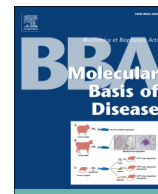




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Guidelines for incorporating scientific knowledge and practice on rare diseases into higher education: neuronal ceroid lipofuscinoses as a model disorder

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ABSTRACT

This article addresses the educational issues associated with rare diseases (RD) and in particular the Neuronal Ceroid Lipofuscinoses (NCLs, or CLN diseases) in the curricula of Health Sciences and Professional's Training Programs. Our aim is to develop guidelines for improving scientific knowledge and practice in higher education and continuous learning programs.

Rare diseases (RD) are collectively common in the general population with 1 in 17 people affected by a RD in their lifetime. Inherited defects in genes involved in metabolism are the commonest group of RD with over 8000 known inborn errors of metabolism. The majority of these diseases are neurodegenerative including the NCLs. Any professional training program on NCL must take into account the medical, social and economic burdens related to RDs. To address these challenges and find solutions to them it is necessary that individuals in the government and administrative authorities, academia, teaching hospitals and medical schools, the pharmaceutical industry, investment community and patient advocacy groups all work together to achieve these goals.

The logistical issues of including RD lectures in university curricula and in continuing medical education should reflect its complex nature. To evaluate the state of education in the RD field, a summary should be periodically updated in order to assess the progress achieved in each country that signed up to the international conventions addressing RD issues in society. It is anticipated that auditing current practice will lead to higher standards and provide a framework for those educators involved in establishing RD teaching programs world-wide.

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Abbreviations: CEMECO, Centro de Estudio de las Metabolopatías Congénitas–Center for Research on Inborn Errors of Metabolism in Córdoba–Argentina; CME, Continuing Medical Education; CPD, Continuing Professional Development; EUCERD, European Union Committee of Experts on Rare Diseases; EURODIS, European Rare Diseases Organization; EUROPLAN, European Project for Rare Diseases National Plans Development; GRDR, Global Rare Disease Patient Registry and Data Repository; IRDiRC, International Rare Disease Research Consortium; NCL, Neuronal Ceroid Lipofuscinoses; NORD, National Organization for Rare Disorders; RD, rare diseases; SLEIMPN, Sociedad Latinoamericana de Errores Innatos del Metabolismo y Pesquisa Neonatal–Latin American Society of Inborn Errors of Metabolism and Neonatal Screening

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1. Introduction

The neuronal ceroid lipofuscinoses (NCLs, also called Batten disease or CLN disease) are relatively uncommon neurodegenerative conditions, typically with an autosomal recessive inheritance pattern and childhood onset. Though each of the NCLs has a distinct genetic etiology, there is some phenotypic convergence between these disorders, which are characterized phenotypically with vision loss (except Kufs), motor and mental decline, seizures and premature death.

Despite their name and individual rarity, collectively, RD is paradoxically relatively common in the general population with 1 in 17 people affected by a RD in their lifetime. Inherited defects in genes involved in metabolism are the commonest group of RD with over 8000 known inborn errors of metabolism. Within the metabolic diseases, a group of over 70 lysosomal diseases represent a very significant health care burden, as they affect 1:5000 live births worldwide. The majority of these diseases are neurodegenerative [1,2]. Although these conditions are individually rare, their cumulative public health burden is substantial, with 6–8% of people having a RD at some point during life.

In the past one to two decades, there has been an increased focus on translational research spanning the spectrum from bench to bedside, including natural history phenotyping studies and more recently, early phase clinical trials for several of the forms of NCL (CLN1, CLN2, CLN3). In addition, diagnostic accuracy has improved as genetic diagnosis becomes increasingly available and affordable. Despite these improvements, there remains a gap in medical knowledge about the NCLs among clinical practitioners, both because of their rarity but also because of the lack of emphasis in medical training upon rare diseases in general and upon the NCLs more specifically. The limitations of translational research in the NCLs are common to other inherited neurodegenerative diseases, especially those with monogenic inheritance such as the lysosomal diseases. The challenges of translational science in these diseases must be addressed *in toto* in an integrated manner, not only in terms of specific medical issues associated with the use of sophisticated diagnostics such as genetic sequencing, but also as complex challenges to institutions and society as a whole.

