improvement. This legislation enacted on December 13, 2016 is undergoing implementation. Continued development of National or Strategic Plans at the individual country level remains essential. Periodic review of existing legislation is required to continue to meet the needs of the global rare diseases community, including access to a rapid diagnosis and available treatments for everyone affected by a rare disease.

34.9 Conclusion

As in every era, the future promises great advances and even greater personalized treatments with the introduction of novel treatments and approaches to care. Regulatory and reimbursement and access to treatment decisions will be based on the accumulation and interpretation of data from even more resources previously used, including active and ongoing monitoring systems. Gathering data from well-constructed epidemiological studies, patient registries, natural history studies and clinical trials extending to post-marketing studies will be supplemented by real world data collected from passive data collection devices on an ongoing basis. The community must facilitate the development of novel approaches and establish the increased confidence and reliability of data from all sources. Information technology resources must be extended to include the rare diseases populations to improve the well-being of all patients on a global basis. Great strides have been made in the patient-centric research and development of products for rare diseases and conditions. These efforts must be stimulated even more if we expect to provide treatments for more than 5% of the patients with diagnosed rare diseases.

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