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Workshop Program

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8.00 | Registration

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CHAIRS: D. TARUSCIO, M. POSADA

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|----------------------|---|
| 9.00 – 9.20 | European initiatives and implementation of the European Reference Networks
J. WALIGÓRA |
| 9.30 – 9.50 | The National Institutional Rare Diseases Registries in Europe
D. TARUSCIO, L. VITTOZZI |
| 10.00 – 10.20 | eHealth Implementation status in EU MS: perspectives on using EHR and other services
Z. KOLITSI |
| 10.30 | Break |
| 11.00 – 11.20 | Ethical and Legal Aspects of Data Linkage and Sharing
M. HANSSON |
| 11.30 – 11.50 | Patients willingness to participate in registries
A. KOLE |
| 12.00 – 12.20 | Patients' empowerment and registries
R BARBON GALLUPPI |
| 12.30 | GENERAL DISCUSSION |
| 13.00 | Lunch break |
| 14.00 | Poster session |

SESSION II - RESULTS, EXPERIENCES AND USE OF REGISTRIES

CHAIRS: MA. STAZI, M. SALVATORE

(*) Presentations selected from the abstracts received

- | | |
|----------------------|--|
| 15.00 – 15.20 | The Eurofever registry
M. GATTORNO |
| 15.30 – 15.45 | Characterization of high-quality Rare Disease Registries by using a data mining approach
(*) A. COI |
| 15.45 – 16.00 | Activities of the National Registry of Hemolytic Uremic Syndrome (HUS) in Italy, 1988-2014
(*) G. SCAVIA |
| 16.00 – 16.15 | Eurocat surveillance: Making Congenital Anomalies Preventable Rare Diseases
(*) A. J. NEVILLE |
| 16.15 – 16.30 | Guidelines for optimal use of registries in trial design for small populations
(*) M.C. JANSEN-VAN DER WEIDE |
| 16.30 – 16.45 | Medicines for paediatric rare diseases in EU and US
(*) V. GIANNUZZI |
| 16.45 | Discussion and Adjourn |

TUESDAY, NOVEMBER 25TH, 2014

SESSION III - THE INTEGRATION OF REGISTRIES WITH OTHER RESEARCH TOOLS

	CHAIRS: P. TASCHNER, L. VITTOZZI
9.00 – 9.20	The Human Phenotype Ontology project S. KÖHLER
9.30 – 9.50	BBMRI-ERIC and Rare Diseases – a platform for sustainability M. PASTERK
10.00 – 10.20	Discovering Value in RD and Registry Data A. BROOKES
10.30 – 10.50	Genetic variation databases and the HGVS nomenclature P. TASCHNER
11.00 – 11.20	Bring Your Own Data parties and beyond: make your data linkable to speed up rare disease research M. ROOS
11.30	Break
12.00 – 12.20	The European Society for Immunodeficiencies (ESID) Registry: recent advancements in the epidemiology of Primary Immunodeficiencies and how does that translate in clinical care N. MAHLAOU
12.30	GENERAL DISCUSSION
13.00	Adjourn

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R. Barbon Galluppi – *UNIAMO FIMR onlus*
Aj. Brookes – *University of Leicester, UK*
A. Coi – *Istituto di Fisiologia Clinica, Consiglio Nazionale delle Ricerche, Pisa, Italy*
M. Gattorno – *IRCCS G. Gaslini, Italy*
V. Giannuzzi – *Fondazione per la Ricerca Farmacologica Gianni Benzi onlus*
M. Hansson – *Centre for Research Ethics & Bioethics, Sweden*
M.C. Jansen-van der weide – *Academic Medical Center, The Netherlands*
S. Köhler – *Charité - Universitätsmedizin Berlin, Germany*
A. Kole – *Eurordis Rare Diseases Europe, France*
Z. Kolitsi – *Aristotelean University of Thessaloniki, Greece*
N. Mahlaoui – *Hôpital Universitaire Necker-Enfants Malades, France*
J. Waligóra – *Directorate General Health and Consumers European Commission*
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Preface

Luciano Vittozzi, Marco Salvatore, Domenica Taruscio

NATIONAL CENTRE FOR RARE DISEASES, Istituto Superiore di Sanità, Via Giano della Bella 34, Rome, e-mail: epirare@iss.it

In line with the aims of the EPIRARE project¹, the EPIRARE Workshops have been convened to facilitate the cross talk among the different stakeholders of rare disease registries, in order to share issues and solutions and increase the visibility of the registration activities.

Two previous EPIRARE Workshops, in 2012 and 2013, have brought together patient associations, clinicians, policy makers and the industry, mainly to discuss their needs regarding registries and to show the importance of the registry management not only with reference to scientific questions, but also to the patient expectations and to the communication of results beyond the scientific community.

This third EPIRARE Workshop extended its focus on the developments going on in bioinformatics and communication technology, which may have great relevance for genomic and clinical research and for the health care of rare diseases. The workshop general discussion highlighted the importance of keeping the patient's interest in the centre of the many different approaches presented, to break the silos in which knowledge is being developed, which means unnecessary and useless fragmentation of tools, references and standards. Therefore, all the participants agreed with the proposal to establish a frequent and regular exchange, based on physical meetings and telephone conferences, among the main initiatives in the different scientific and technological domains.

This supplement includes short papers of the invited presentations and the abstracts submitted by registered participants following the call of the organizers to submit contributions in the following four topics:

1. Contribution of registration activities to recent advancements in the natural history, epidemiology and pathogenesis of rare diseases as well as patient care and quality of life;
2. Practical and innovative applications of registries, such as recruitment of patients in clinical trials, social and health service planning, patients' support networks and integration with other initiatives, such as biobanks and databases for genomic and phenomic analysis;
3. Lessons learned in the management of RD registries, e.g. regarding financial sustainability, quality assurance, ethical issues and patients' confidence, data protection, ownership and accessibility, as well as patients' contribution, involvement and advocacy initiatives;
4. The impact of e-health initiatives, new communication technologies and social networks.

Five abstracts, among those received, were selected by the Workshop Scientific Committee for oral presentation. All other abstracts were presented as posters.

¹ The project "Building Consensus and Synergies for the EU Registration of Rare Disease Patients" (EPIRARE) has been co-funded by the European Union within the Action Program on Health (Grant n. 20100212), and was carried out from April 2011 to April 2014.

eHealth Implementation status in EU MS: perspectives on using EHR and other services

Zoi Kolitsi

Informatics and Information Security Laboratory, Aristoteleio Panepistimio Thessalonikis, Greece

INTRODUCTION

Health in CEF

EThe eHealth Network, which has been established through Article 14 of Directive 2011/24/EU, is a critical element of the European eHealth Governance (1); its objective is to facilitate the cooperation and the exchange of information among Member States, to work towards delivering sustainable European eHealth systems and services and interoperable applications. During its Spring 2014 meeting the eHealth Network endorsed four priority areas of cross border services to be considered for support by the Connecting Europe Facility (CEF), namely, cross-border patient summary services; cross-border ePrescription and eDispensation services eHealth services for European Reference Networks and Infrastructure services for European patient registries.