Multidimensional aspects were considered in order to identify the most appropriate guidelines to improve education on RD by seeking the views of different stakeholders. The perspectives from science and technology, health, education, civil society and the pharmaceutical industry (Table 1) were taken into account. Using NCLs as a forum for addressing medical education in RD, the major focus was to propose guidelines for enhancing scientific knowledge and clinical practice in the RD in higher education and continuous learning programs. The resulting recommendations arose from a workshop conducted on October 27th, 2014 at the National University Cordoba, Argentina, a

post-Congress activity of the 14th International Conference on Neuronal Ceroid Lipofuscinoses (Batten Disease). Participants at this workshop included medical faculty members with clinical and research experience in RDs, addressing but not limited to the NCLs, and an international panel of NCL researchers and clinicians [3].

2. Methods

The international panel of delegates from academic centers in Argentina, Germany, Italy, the United Kingdom and United States participated in the post-congress Workshop to discuss the current global state of medical education and training in RD, gaps in education and proposed solutions. Delegates were tasked with identifying broad, cross-disciplinary recommendations appropriate for all levels of medical education, from medical curricula through to continuing medical education (CME) teaching.

We also conducted a literature search *via* PubMed (www.ncbi.nlm.nih.gov/pubmed/) using the key words “rare diseases” and “medical education” in the title as well as the abstract. The publication dates were limited to ten years starting in 2004, to include the recent classification changes. Each result was analyzed automatically by the search machine for its relevance to the subject of medical education in rare diseases. References meeting these criteria were retrieved and reviewed to further determine if it matched the topics highlighted in the Workshop. The main stakeholders identified and their actions/goals are summarized in Table 1.

In addition to a literature search, we examined the websites of a variety of international organizations devoted to RD, in order to determine if these organizations described programs or initiatives relevant to medical education (including Orphanet, NORD, EURODIS, GRDR and IRDiRC).

3. How can the complexity of the RD field highlight education gaps?

3.1. Scientific and technology Institutes/Research Institutes

Research in RDs is chronically underfunded relative to common neurodegenerative diseases [4]. This is despite the fact that single gene disorders such as the RDs are easier to dissect at the molecular and cellular levels, and therefore paradoxically advances in treatment are much greater in RDs than in common polygenic diseases. Indeed discoveries of disease mechanisms in RDs may well inform our understanding and treatment of common human diseases. For example, links between lysosomal diseases and common diseases have been made. This includes links between the lysosomal disease Gaucher disease and the development of Parkinson's disease. Another lysosomal

Table 1
Complexity of translational research on RD.

Stakeholder	Actions/goals
Scientific and technology institutes/research institutes	Generate knowledge and techniques on experimental models, cell biology, biochemistry, enzymology, proteomics, genomics, pharmacology, clinical analysis, microscopy, image analysis, epidemiology, bioethics, etc.
Healthcare Systems	Provide neurology, pediatric neurology, neuropathology, genetics, radiology, ophthalmology, orthopedics, gastroenterology, nutrition and other medical specialties.
Extended clinical care and delivery	Provide intramural and extramural care in kinesiology, speech therapy, nursing, aqua therapy, equinotherapy, patient management at home, hospice, etc.
Centers of excellence	Develop training in public hospitals to manage patients affected by RDs and employ specific algorithms for different RDs based on the evolution of diseases, shortening the time to diagnosis and providing access to available therapies. Provide coordination and liaison between institutions involved in translational research. Coordinate children and adults for continuity of care and hospital treatments over time.
Patients and patients advocacy groups	Advocate for the rights of patients and their families in the framework of existing laws and promote new legislation. Generate a system of solidarity between people with common needs, lowering anxiety and feelings of isolation of affected groups.
Industry	Develop orphan drugs using scientific and technical knowledge from academia and provide information on safety and quality standards.
International and national (regional) regulations and conventions	International and National Organizations, Health Systems, Parliaments, etc. that regulate and follow the compliance of law in the RD field.
Academia, health science and medical schools	To train scientists and professionals with expertise in all fields above.

disease, Niemann–Pick type C (NPC) is linked with Ebola virus (NPC1 the protein that is defective serves as its receptor) and NPC patients develop Alzheimer's symptoms and pathology [5,6]. The NCL diseases are prone to epilepsy and therefore studying these single-gene disorders will inform us about epilepsy and its causes. A major challenge for the RD field is that publishing in high impact journals is difficult due to lack of awareness about the significance of these diseases by journal editors and reviewers. Case reports describe these very infrequent and normally complex cases. Although case reports may rarely provoke a change in working practice, they nonetheless provide important information. They sometimes can serve as the catalyst for future clinical trials. If this information is not available, the physician will have to start from a position of minimal baseline information/insight. Furthermore, it is in this type of situation when health professionals will refer to scientific literature to find solutions to a problem [7,8].