The first two of these services – Cross Border Patient Summary and ePrescription/eDispensation - have been piloted on a large scale in epSOS and have been identified as meeting the eligibility criteria for CEF in 2015. These services should be considered within the broader mandates of the cross border Directive, which aims to support movement of patients and/or information across borders in the context of the provision of care. Continuity of care is recognized as one of the major objectives and as such it is supported by several legal provisions such as for recognition of prescriptions and for increased co-operation between Member States (MS).

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The other two services, supported by the eHealth Network - European Reference Networks and Interoperable Patient registries - will be taken into consideration in the WP 2016.

EXPAND is providing a bridge between epSOS and CEF and is preparing the relevant assets for hand over to CEF towards deployment of eHealth services. It also aims to demonstrate expandability beyond the epSOS eHealth services to other priority services of the Directive, including but not limited to, services for Registries and European Reference Networks.

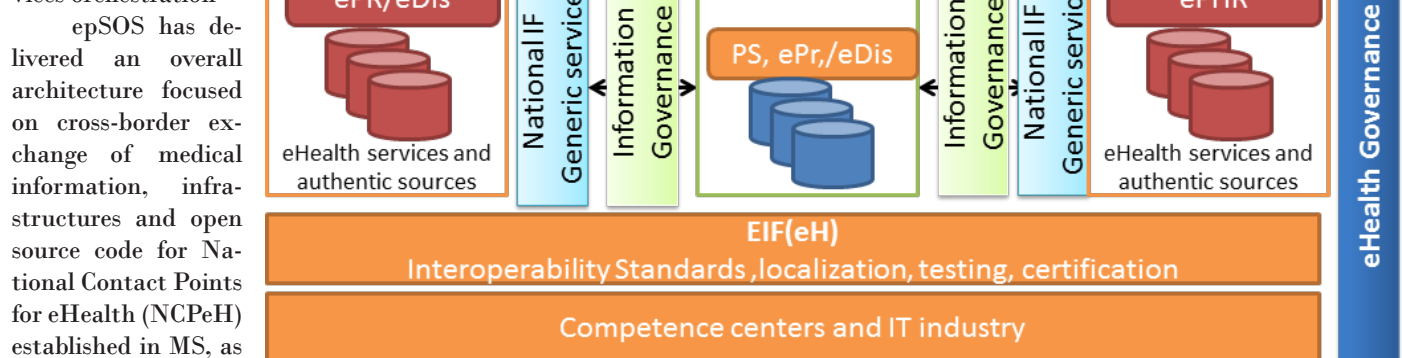
METHODS

The role of EXPAND

Cross border eHealth deployment requires EU and national/regional level services orchestration, as shown graphically in **figure 1**. The ability to link national infrastructures in a cross border care continuum implies that National Infrastructures are compliant to EU level interoperability agreements i.e., have implemented EU specifications for cross boarder services; incorporate appropriately localized EU level interoperability components; are connected to EU level core eHealth services via localized generic services and observe the requirements of the EU level (information) Governance.

The services shall also employ re-usable Digital Services Infrastructures (DSIs) which are being developed in the eSENS cross sectoral project and particularly, electronic identification/signature services and an electronic interaction building block of eHealth.

Figure 1. Cross border – national/regional eHealth services orchestration



epSOS has delivered an overall architecture focused on cross-border exchange of medical information, infrastructures and open source code for National Contact Points for eHealth (NCPeH) established in MS, as well as legal agreements, all of which can be re-used for expanding to other services. epSOS also delivered some use case specific assets in the form of interoperability specifications and semantic assets that collectively made the provision of these services possible on a pilot basis. IHE profiles incorporating epSOS specifications are currently under consideration by the European Multi Stakeholder Platform (MSP) on ICT standardization¹. Last but not least, epSOS issued a set of recommendations for long term sustainability.

The work hypothesis for EXPAND is that it is possible to swiftly expand the portfolio of available cross border eHealth services by exploiting “appropriate” eHealth assets, developed in various international or national/regional initiatives.

In order to test this hypothesis, EXPAND is working on a comprehensive framework for assessment of eHealth assets, including criteria for acceptance and quality labeling of resources. EXPAND is employing a signposting approach paradigm by bringing together and publishing or referencing a body of interoperability assets derived from multiple projects, including epSOS, and by offering these in a way that is organized by use case and clinical scenario. Eventually, by doing so, the project will be expanding on the current epSOS concept of unscheduled care use case for the exchange of medical summaries, to examine planned care scenarios. The assets themselves will be developed and maintained by their “owners” i.e., initiatives and projects at EU and at national level.

Interoperability Assets

Key resources for launching cross border eHealth services may be grouped in the following categories:

A) National/regional eHealth infrastructures, interoperability assets and authentic sources, provided by MS are part of the existing national /regional eHealth infrastructures. They are expected to continue to evolve in convergence with EU level standards and specifications. Eventually cross border services may be seamlessly integrated in national services.

B) EU interoperability assets and authentic sources to be developed maintained and managed at EU level (eHealth specific and horizontal). These include interoperability specifications, open source software, semantic resources, a testing platform and

¹ The MSP advises on matters related to the implementation of ICT standardization policies including on the endorsement technical specifications for public procurements, developed by Standardization organizations.

tools, as well as interoperability agreements and the European eHealth Interoperability Framework. These assets should be made available through authentic sources i.e. based on facts, accurate or reliable (e.g. an asset registry).

C) EU organizational structures and governance to deliver maintain and manage EU eHealth interoperability assets. They include assets held by MS in the form of localized EU level assets and national connectors to EU level central services.

CONCLUSIONS

In view of the stated eHealth Network priorities for cross border services that support cross border objectives for registries and European Reference Networks, it is important to engage in an exercise to explore potential use cases in these two areas of activities to be supported by CEF. Mature assets for such use cases need to be also identified and prepared by their creators for deployment in CEF. This will benefit from a closer co-operation between the eHealth and the public health communities that have largely worked so far quite isolated from each other.

It is important to note that CEF will offer a short time window of European funding for core and generic or specific eHealth priorities, but beyond 2020 these services must be self sustainable. The activities within CEF should therefore lead to permanent solutions based on optimizing multi-stakeholder value chains that maintain a perpetual cycle of investments in interoperability, that become embedded within the larger health care ecosystem and health ICT sectors.