Increased research funding would allow greater progress and foster international cooperation. As no individual country has sufficient patients within its borders to improve diagnosis and therapy alone, international initiatives are therefore essential. Because of the rarity, no single institution, and in many cases no single country, has sufficient numbers of patients to conduct clinical trials and translational research. Geographic spread of patients has been a major impediment to recruitment into clinical trials [9]. Universities, Governments, and National and International Scientific Agencies should increase the funding support for RDs, as all the activities outlined above need long term ring-fenced financial support to succeed. The mechanistic links between rare and common diseases means this investment will benefit rare and common diseases alike.

3.2. Healthcare Systems

Diagnostic delay is a major challenge particularly as we now have disease-modifying therapies for some of these RDs. Very significantly, diagnostic delay means families may well have multiple children before the affected child is diagnosed [10]. Getting an accurate diagnosis remains a major challenge for many people with RD and is vital to ensure that informed reproductive choices can be made.

The technologies of molecular, cellular, emerging analytical technologies and bioinformatics also need teaching in the context of RD research and treatment. Progress in developing therapies has resulted in the approval of nine enzyme replacement therapy products for Lysosomal Disease by the FDA of the USA [11]. These clinical trials have demonstrated how important good trial design and validated biomarkers are to the success of clinical trial outcomes and when dealing with small patient numbers a different regulatory paradigm is needed. These aspects need to be taught at all levels of basic and translational science in the RD field. Translational science needs to be a priority in both medical and research specialty teaching. Indeed, translational research and education must go hand in hand.

3.3. Clinical care and delivery

The national care system for neurodegenerative diseases must be expanded to include children and young adults with RD. The care costs must be met by the state. Separate funding to pay for RD therapies is needed in each country, as these therapies are expensive due to low patient numbers. Also, where effective therapies have been developed, they often involve lifelong treatment (e.g., enzyme replacement) rather than a one-time intervention. This also increases the cost. Also, many available treatments, though effective, are not curative. Therefore, patients still require ongoing care and services, albeit perhaps at a lower level than if they had not received any treatment at all. RDs are interdisciplinary and bringing specialists together into specialist centers will speed progress and improve patient outcomes.

3.4. Centers of excellence

Centers of excellence on RDs are essential to ensure expert clinicians who have seen multiple cases, treat patients. This is adopted in some but not the majority of countries.

These centers should be comprised of experts in different areas of knowledge. The experts within each Center also need to work together in an interdisciplinary team (Neurologists, Radiologists, Ophthalmologists, Cardiologists, Biologists, Biochemist, Geneticists, Molecular Biologists, Nutritionists, Dentists, Psychiatrists, Psychologists, etc.) for the study of RDs. In this sense, Centers of Excellence provide a “medical home” for individuals with RD and speeds the process of achieving a diagnosis. A great advantage of this model is the association among these Centers of Excellence with Universities to conduct research to understand disease mechanisms and innovate new therapies. Consolidating patient cohorts also allows for: better physician/practitioner learning clinical database design, enrollment and maintenance establishment of biorepositories. This must be done at both the national and international levels.

3.5. Patients and parents advocacy groups

The lysosomal disease community is very active at the clinical, scientific and patient organization levels. However, access to clinical and social care is very variable between and even within countries posing a significant challenge to the health system and patients and their families [12]. The key limitations include lack of knowledge about RDs, insufficient medical research on causes and the course of RDs, as well as challenges for patient organizations to work together and pool their resources and know how.

The main role of patient's organizations is to advocate to improve legislation through the generation and/or regulation of national and international laws for RD using the highest standards. The individual countries through these national laws should provide medicines, social care, help improve and speed the process of diagnosis, follow patients' long term and provide genetic counseling and other services.

Families need to organize themselves in NGOs to raise awareness using a variety of media (radio, television, magazine articles etc.) to raise awareness and advocate approaches to solve the problems they face (e.g. diagnostic delay and access to treatments) in order to make the challenges associated with RDs visible to the whole of society. They can also highlight best practice in different countries so that more regions improve their health care systems to better treat patients with RDs. The creation of Web pages with comprehensive and fully integrated information on RDs, with options that include different languages, access for families and health care professionals and include information about Centers of Excellence and Family Associations, provide a very useful tool (Table 3). This is necessary and important because families have Internet access, but can't easily evaluate the quality of the information provided on the various disparate web sites that currently exist. Dedicated professionals or experts in RDs are needed to validate and filter the information to maximize the benefit of this information. Advice on unproven/unregulated experimental therapies and their risks also needs to be available to patient's families understandably desperate for supposed “cures” for their children.