REFERENCES

1. Kolitsi Z, Thonnet M. New Directions in eHealth Governance in Europe Managing eHealth From vision to reality. Palgrave MacMillan; 2014

Patient Willingness to Participate in Registries

Kole, A.¹ Ensini, M.², Santoro, M.³, Faurisson, F.⁴, McCormack, P.⁵, Houyez, F.¹

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BACKGROUND

Patient data collection and data sharing represents fundamental research efforts upon which a number of critical activities are based. This is particularly true for rare diseases (RD), which due their low prevalence require a comprehensive registration of patients often scattered across countries and data collections. Upstream, the ability to collect and link clinical and genetic data in registries is crucial to translational research contributing significantly to the identification of genes associated with disease, an understanding of the frequency of genetic variants in populations. Downstream, data collection, sharing and analysis leads to a better understanding of the reasons for drug reactions in the clinical trial or post-marketing context. As globally accepted standards, congruent policies and favorable resources facilitating data collection and sharing are being developed, the European Organisation for Rare Diseases (EURORDIS) has been actively unifying the voice of European rare disease patients on the subject of data collection and data sharing to ensure that these efforts remain patient-centric.

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METHODS

The work represented here is part of an extensive on-going consultation process with rare disease patients and representatives from 2010 until present that includes:

- » A quantitative survey on patient experience and expectations with respect to several aspects of patient data collection and registration.
- » Ongoing qualitative research investigating patient perspectives on sharing and integration of –omics, registry and biobank data
- » Consultation of EURORDIS working groups on the EMA policy regarding transparency of clinical study reports from marketing authorisation application
- » Future reflection process and consultation with EURORDIS working groups on the publication of individual patient data in the clinical study context

RESULTS

Patient Survey on data collection and registration

In the context of the EPIRARE project, a survey of 3437 people living with rare diseases in Europe was completed between 1 July, 2012 until 1 February, 2013. Overall, respondents expressed a preference for registries that allow healthcare and social planning (42.3%) in addition to treatment evaluation (33.8%). A strong preference was observed to make the most of patient data, even when a registry closes (76.9%). To be best informed about their participation, respondents particularly preferred receiving information about the registry's aims (66.0%). Similarly, a large majority of respondents underscored the importance of patient representation in the governance of patient registries (76.3%) and access to their own data (88.8%). Above all, respondents reported being in favor of a common European registry infrastructure (90.7%) and uniform legislative framework across Europe (84.8%).

Empirical research in data sharing and integration

Throughout May and June 2014, 52 patients participated in 5 focus group discussions at EURORDIS events to collect data exploring the views of rare disease patients about linking and sharing data as part of its work in the RD Connect project. Participants discussed prepared scenarios which were recorded, transcribed and are currently undergoing analysis. Findings will be published in an academic article to be submitted early in 2015. Overall, rare disease patients recognize the importance of data sharing and integration in facilitating breakthrough discoveries in rare disease research, but express a range of expectations under which conditions this sharing and integration must be executed as integration of clinical and genetic data heightens real and perceived risk of patient identification and data misuse.

EURORDIS position on transparency of clinical study reports

After a lengthy debate with internal working groups, EURORDIS supported and influenced the EMA policy on publication of clinical trial data in which summary results of clinical trial data of medicinal products with marketing authorization in Europe are to be made public. Data can be viewed and downloaded to ensure that it can be analyzed and re-evaluated as required while respecting the interests of original sponsors and, above all, the interest of the patients.

Consultation on publication of individual patient data from clinical studies

Access to individual patient data from clinical studies has raised even more concerns than access to clinical study reports, as real risks for patient identification, particularly for rare disease patients exist.

An internal EURORDIS working group has agreed on a model of controlled access, with an independent review process as the best way to ensure appropriate access to clinical trial data. This model gleans lessons from existing data access committees such as those that oversee data requests in genomics studies and cohort studies.

Further consultation will seek to clarify which data should be shared, with whom and for what purpose, but any mechanism proposed will be both proportionate and realistic. For example, with appropriate consent and where it is feasible to do so, the framework should ideally include sharing of retrospective data. It is recognized, however, that there are considerable practical implications to re-consent in such contexts and the resource requirements, particularly for non - commercial trials, are significant. Nevertheless, trial participants' wishes are paramount and strong governance structures and processes need to be in place to ensure participant confidentiality is protected. It is essential to safeguard the privacy and confidentiality of research participants and ensure that data is used in line with the consent provided.

Beyond individual informational risks, another great risk in the publication of individual patient data is the potential divergence of findings in secondary analyses resulting from differing analytical methods or standards. Subsequent public controversies could lead to a public mistrust of the validity of clinical studies. To prevent this a scientific dialogue among those accessing clinical study data will be encouraged.

CONCLUSIONS

Patient perspectives on these topics are often divergent depending on a number of contexts and variables, however, major themes and expectations have emerged. The results of this consultation process and the evidence-based advocacy positions and policy proposals that follow will support the strategic objective of the European Commission in the creation of a European Platform for Rare Diseases Registration, the European Medicines Agency policy on publication of clinical trial data and will serve as tools for all stakeholders driven to establish new or better adapt existing data collection and sharing platforms in line with the highest European standards.

REFERENCES

1. Guiding Principles for Responsible Clinical Trial Data Sharing: Discussion of the Institute of Medicine Study Interim Report. Friday 31 January 2014, The Wellcome Trust.

The Eurofever registry

Silvia Federici, Marco Gattorno, on behalf of the Eurofever project and PRINTO

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INTRODUCTION

Autoinflammatory diseases (AID) are rare disorders secondary to mutation of genes involved in the regulation of innate immunity. After the identification of the first gene in 1997, responsible for Familial Mediterranean fever (FMF), a number of monogenic and multifactorial diseases have been identified or reclassified as autoinflammatory in aetiology. Although expanding rapidly, our knowledge of autoinflammatory diseases is still very limited. The main limitation is related to the extreme fragmentation of the diagnosed cases that are spread over different centers and countries. The fragmentation of the information, together with the extreme rarity of these conditions and their phenotypic variability still lead to a delayed diagnosis and, even once a diagnosis has been reached, is often difficult to provide patients and parents with definitive answers as to the best treatments available and their long term prognosis. Here hence the general aim of the Eurofever Project was to build an international registry in order to collect homogeneously clinical, biological and response to treatment information of patients affected by Autoinflammatory disease coming from different centers and countries. In particular the aims of the project were: i) to promote awareness and enhance early recognition of these diseases among the medical community; ii) to provide clear and comprehensive information to families and patients affected by these conditions, iii) to improve knowledge of the clinical presentation, response to treatment and long term complications of these disorders.

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PATIENTS AND METHODS

A web-based registry collecting baseline and cross-sectional clinical information on AID have been created and is now available in the member area of the PRINTO web-site (www.printo.it). The registry is open to all pediatric and adult Centers with a specific interest in Autoinflammatory diseases. To build the Registry, experts in autoinflammatory diseases were initially asked to identify those variables they considered of interest for each disease. A draft data collection form was then sent to all the experts for their review. Five main categories were considered: i) baseline information, ii) clinical manifestations, iii) laboratory examinations, iv) imaging and other diagnostic procedures, and v) response to treatments. Further revisions of the forms were subsequently evaluated by the experts with a final approval of the definitive version by nominal group technique during a Consensus Meeting in March 2009. Genetic testing was not mandatory for inclusion. Where performed, details on the genetic analysis were sought: gene screened, extent of the analysis, mutations detected (according to the Infever database). Finally, information on consanguinity and any relevant family history was collected. Patient data was anonymised and cases identified by alphanumeric codes. Patients affected by the following monogenic autoinflammatory diseases were initially considered: Familial Mediterranean Fever (FMF), Cryopyrin-associated periodic syndromes (CAPS), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), Blau syndrome, pyogenic arthritis, pyoderma and acne (PAPA) syndrome, deficiency of IL-1 receptor antagonist (DIRA), NLRP12-mediated periodic fever. Information on CRMO, Behçet's disease, PFAPA and undefined periodic fevers were also collected. More recently implementation with newly described AID (CANDLE, DITRA, Schnitzler, Majeed, SAVI) has been performed with the consequent modification of the clinical forms.

RESULTS

Up to date 3058 patients (children and adult), from 102 centers in 38 countries, have been enrolled in the registry. Baseline demographic data (country of residence, disease onset, disease duration, mutations, family history ect) from all patients are now available. In 2369 (77%) complete information on clinical manifestations and responses to treatments is also available. The disease distribution of enrolled patients is: FMF 876 (693 with complete clinical data); TRAPS 268 (226 complete); CAPS 284 (208 complete); MKD 188 (164 complete); Blau syndrome 71 (22 complete); PAPA 27 (22 complete); NLRP-12 mediated periodic fever 14 (9 complete); Schnitzler syndrome 1 patient, DIRA and Majeed 3 and 2 patients, respectively (all with complete clinical data).

Among multifactorial autoinflammatory diseases: PFAPA 600 (376 with complete clinical data); CRMO 414 (391 complete); paediatric Behçet disease 92 (72 complete) and 216 patients with undefined periodic fever (180 complete).

So far nine papers involving 56 different authors and 32 centers have been published in high-rank international journals, providing original information on: i) epidemiological distribution of AID in Europe, ii) genotype-phenotype correlation in TRAPS and CAPS, iii) influence of environment in FMF, iv) response to treatment in autoinflammatory diseases, v) elaboration of a new disease activity score.

DISCUSSION

Taking advantage of the large PRINTO network we were able to involve for this brand new initiative in the autoinflammatory diseases several paediatric and adult centres known to have an interest in the diagnosis and management of these patients. This was made simpler by the involvement of other parallel initiatives such as Eurotraps (<http://fmf.igh.cnrs.fr/ISSAID/EUROTRAPS/>) and Hyper IgD registry (<http://hids.net>) and international scientific societies (PRES, ISSAID). The ability to integrate with pre-existing registries and resources such as Infevers (<http://fmf.igh.cnrs.fr/Infevers>) shows the power of web-based initiatives in collecting, collating and distributing data in rare diseases and in promoting networks of interested centres which can provide mutual support in diagnosis and management of these conditions.

One of the most pressing issues in the rare diseases is delayed diagnosis. Autoinflammatory attacks are extremely unpleasant and frequently preventable with current treatments. Moreover untreated patients carry a risk of increased morbidity and above all the development of irreversible long term damage. The dramatic decrease in diagnostic delay in the last decade is, to some extent, due to the recent recognition of these diseases as autonomous clinical entities and to the relatively widely availability of genetic testing in the last few years. Nonetheless the diagnosis of AID relies on a clinical suspicion and many cases are missed due to poor recognition of these exceptionally rare conditions. To face this issue, thanks to the large amount of clinical data collected in the registry, we are currently developing evidence-based clinical/classification criteria for the diagnosis of a group of AID, named periodic fever syndromes, that may represent a useful tool for the diagnosis of these patients in the clinical setting.

Moreover we are currently working to make the registry longitudinal with the aim of collecting data on a yearly bases. This is of particular interest, mainly in rare orphan diseases, for a better understanding of the long term response to treatment and safety of biologic drugs commonly used in these patients.

Approximately 75-80% of patients with clinical features consistent with AID have no recognized mutations in any of the known genes. A large cohort of patients with undefined periodic fevers might possibly allow the identification of novel genes in this challenging disease group. In any case, the identification of "genetically negative" patients with a well characterized clinical phenotype (i.e. CAPS-like patients) and the cohort of individuals and families with an undefined periodic fever syndrome may represent a future resource for linkage and/or next generation sequencing analyses.

CONCLUSIONS

A large registry of patients with Autoinflammatory diseases is available and, despite the expiring of the initial grant, the enrolment is still ongoing with an increasing number of centres involved. Eurofever represents a good example of how a disease-oriented registry can provide relevant scientific answers to many unknown clinical aspects of ultra-rare diseases. This aspects was the main reason of the relevant success of the enrolment we have observed.

REFERENCES

1. Toplak N, Frenkel J, Ozen S, Lachmann HJ, Woo P, Koné-Paut I *et al.* An International registry on Autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis.* 2012 Jul;71(7):1177-1182.
2. Ozen S, Demirkaya E, Amaryan G, Koné-Paut I, Polat A, Woo P *et al.* Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. *Ann Rheum Dis.* 2014 Apr;73(4):662-7
3. Lachmann HJ, Papa R, Gerhold K, Obici L, Touitou I, Cantarini L *et al.* The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Ann Rheum Dis.* 2013 Aug 21. doi: 10.1136/annrheumdis-2013-204184

The Human Phenotype Ontology project

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The free-text representation of phenotype information has long complicated computational exploitation of the human phenotype and its relationship to the genome. A major factor was the lack of a structured and well-defined vocabulary. Since 2008 the Human Phenotype Ontology (HPO) project has provided a resource for complementing free-text descriptions and thus enabling computer-based analyses of phenotypes. The HPO project provides two main resources, an ontology of signs and symptoms, or phenotypic abnormalities, and a set of annotations, whereby each annotation associates a class of the HPO with a hereditary disease (1). The resources of the HPO project are constantly updated and are freely available at <http://www.human-phenotype-ontology.org>. Currently, the ontology consists of a well-defined set of 10,776 classes (terms) and 14,390 subclass relations between the classes of the HPO. At the moment we provide HPO-annotations for 7,278 human hereditary syndromes listed in OMIM, Orphanet and DECIPHER. Several meta-attributes such as frequency, clinical modifiers, or literature references are available for each HPO annotation.