International alliances of patient groups will help foster new groups in different countries and support their initiation. Legal frameworks to promote the formation of patient organizations and providing representatives for these activities in national parliaments would be highly desirable. According to the European Commission RD 2014 [1], recommendations are to have financial support through the tax system for companies to promote the funding of patient organization and scientific meetings. Equality of access between companies and the research community needs to be ensured. Company registries need to be open.

Patients should have ownership of registries and manage governance and ethical issues, although this is not yet common practice.

3.6. Industry

RD has traditionally received far less attention from pharmaceutical companies than more common diseases. RD have often been overlooked because of a myriad of reasons including: lack of research on the disease state, difficulty in finding and retaining patients to participate in clinical trials, getting coverage approvals from payers, spreading market awareness about the disorder and the financial return of such therapies [13,14].

Investigating the strengths and limitations of the current development pathways for new drugs, medical devices, and biologics for rare diseases would give a basis for further and innovative developments.

Significant collaborative partnership is required in areas of medical research and product development. The relationships between the pharmaceutical industry, foundations, patient-advocacy groups, academic and government investigators and funding programs, regulatory bodies, and reimbursement agencies need to be analyzed in an educational context to evaluate their impact on people with RDs [15]. The scientific and technical knowledge should be translated in order to develop safe drugs with greater efficacy and better quality standards and that are accessible to all patients.

3.7. International and national (regional) regulations and conventions

1. The recent report of the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD) aims to provide an informative and descriptive overview of RD activities at the European Union (EU) and Member State (MS) level in the field of RD and orphan medicinal products up to the end of 2013. Regarding educational issues, some countries have made remarkable progress. For example, France was the first EU country to adopt, at the end of 2004, a comprehensive RD plan with allocated funding, including the key objective to train health professionals to better identify RD. Greece has upgraded services for diagnosis, therapy and rehabilitation of RD patients with emphasis on training of health care professionals to improve diagnosis and access to high quality health care. Bulgaria has created and endorsed the professional qualification of medical specialists in the field of early diagnostics and prevention of RD.

The Spanish strategy for RDs includes education and training. The evaluation has also shown that it is necessary to implement actions aimed at collecting and disseminating information and resources available on RDs, to increase training of primary health care professionals, on diagnosis of RDs and to establish adequate criteria for referral, to improve the availability of basic health information to the teaching staff that cares children with RDs.

The Czech Republic National Strategy includes the goal of improving information and education. The Netherlands has made a statement about the key bottlenecks for the plan, including lack of knowledge about RDs, insufficient medical research on causes and the course of RDs as well as the inability of some patient organizations to work well together. The plan recommends emphasizing knowledge about RDs through training and the establishment of expert centers, making information widely accessible to diverse audiences; making financial resources available for research and development of treatments as well as maintaining consistent policy for claims and reimbursement of orphan drugs. In 2013 the United Kingdom Government published a strategy on rare diseases, that contains over 50 commitments in 5 main areas, with the aim of ensuring that people living with a rare disease have access to the best possible evidence-based care and treatment from health and social services, via working together with charities, researchers and industry [16]. In Germany a total of 52 policy proposals have been included in the

respective plan covering 7 action fields one of them related to Information Management, Medical and Dental Training and Continued Education.

2. The National Organization for Rare Disorders (NORD) [17] in the USA, is a unique federation of voluntary health organizations dedicated to helping people with rare “orphan” diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

When NORD conducted an informal survey on this topic among social media followers, they found that it took five years or longer to get an accurate diagnosis for 40% of those who responded (NORD). This situation highlights that getting an accurate diagnosis still remains a major challenge for many people with RDs. The US Food and Drug Administration, a governmental agency, also has the “Office of Orphan Products Development” which is a specific office within the FDA to advance treatments for rare diseases [18]. Within the National Institutes of Health (NIH), there is the Office of Rare Disease Research (ORDR) to identify, stimulate, coordinate, and support research to respond to the needs of patients who have any one of the approximately 6800 rare diseases known today [19].

3. The Charter on Human Rights and Bioethics, of the United Nations, 2005 [20]: in dealing with ethical issues raised by medicine, life sciences, and associated technologies as applied to human beings. The Declaration, as reflected in its title, anchors the principles it endorses in the rules that govern respect for human dignity, human rights and fundamental freedoms. By ensuring bioethics in international human rights and by ensuring respect for the life of human beings, the Declaration recognizes the interrelation between ethics and human rights in the specific field of bioethics.