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Several large-scale projects worldwide utilize the HPO for describing phenotype information in their datasets, e.g. DECIPHER, the NIH Undiagnosed disease program and the 100,000 Genomes Project of Genomics England. A large proportion of HPO classes feature cross-reference mappings to other phenotype vocabularies such as London Dysmorphology Database (LDDb), Orphanet, Med-DRA, UMLS and phenoDB. The UMLS is planning on integrating the entire HPO in 2015. This enables integration of existing datasets and interoperability with several other biomedical resources.

In addition, we are currently developing and revising logical definitions for HPO classes using terms from specialised ontologies. These specialised ontologies represent the entities that are affected by the abnormalities present in HPO. We make use of ontologies for cell types, chemicals, cellular processes, molecular function, embryology, anatomy, pathology and other domains. Additionally we use PATO, an ontology of phenotypic qualities, containing classes such as „broken“ or „increased size“.

For example, we have defined the HPO class “Abnormality of the face” as:

has_part some

(quality

and (‘inheres in part of’ some face)

and (‘has component’ some abnormal))

Here, the italic words are references to other ontologies, e.g. the class face from the UBERON ontology.

Because the creation of such definition is a coordinated effort between several providers of phenotype information from different organisms such as mouse and zebrafish, this results in resource with interoperable phenotype information between different species. The logical definitions make the phenotype classes available for processing with automated reasoners. A computational reasoner can infer logical consequences that are implicitly contained in the logical definitions and the referred ontologies. Thus a reasoner can infer that the phenotype class “Short snout” from the mammalian phenotype ontology (MP) must be a subclass of the above-defined human phenotype “Abnormality of the face”. We have generated a cross-species phenotype ontology (Uberpheno) for human, mouse and zebrafish that contains phenotype classes from the Human Phenotype Ontology, Mammalian Phenotype Ontology, and generated classes for zebrafish phenotypes. Due to historical reasons and in order to constantly increase the quality of Uberpheno (2), the HPO team is currently revising all of the logical definitions already existing for HPO classes.

We have used the Uberpheno ontology to enable phenotype-driven investigation of Copy-Number Variations (CNVs) seen in patients with developmental delay or unexplained congenital malformations (3). Often the CNVs are identified via techniques such as array comparative genome hybridisation (aCGH). Afterwards, lists of known and unknown duplications and deletions have to be manually investigated in order to distinguish pathogenic from benign CNVs. A critical and time-consuming part of this process is the comparison and alignment of the individual’s phenotypic abnormalities with the phenotypes associated to the genes located in each CNV. For this purpose, one has to manually identify which Mendelian disorders are associated with each gene and which phenotypes of the disorder might align with the patient’s phenotype.

Often there is not much known about the genes in human. An additional source of data is model organism phenotype data. In the Uberpheno annotation data we have collected phenotype information for almost 6000 genes, where no information from human disease is available, but the orthologous gene has been knocked out or knocked down in a model organism. These model organism phenotypes from mouse and zebrafish can now automatically be aligned with the patient phenotypes. For this, we have developed a software tool that is aimed at prioritisation of pathogenic CNVs as well as for visualisation of gene-to-phenotype connections (Phenogram).

The software implements a combined ranking scheme based on phenotypic matching, degree of overlap with known benign or pathogenic CNVs and the haploinsufficiency score. This scheme leads to significant improvements compared to rankings that do not exploit phenotypic information. Integrating and visualising cross-species phenotype information on the affected genes may help in clinical diagnostics of CNVs.

This is only one example of phenotype-driven interpretation of genomic variation using data from the Human Phenotype Ontology project. For next-generation sequencing results, we established a computational method called Phenotypic Interpretation of eXomes (PhenIX) that evaluates and ranks variants based on pathogenicity and semantic similarity of patients’ phenotype described by HPO classes to those of almost 4000 Mendelian diseases. In summary, the HPO provides a flexible and sound basis for computational phenotypic analysis that has been used by our team and others to develop computational tools for differential diagnostics and translational research.

REFERENCES

1. Köhler S, Doelken SC, Mungall CJ, Bauer S, Firth HV, Bailleul-Forestier I, *et al.* The Human Phenotype Ontology project: linking molecular biology and disease through phenotype data. *Nucleic acids research*. 2014;42(Database issue):D966-74.
2. Köhler S, Doelken SC, Ruef BJ, Bauer S, Washington N, Westerfield M, *et al.* Construction and accessibility of a cross-species phenotype ontology along with gene annotations for biomedical research. *F1000Research*. 2013;2:30.
3. Köhler S, Schoeneberg U, Czeschik JC, Doelken SC, Hehir-Kwa JY, Ibn-Salem J, *et al.* Clinical interpretation of CNVs with cross-species phenotype data. *Journal of medical genetics*. 2014;51(11):766-72.

Genetic variation databases and the HGVS nomenclature

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Genetic variation databases collect and share information about genes, variants and phenotypes (diseases) from research and diagnostic labs. The usefulness of these databases depends on easy accessibility and the quality and quantity of the data. New sequencing technology generates variant data for whole exomes and genomes requiring interpretation. Therefore, efficient data sharing is becoming more important and strongly advocated by the Human Variome Project (HVP, <http://www.humanvariome.org>) as a solution to crack genetic disease. Apart from a change in attitude and the removal of political and legal issues, this requires the use and development of (new) guidelines to achieve standardization, harmonization and interoperability between databases, including patient/disease registries and biobanks. Merging different databases using common software is one way this can be accomplished. Several standards and ontologies have been and are being developed, but many of these have not yet been implemented in databases covering most genetic information related to disease.

The standard nomenclature for sequence variant reporting in relation to genetic disease is a notable exception based on the recommendations for variant description of the Human Genome Variation Society (HGVS) (see <http://www.hgvs.org/mut-nomen/>). Several extensions have been suggested to cover more complex rearrangements¹. Recently, the Sequence Variant Description Committee has been established under the auspices of the HGVS, the Human Variome Project (HVP, <http://www.humanvariome.org>) and the Human Genome Organisation (HUGO, <http://www.hugo-international.org/>). This committee will discuss issues regarding extension and improvement of the HGVS nomenclature with the aim to cover all cases needing detailed descriptions of observed sequence alterations.

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The LOVD platform (Leiden Open-source Variation Database, <http://www.LOVD.nl>) provides simple standardized submission of new data, instant updates after curation and easy maintenance³. Errors in and consequent confusion from sequence variant reporting in relation to genetic disease is highly undesired. Although the standard nomenclature has been largely accepted world-wide, errors in reporting remain. To promote error-free reporting the Mutalyzer sequence variation nomenclature checker (<https://mutalyzer.nl>) has been developed². During variant submission in LOVD, descriptions can be checked using the Mutalyzer Sequence variation nomenclature checker. Construction of variant descriptions accepted by Mutalyzer requires basic knowledge of the standard nomenclature and comparison of the reference sequence and the variant sequence. Its Name Generator helps users unfamiliar with the nomenclature with the step-wise construction. Both LOVD and Mutalyzer are open source software and have received the recommended system status of the Human Variome Project (<http://www.humanvariome.org>).

The LOVD platform is currently used by more than 99% of the gene variant databases. LOVD system advantages: simple standardized submission of new data, instant updates after curation and easy maintenance. Eighty-six public installations contain over 3 million variants, of which around 2.4 million unique in over 200,000 individuals (November 11, 2014). Seventy-five percent of all gene databases with a curator is LOVD-powered. Many of the databases still employ LOVD2, but these are gradually being migrated to the more versatile LOVD3 platform. Curators are still needed for several genes. If you and your collaborators are researchers or clinicians with adequate knowledge about specific rare diseases, please join the effort. The LOVD-team organizes regular training to help curators improving their databases.

The LOVD3 shared database (<http://databases.lovd.nl/shared/>) has been prepared for more than 22,000 genes and already stores over 195,000 variant observations (November 11, 2014). Databases for genes of interest can be found by searching for the HGNC gene symbol. The Dutch and Belgian working group for Breast Cancer DNA Diagnostics (LOB) has decided to share >7500 variants detected in the BRCA1/2 genes in breast cancer families since 1997. Although most data are publicly accessible online, some data (detailed phenotype information) are shared by consortium members only using the new LOVD3 access level, designated “collaborator”. Others can see whether such information is available (password protected file links), giving them the option to contact the submitter for further details. Members can contribute their opinions about variant classification, increasing its consistency, but being aware of potential misinterpretation they have reservations sharing this information. Data are stored variant-by-variant and connected to each individual patient and submitting diagnostic lab. Users can perform queries per gene or individual, use other linked resources of interest, view data tracks in genome browsers and use web services to access variants stored in other gene variant databases. Other efforts include: world-wide BRCA variant data sharing (Human Variome Project and Global Alliance for Genomics and Health); Insight Consortium colon cancer variant database; country-specific data views (Finnish Disease (FinDis) portal). The latter demonstrates that it is not necessary to set up a new (national) database, which has to be queried separately by potential users.

The LOVD3 shared database also supports matchmaking activities: both phenotype descriptions and/or gene variants can be submitted with the request to assign the so-called VIP-status for both variants and phenotypes demanding specific attention. Within 3 weeks, this successfully brought researchers into contact, cracking rare disease cases and resulting in a high-impact publication.

Similar activities have been developed by other databases. To facilitate central queries of all databases including LOVD, the Global Alliance for Genomics and Health has set up different working groups for match-making (Matchmaker Exchange) and simple queries (Beacons)(See <http://ga4gh.org/#/matchmaker> and <http://ga4gh.org/#/beacon/bob> for more detailed information).

The LOVD platform can support variant and (top level) phenotype sharing via links to and from patient/disease registries and biobanks. Submission to gene variant databases can also help to improve the quality of variant descriptions in these registries. Use of standards and ontologies by gene variant databases and patient/disease registries and biobanks is expected to improve data interoperability. This likely supports selection of individuals for specific basic and clinical investigations leading to further insight into mechanisms of disease and potential treatment options.

In your web browser, use the link <gene_symbol>.lovd.nl (e.g., APC.lovd.nl) to find all databases known to us for this gene.

REFERENCES

1. Taschner PE, den Dunnen JT. Describing structural changes by extending HGVS sequence variation nomenclature. *Hum Mutat.* 2011; 32:507-11.
2. Wildeman M, van Ophuizen E, den Dunnen JT, Taschner PE. Improving sequence variant descriptions in mutation databases and literature using the Mutalyzer sequence variation nomenclature checker. *Hum Mutat.* 2008; 29:6-13.
3. Fokkema IF, Taschner PE, Schaafsma GC, Celli J, Laros JF, den Dunnen JT. LOVD v.2.0: the next generation in gene variant databases. *Hum Mutat.* 2011; 32:557-63.

Bring your own data parties and beyond: make your data linkable to speed up rare disease research

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ABSTRACT

Rare disease registries collect highly valuable information for patients, clinicians, and biomedical researchers. The benefits of combining data across registries and other types of collections cannot be achieved when registries are built as closed data silos. We present seven key aspects of a 'Linked Data' approach that helps patient registries to prepare data collections for questions across resources, and first conclusions of the 'Bring Your Own Data' workshop (BYOD) that we organized as a satellite of the EpiRare meeting, 26-27 November 2014 in Rome. The participants of the BYOD created first linked data that revealed phenotypes as a common data element for questions across registries and biobanks. While Linked Data technologies provide a promising approach to enrich data from rare disease patient registries and biobanks, we find that BYODs are currently a useful and essential mechanism to overcome bottlenecks in creating linked data.

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INTRODUCTION

Rare disease registries collect highly valuable information for patients, clinicians, and biomedical researchers. Clinicians may use registries as an aid to find patients for clinical trials, while researchers look for information to understand the mechanisms of disease and clues for novel treatments or biomarkers, while patients look for information about their condition or a means to contribute to research. We therefore see a growing number of disease-specific patient registries. However, beyond the single registry lie the benefits of comparing data, within and between collections, and relating aggregate studies to the individual patient data as a step towards personalized medicine. Moreover, combining different kinds of collections can add further value to patient registries. Examples are drug information [1], [2], curated data from Orphanet [3], and locus-specific databases [4] which adds enhanced flexibility and functionality and has the capacity to store sequence variants in multiple genes per patient. To reduce redundancy, patient and sequence variant data are stored in separate tables. Tables are linked to generate connections between sequence variant data for each gene and every patient. The dynamic structure allows database managers to add custom columns. The database structure supports fast queries and allows storage of sequence variants from high-throughput sequence analysis, as demonstrated by the X-chromosomal Mental Retardation LOVD installation. LOVD contains measures to ensure database security from unauthorized access. Currently, the LOVD Website (<http://www.LOVD.nl/>). However, these benefits become difficult to achieve when registries are built as closed data silos, with independent formats and data models.

Therefore, we present seven key aspects of an approach that helps patient registries to prepare data collections for questions across resources, and COEUS as a toolkits to assist this approach. Finally, we present first conclusions of the ‘Bring Your Own Data’ workshop (BYOD) that we organized as a satellite of the EpiRare meeting. A more elaborate report will be published elsewhere.

METHODS

The method that we propose is based on using Linked Data and ontologies for biomedical data [5]–[10] as data are frequently being updated in a decentralized environment, provenance information becomes critical to providing reliable and trustworthy services to scientists. This article presents design patterns for representing and querying provenance information relating to mapping links between heterogeneous data from sources in the domain of functional genomics. We illustrate the use of named resource description framework (RDF). We consider seven key aspects in relation to the first rare disease BYOD, a ‘hands-on’ workshop that brought Linked Data experts and representatives of registries and biobanks together to build first prototypes.