The relationship of Bioethics education, training and information is considered by Article 23: In order to promote the principles set out in this Declaration and to achieve a better understanding of the ethical implications of scientific and technological developments, in particular for young people. States should endeavor to foster bioethics education and training at all levels as well as to encourage information and knowledge dissemination programs about bioethics.

4. The purpose of the Convention on the right of persons with disabilities [21] is “to promote, protect and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity. Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others”. This convention used a different approach than the RD specifically.

5. The health-related quality of life (HRQOL) in children with inborn errors of metabolism IEM and co-existent movement disorder is significantly reduced compared to other chronic, stigmatizing disorders. Delay in adaptive functioning and a more severe movement disorder were associated with a lower HRQOL. Accurate classification of movement disorders, particularly in the context of complicated, multi-organ disorders, is likely to aid therapeutic management, especially since effective therapeutic options are available. It is necessary for greater awareness of the presence of movement disorders since targeted therapies might lead to improved motor function and possibly subsequent overall quality of life [22]. Research data on psychosocial factors in rare inborn errors of metabolism patients are generally sparse. However, the growing interest in the topic is underlined by the fact that seven of the 11 articles reviewed were published in 2012 or 2013. Multicenter studies and the use of a standardized, disease-specific assessment tools are needed to establish health-related quality of life-as an important additional outcome parameter in patient-centered research and clinical trials on RD [23].

6. A call for action to improve access to care and treatment for patients with rare diseases in the Asia-Pacific region to improve access to care

and treatment for patients with RD by looking into three main areas: (a) developing legislative definitions to confer enforceable protection, (b) creating or strengthening policies by objectively measuring the impact brought about by rare diseases and establishing platforms to reach out to the rare disease community, and (c) fostering collaboration across sectors and countries. It is hoped that these suggested actions can catalyze discussions and progress in the region [24].

The Human Varioma Project (HVP) [25] was started in 2006. The goals are many but primarily to generate a complete record including genetic data and all other information that may modify the clinical phenotype. It is an international megaproject. Collection is done at a national and at a regional level. It has now expanded to an active and growing Consortium of 81 countries that collaborate to develop and maintain the necessary standards, systems and infrastructure to support global-scale genomic knowledge sharing.

7. In Latin America, the Center for Research on Inborn Errors of Metabolism in Córdoba-Argentina (CEMECO) has gathered experience for more than 30 years in translational research and providing services to RD affected patients. The field of RD is very active in Latin America and the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening (SLEIMPN) organizes conferences in the region every two years. It recently developed an online Journal based in Brazil devoted to RDs and associated issues, entitled the Journal of Inborn Errors of Metabolism and Screening (JIEMS) [26]. A National Law for RD was approved by the National Parliament of Argentina in 2011 [27].

3.8. Academia, Health Science and Medical Schools

In contrast with the remarkable progress made by government agencies on the RDs, the academic sector lacks initiatives to improve the knowledge of health professionals on complex topics such as RDs. To train scientists and other professionals in RD changes are needed in Academia, Health Science Training and Medical Schools.

RD education is lacking worldwide, particularly in medical training with no specialized courses on the clinical picture, models of disease, therapeutic interventions and the social and ethical issues around RDs. Another deficit in the Health Sciences curricula is related to the teaching of clinical features of patients affected with RD. Medical doctors cannot suspect or study conditions that they do not know exist. Therefore, it is important to ensure the inclusion of RDs early in medical careers and promote postgraduate courses for different medical and connected specialties involved in the care of children.

Education on clinical research and experimental medicine, and its role in understanding diseases and developing novel therapies is not taught in most universities. The translational process needs to be explained and stimulated through teaching and links with basic and pharmaceutical industry scientists [28]. Teaching needs to focus on how to maximize patient, scientific and company interactions.

The teaching of ethical issues is essential for research with both humans and in animal models [29]. Patients with low income often fail to access specialized services and treatments leading to social and medical inequality. Therefore, it is important to develop recruitment and subject engagement practices that will increase diversity with respect to access and participation in clinical trials. The ethical and practical challenges associated with tissue banks, organ donation post-mortem and the sources of control human material also need greater discussion and teaching [30].