1. Making registry and biobank data interoperable is a multi-layered challenge

We define three layers to making registry and biobank data interoperable: (i) the social process of reaching consensus in a community about what is measured and how, (ii) the classification of information with commonly used ontologies, (iii) making information computer-readable. The latter allows computers to assist in comparing data correctly. Ontologies stimulate reaching consensus and are available in computer readable format.

2. Uniform Resource Identifiers

The cornerstone of Linked Data is the Uniform Resource Identifier (URI) [11]. It reuses the technology that made the World Wide Web successful. URIs have three desirable properties: (i) they provide a globally unique identifier for any piece of information that we wish to link (e.g. genes, phenotypes, drugs, persons, etcetera); (ii) each URI is a globally unique reference, e.g. the Document Object Identifier (DOI) is a URI that refers to a publication; (iii) URIs are computer-readable.

3. Triples of URIs represent human readable statements

The Resource Description Framework (RDF) is an international standard that defines the use of triples of URIs for ‘subject-predicate-object’ statements. For instance,

```
<http://purl.obolibrary.org/obo/OGG\_3000003064>  
<http://purl.bioontology.org/ontology/SNOMEDCT/246075003>  
<http://ontology.neuinfo.org/NIF/Dysfunction/NIF-Dysfunction.owl#birnlex\_12500>
```

states that HTT is a causative agent of Huntington’s Disease². Triples can be chained to form a larger knowledge graph. In RDF, pieces of information do not need to be in one location (note the ‘address’ part between ‘http:’ and the final identifier). Because a URI is a reference, more triples about the URI can usually be retrieved from the referenced location.

When the predicate is ‘is of type’, then the object is typically an ontology class that makes the intended meaning of the subject clear to the computer. For example, we can state in URI form that an observed phenotype in a registry is classified as a type of Chorea as defined in the Human Phenotype Ontology [12] available at <http://www.human-phenotype-ontology.org>, provides a structured, comprehensive and well-defined set of 10,088 classes (terms).

4. URIs make combining information (almost) trivial

2 This is a simplified example for sake of argument. More triples are needed for a more realistic representation, or a less expressive predicate such as ‘associated with’ should be used.

A consequence of the use of URIs is that the same URI in two registries can be a point of integration. For instance, when one registry has tissue information linked to proteins, while another has phenotype information linked to proteins, then tissues and phenotypes become automatically linked through shared protein URIs when the two sources are combined. We can then retrieve the tissues where proteins are found that are associated with a certain phenotype. We can subsequently query biobanks for samples via the tissue URIs. When different URIs for the same data were used then standard mapping relations can be used to resolve these mismatches [13]

5. RDF as exchange format

RDF is useful as an exchange format between resources. Each resource can use its own internal representation, but use RDF as export format. RDF is largely self-explanatory for computers, and adds to the growing 'Linked Data cloud' [14]. Conversely, data can be imported from this cloud and converted to internal formats.

6. Flexibility

An advantage of data models defined with URIs and ontologies is the flexibility to customize classes or provide mappings to specific resources-specific data models. Registries may share common data elements, but will also contain many specific data elements. In RDF, specific data elements are linked to more general common concepts. A mock example may clarify: suppose that three registries have specific data elements for consumption of coffee, tea, and cola respectively. However, because these are all subclasses of 'caffeine consumption' in a general ontology, we can easily perform a caffeine consumption analysis when the RDF of the registries is combined with the ontology.

7. Linked Data is not Open Data

The final aspect we wish to highlight, especially for patient registries, is that Linked Data does not equal open public data. The approach only makes data linkable. Making it publicly accessible requires extra steps that are under control of the data owner.

RESULTS & DISCUSSION

We applied these aspects in the first RD-Connect 'Bring Your Own Data' workshop (BYOD) that we organised as a satellite of the November 2014 EpiRare meeting in Rome³. The starting point was a user question to drive the process towards first RDF data. We split into 4 groups. Two groups worked on enabling the selection of patients across several registries based on pre-set criteria. One worked on enabling the selection of samples from biobanks based on phenotype information, and on a case to strengthen the ID card system with Orphanet and vice versa using RDF as the intermediate. Finally, one group worked on generating reports for variants by linking variants to pathways and phenotypes that were available in RDF.

We found two bottlenecks for the process that confirmed previous findings: (i) defining the user questions, (ii) finding appropriate URIs among all ontologies and other sources of identifiers. The first is interesting because it shows that we still have to learn how to exploit Linked Data. The second is a clear call to the Linked Data community to produce better software such as Zooma [15] and guidelines to facilitate this process [16], [17], but also that at this time BYODs are an essential mechanism to overcome this bottleneck. The conversion process itself is becoming less of a bottleneck with tools such as D2R and COEUS [18], [19]. These tools partially automate the first steps of converting datasets in legacy formats into RDF triples.

Interestingly, phenotypes were a common factor for all the groups. A consequence is that the 'Linked Data cloud' that was generated at the BYOD enables us to use phenotypes as a common element for questions across the RDF that was generated in the BYOD. It is noteworthy that the four groups did not know they were enabling this. We therefore argue that this is a useful 'bottom-up' approach to complement a more top-down approach to define (and enforce) common data elements between registries. We argue that when the three layers of interoperability are all addressed (aspect 1), then the demands for each individual layer are reduced. For instance, if we agree on the use of common ontologies, then we can allow more freedom towards common data elements and database schema's.

The backbone of the approach is a Linked Data-based architecture to connect distributed and heterogeneous data sets. One group applied COEUS for rare disease patient registries. COEUS is a semantic web application framework to deploy multiple registry add-ons, each extracting anonymized data from the associated registry [19]. These data were translated and mapped to an ontology that can be used as a common reference for all rare diseases registries. This results in a unique semantic layer covering the various patient registries, which we can access using federated querying. Ultimately, this strategy empowers a transparent view through connected registries, enabling state-of-the-art semantic data sharing and access. At the BYOD we discussed how federated querying may enable extracting information related to patients without ever extracting a patient URI, for instance by using phenotypes as common element.

³ <http://epirare.eu/>

CONCLUSION

The BYOD for patient registries and biobanks created first ‘Linked Data’ to enable questions across these resources. In some cases first queries could be performed, while in others a ‘blocker’ was encountered. For instance, for the variant annotation case essential data from the correct genome assembly was temporarily unavailable. We concluded that we would need a follow-up to the BYOD to make the resulting Linked Data more robust and usable outside the BYOD, possibly again in the form of a hackathon. This would also give more time to explore the Linked Data cloud that was generated by the four groups together.

We found that the generality and long-term benefits of the approach were not always clear to all participants, and thereby the added value in comparison to other approaches that do not use the Linked Data approach. We are aware that the added value of Linked Data grows as more sources adopt these standards. The process is slowed down by scepticism towards sharing data, which often have a social and psychological basis.

In summary, we believe Linked Data technologies provide a promising approach to connect and enrich data from rare disease patient registries and biobanks.