Mechanisms to prevent potential corruption and manage conflict of interest and best practice guidelines should also be developed in parallel and should not be viewed as an obstacle to cross-sector collaborations. Regulatory agencies need to be educated on the fact that trial design and implementation differs in the RD field in order to preserve the principles proclaimed in the Charter on Human Rights and Bioethics, of the United Nations 2005 [20]. Some countries have similar declarations or national acts.

Screening and prevention strategies, including pre-natal diagnosis and pre-implantation embryo selection techniques need considering in the RD context [31]. International patient registries need creating/unifying and must be governed in perpetuity by the patient communities/researchers not by the pharmaceutical industry. International equity needs to be achieved for reproductive choices, including screening, termination of pregnancy and access to embryo selection technologies. Quality of life is sanctity of life [22,23].

Any professional training program on NCL or other RDs must take into account the medical, social and economic burdens associated with RDs:

1. To understand the widespread impact of NCL as RDs: with an estimated 8000 or more different metabolic RD in the world, there are many individuals who require specialized services and understanding of their rare condition.
2. To appreciate the need for interdisciplinary care of children: it is important for children to have a team of health care providers who communicate with one another and work together for the benefit of the child.
3. Importance of supporting the psychosocial needs of the family: in educational settings, medical students, residents, fellows should all receive training in how to be sensitive to the needs and burdens upon the family, in relation to the child's illness. They should be trained in how to give the diagnosis with sensitivity and compassion and provide information on organizations devoted to supporting individuals and their families affected by RD.
4. Importance of training in ethical matters related to both clinical care and clinical research.
5. Importance of training (at the post-graduate level – for residents/fellows) in the fields of clinical research and experimental therapeutics. In the course of their clinical training, physicians can learn how to administer a particular treatment, but better still, we urge a model in which physicians will have opportunities to be trained in how to investigate and develop new treatments – to not simply become physicians who “use” the existing science to treat children, but rather, professionals who contribute to the development of new knowledge.

The suggested guidelines specific to NCL are intended to highlight the importance of the following items:

1. To recognize the differences among the different genotypes and phenotypes of the NCLs. Not all NCLs are created equal. For example, children with CLN1 and CLN2 diseases often develop intractable seizures, whereas seizures are less common and more easily managed in CLN3 disease [32]. Thus, seizure management will be different and may be specific to the genetic type. Indeed, some commonly used drugs are detrimental for NCL patients, clinicians need to know this [33].
2. To develop confidence in providing care for children with the NCLs. It would be very helpful to have consultation with an expert, and from that consultation, local physicians should begin to feel confident in following the treatment plan suggested by the expert disseminating this knowledge and best practice. Also, though some symptoms are uniquely managed because of the NCL diagnosis, many can be managed with the existing good standard of care.
3. To shorten the time to diagnosis. There should be training in how to access diagnostic services including newborn screening and the financial resources available to pay for the diagnostic testing so that economically disadvantages families are not prevented from receiving diagnosis in a timely fashion.
4. To provide care (or arranging care) for associated features. For example, a dentist who has cared for many children with other RDs is aware that these children require specialized attention and that often their dental health is neglected (P. K de Hidalgo, personal communication). Though poor dentition is not an NCL-specific symptom,

it can develop simply because these children are difficult to care for in general. Dental health is one example, but there are many other general health issues that need to be considered as well.

- The changes in the medical and health science undergraduate curricula could begin with the identification of spaces in current courses where an introductory lecture on RDs can be inserted. This would cover: general concept of genetic disorders; lysosomal diseases in general; clinical presentation; existing therapies and experimental approaches. At the Postgraduate level: workshops can be run with the aim to go into more detail of a particular disease (NCL), genetic causes, cell biology, model systems, experimental therapies and future prospects for trials. The logistical issues include the need to know current course structures and where best to place these lectures (in a RD theme), the selection of an adequate lecturer or team to deliver these lectures, the reinforcement of ideas through tutorials (on line or face to face) and the assessment of the students *via* exams. In recent years, some innovative learning approaches have been proposed to increase health professionals training and awareness on RD [34,35].

4. Discussion

The delegates agreed on the need for an innovative integration of RDs into the medicine curriculum as well as in Continuing Professional Development (CPD) and Continuing Medical Education (CME). The complexity of RDs requires a broad understanding of a variety of concepts including the implications of diagnostic delay, quality of life, respect for patient's family opinions, equity of access to treatments, all within a strong ethical framework. The literature retrieved from bibliographic databases, such as PubMed, was very limited on the topic of educational issues in RDs. Even when the numbers of citations on RDs was expanded to include the last 10 years (from 5754 in 2005 to 12,646 in 2014), the articles regarding medical education numbered 377 for the entire period. When these articles were manually analyzed their relevance was very low. Only one article from the 377 includes in the title both term "Rare diseases" and "medical education" [36]. In the Orphanet Journal of Rare Disease (OJRD) a search in the same period retrieved 64 citations and only 2 included both terms in the title [34,37]. Both citations are abstracts of oral presentations from the 5th European Conference on Rare Diseases (ECRD 2010). More relevant information can be accessed on web sites such as Orphanet, NORD, EURODIS and others.

These data support the conclusion that the issue of medical education in RDs is not "specifically" described in the articles analyzed, although in some paragraphs tangentially mentioned the necessity of including RDs in the curricula.

Table 2 reports on the current situation of education on RD in a condensed format. The Table summarizes the recommendations and targets for challenges to be accomplished by different countries with regard to the international regulations and conventions. To follow the progress and evaluate the state of the education in the RD field, such a summary should be periodically updated in order to assess the progress achieved in each country that signed the international conventions involving RD issues. Table 3 provides a list of NCL resources. There are other sites that have a more focused emphasis on registries (DEM-Child; Massachusetts General Hospital's Registry & tissue bank).

5. Challenges

Health care professionals need formal training in RDs as a cornerstone of medical training. Getting an accurate diagnosis in a rapid timeframe is essential but still remains challenging even in developed countries. Other challenges include developing the basic tools researchers need, such as longitudinal natural history studies and encouraging a more collaborative approach to medical research, as is advocated in a new law enacted in recent years (26,689 2011-Argentina the National Pediatric Research Network Act of 2013-USA). Funding of basic and applied research in RDs is essential. This should be significantly expanded and ring-fenced for RDs.

The new initiative on Precision Medicine [38] will encourage and support the next generation of scientists to develop creative new approaches for detecting, measuring, and analyzing a wide range of biomedical information. The RD community can contribute very significantly to this endeavor.

Assuring patient access to therapies remains a challenge and must be one of the priorities to resolve. Far too often, we see individuals and families struggling to gain access to the medical care and services they need. To address the challenges and find solutions is necessary that individuals in the government and administrative authorities, academia, teaching hospitals and medical schools, the pharmaceutical industry, investment community and patient advocacy groups all work together to achieve these goals. The fundamental conclusion from the workshop is that we must start with better education on RDs as without

Table 2
Model for strategies and guidelines for education improvements on RD. Modified from <http://www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf> and integrated with the general conclusions and guidelines.

Current situation	Recommendations		Target of recommendation
Lack of awareness and identification of RD among healthcare professionals, resulting in a delay in diagnosis or misdiagnosis of RD patients.	1. Increase healthcare professionals' knowledge and awareness of RD: 2. Need for improved linkage between specialist centers and local healthcare professionals.	a. RDs module in medical curriculum. b. CPD/CME training. c. Medical care providers training in basic genetics. d. e-learning packages by qualified professionals.	Medical and health science schools. Health departments The Academia under the guidance of National Health Systems Clinical service managers, healthcare professionals. National Health System, patient organizations. Commissioners. Rare Disease ONGs TV media set
Difficult for both professionals and patients to access reliable, up-to-date information on RDs and who the specialist(s) is/are in a particular condition.	3. Improve access to reliable information on RDs to make it easier for the public and professionals to obtain information.	a. Online portal linking to reliable information and guidelines. b. Appraisal of healthcare professionals' information needs and gaps in existing resources. c. Ensure Orphanet funding. d. Responsible clinician in a Directory of Genetic Testing. e. Training on the use of diagnostic tools as part of projects. f. Guidelines "index of suspicion" to doctors.	All health departments. Joint Committee on Medical Genetics, Colleges and Deans of Health science and medical schools Department of Health. Funding bodies. Joint Committee on Medical Genetics.

Table 3
NCL and general rare disease patient support and advocacy groups.

Organization	Country	Website
NCLs		
Asociación Española de Familias Afectadas por Lipofuscinosis (Aefal)	Spain	www.aefal.org
Associazione Italiana per la NCL	Italy	www.ceroidolipofuscinosi.it
Australian Batten Disease and Support Association	Australia	www.battens.org.au
Bartimeus	Netherlands	www.bartimeus.nl
Batten Disease Family Association (BDFA)	United Kingdom	www.bdfa-uk.org.uk
Batten Disease International Alliance (BDIA)	United Kingdom	www.bdfa-uk.org.uk/batten-disease-international-alliance
Batten Disease Support & Research Association (BDSRA)	USA	www.bdsra.org
Bee for Battens	Ireland	www.beeforbattens.org
Beyond Batten Disease Foundation (BBDF)	USA	www.beyondbatten.org
Contact Punkt NCL	Belgium	www.contactpuntncl.be
Dansk Spielmeier–Vogt Forening/Danish NCL Family Association	Denmark	www.dsvf.dk
Finnish INCL Association (Suomen INCL yhdistys)	Finland	www.incl.fi
“Life” Association against child rare illness	Serbia	www.zivotorg.org
Lyosomal Diseases New Zealand (LDNZ)	New Zealand	www.ldnz.org.nz
NCL-Gruppe Deutschland e. V.	Germany	www.ncldeutschland.de
NCL Resource – a gateway for batten disease	United Kingdom	www.ucl.ac.uk/ncl/familysupport.shtml
Norsk Spielmeier–Vogt Forening (NSVF)	Norway	www.nsvf.org
SSVF – Svenska Spielmeier–Vogt Föreningen	Sweden	www.ssvf.nu
The Children’s Brain Diseases Foundation (CBDF)	USA	nd
Rare Diseases in General		
Alianza Iberoamericana de Enfermedades Raras (ALIBER)	Argentina, Brazil, Colombia, Ecuador, Guatemala, Mexico, Portugal, Spain, Uruguay and Venezuela	www.aliber.org
Asociación de Pacientes de Enfermedades Lisosomales	Argentina	www.apelra.org.ar
Canadian Organization for Rare Disorders (CORD)	Canada	www.raredisorders.ca
Children Living with Inherited Metabolic Diseases (Climb)	United Kingdom	www.climb.org.uk
Contact a Family	United Kingdom	www.cafamily.org.uk
Fundación Geiser	Argentina	www.fundaciongeiser.org
Gene Reviews	USA	www.genereviews.org
International Conferences for Rare Diseases and Orphan Drugs	Sweden	www.icord.se
National Center for Biotechnology Information–Genetic Testing Registry	USA	www.ncbi.nlm.nih.gov/gtr
National Organization for Rare Disorders (NORD)	USA	www.rarediseases.org
ORDR Office for Rare Disease Research	USA	www.rarediseases.info.nih.gov
Rare Diseases Europe (EURODIS)	Europe (International)	www.eurodis.org
Clinical Care & Research Centers for the NCLs		
Blue Bird Circle Clinic Texas	USA	www.texaschildrens.org
Centro de Manejo Integral de Enfermedades Raras (CEMINER)	Chile	www.redclinica.cl
Children’s National Hospital Columbus, OH	USA	www.nationwidechildrens.org
eUniversity of Rochester Batten Center, NY	USA	www.urmc.rochester.edu/neurology/batten-disease-center
Evelina London Children’s Healthcare: Batten disease service London	United Kingdom	www.evelinalondon.nhs.uk/our-services/hospital/batten-clinic/overview.aspx
Gifu University	Japan	www.hosp.gifu-u.ac.jp/eng/index.html
Hospital de Clinicas–Porto Alegre	Brasil	www.hcpa.ufrgs.br/
Hospital das Clinicas–Universidade de Sao Paulo	Brazil	www.hc.fm.usp.br
Hospital de Niños de Córdoba	Argentina	www.Hospitaldeninos.com/ar/hn/index.php
Instituto de Errores Innatos del Metabolismo Pontificia Universidad Javeriana	Colombia	www.javeriana.edu.co/ieim
Instituto de Nutrición y Tecnología de los Alimentos	Chile	www.inta.cl
Instituto Nacional de Medicina Genómica	Mexico	www.inmegen.gob.mx
Instituto Nacional de Pediatría	Mexico	www.pediatría.gob.mx
Massachusetts General Hospital Boston	USA	www.massgeneral.org
Orphanet	Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Israel, Italy, Latvia, Lebanon, Lithuania, Morocco, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom	www.orpha.net
SeeAbility	United Kingdom	www.seeability.org/our-specialisms/book/juvenile-batten-disease
Servicio de Neurología Hospital Clínico San Borja-Arriarán	Chile	www.hospitalclnicosanborjaarriaran.gob.cl
Women’s and Children’s Hospital, N. Adelaide	Australia	www.wch.sa.gov.au

this cornerstone these goals will remain an aspiration and not become a reality.

Conflict of interest

We declare no conflicts of interest.

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