REFERENCES

1. E. L. Willighagen, A. Waagmeester, O. Spjuth, P. Ansell, A. J. Williams, V. Tkachenko, J. Hastings, B. Chen, and D. J. Wild, “The ChEMBL database as linked open data,” *J. Cheminform.*, vol. 5, no. 1, p. 23, Jan. 2013.
2. A. J. Williams, L. Harland, P. Groth, S. Pettifer, C. Chichester, E. L. Willighagen, C. T. Evelo, N. Blomberg, G. Ecker, C. Goble, and B. Mons, “Open PHACTS: semantic interoperability for drug discovery,” *Drug Discov. Today*, Jun. 2012.
3. “Orphanet: an online database of rare diseases and orphan drugs,” 1997. [Online]. Available: <http://www.orpha.net/>. [Accessed: 01-Dec-2014].
4. I. F. A. C. Fokkema, P. E. M. Taschner, G. C. P. Schaafsma, J. Celli, J. F. J. Laros, and J. T. den Dunnen, “LOVD v2.0: the next generation in gene variant databases,” *Hum. Mutat.*, vol. 32, no. 5, pp. 557–63, May 2011.
5. C. Bizer, T. Heath, and T. Berners-Lee, “Linked Data,” *Int. J. Semant. Web Inf. Syst.*, vol. 5, no. 3, 2009.
6. J. Zhao, A. Miles, G. Klyne, and D. Shotton, “Linked data and provenance in biological data webs,” *Brief. Bioinform.*, vol. 10, no. 2, pp. 139–152, Mar. 2009.
7. L. J. G. Post, M. Roos, M. S. Marshall, R. Van Driel, and T. M. Breit, “A semantic web approach applied to integrative bioinformatics experimentation: a biological use case with genomics data,” *Bioinformatics*, vol. 23, no. 22, pp. 3080–7, 2007.
8. A. Zappa, A. Splendiani, and P. Romano, “Towards linked open gene mutations data,” *BMC Bioinformatics*, vol. 13, no. Suppl 4, p. S7, 2012.
9. K. Wolstencroft, S. Owen, M. Horridge, O. Krebs, W. Mueller, J. L. Snoep, F. du Preez, and C. Goble, “RightField: embedding ontology annotation in spreadsheets,” *Bioinformatics*, vol. 27, no. 14, pp. 2021–2, Jul. 2011.
10. Z. Tatum, M. Roos, A. P. Gibson, P. E. Taschner, M. Thompson, E. A. Schultes, and J. F. Laros, “Preserving sequence annotations across reference sequences,” *J. Biomed. Semantics*, vol. 5, no. Suppl 1, p. S6, 2014.
11. W. URI Planning Interest Group, “URIs, URLs, and URNs: Clarifications and Recommendations 1.0.” [Online]. Available: <http://www.w3.org/TR/uri-clarification/>. [Accessed: 01-Dec-2014].
12. S. Köhler, S. C. Doelken, C. J. Mungall, S. Bauer, H. V Firth, I. Bailleul-Forestier, G. C. M. Black, D. L. Brown, M. Brudno, J. Campbell, D. R. FitzPatrick, J. T. Eppig, A. P. Jackson, K. Freson, M. Girdea, I. Helbig, J. A. Hurst, J. Jähn, L. G. Jackson, A. M. Kelly, D. H. Ledbetter, S. Mansour, C. L. Martin, C. Moss, A. Mumford, W. H. Ouwehand, S.-M. Park, E. R. Riggs, R. H. Scott, S. Sisodiya, S. Van Vooren, R. J. Wapner, A. O. M. Wilkie, C. F. Wright, A. T. Vulto-van Silfhout, N. de Leeuw, B. B. A. de Vries, N. L. Washington, C. L. Smith, M. Westerfield, P. Schofield, B. J. Ruef, G. V Gkoutos, M. Haendel, D. Smedley, S. E. Lewis, and P. N. Robinson, “The Human Phenotype Ontology project: linking molecular biology and disease through phenotype data,” *Nucleic Acids Res.*, vol. 42, no. Database issue, pp. D966–74, Jan. 2014.
13. K. Alexander and M. Hausenblas, “Describing linked datasets - on the design and usage of void, the ‘vocabulary of inter-linked datasets,’” 2009.
14. “Linked Data | Linked Data - Connect Distributed Data across the Web.” [Online]. Available: <http://linkeddata.org/>. [Accessed: 01-Dec-2009].
15. “ZOOMA < FGPT < EMBL-EBI.” [Online]. Available: <http://www.ebi.ac.uk/fgpt/zooma/>. [Accessed: 01-Dec-2014].
16. “Guidelines | nanopub.org.” [Online]. Available: http://nanopub.org/wordpress/?page_id=40. [Accessed: 19-Sep-2012].
17. “Guidelines for exposing data as RDF in Open PHACTS.” [Online]. Available: <http://www.openphacts.org/specs/2013/WD-rdfguide-20131007/>. [Accessed: 01-Dec-2014].
18. M. Hert, G. Reif, and H. C. Gall, “A comparison of RDB-to-RDF mapping languages,” in *Proceedings of the 7th International Conference on Semantic Systems - I-Semantics ’11*, 2011, pp. 25–32.
19. P. Lopes and J. L. Oliveira, “COEUS: ‘semantic web in a box’ for biomedical applications,” *J. Biomed. Semantics*, vol. 3, no. 1, p. 11, Jan. 2012.

The European Society for Immunodeficiencies (ESID) Registry: recent advancements in the epidemiology of Primary Immunodeficiencies and how does that translate in clinical care

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INTRODUCTION

Primary Immune Deficiencies (PIDs) are a growing group of over 230 different inherited rare disorders caused by mutations in genes encoding proteins involved in the immune system. Left undiagnosed and untreated, PIDs are often chronic, serious or even fatal. The diagnosis of PIDs can be difficult due to lack of awareness and facilities for diagnosis, and management of PIDs is complex. Once recognised, these rare disorders are treatable and in some cases curable (by Hematopoietic Stem Cell Transplantation since 1968 and in some limited cases today by Gene Therapy since 2000). PID management highlights the role of specialised centres, the need for multinational research, the role of national and international patient organisations, the requirement for sustained access to all treatments including immunoglobulin (Ig) therapies and HSCT, which are important considerations for developing countries in terms of management and treatment options. Epidemiological data on PIDs are scarce highlighting the importance of national and international registries (such as the European Society for Immunodeficiencies (ESID) registry). Registries provide insight not only for healthcare professionals but also for patients and for healthcare policies makers, services and government agencies, particularly to ensure that PID patients world-wide have access to appropriate and sustainable medical and support services.

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WWW.RAREBESTPRACTICES.EU

METHODS

Since 2004, ESID (www.esid.org) runs a European-wide online registry for PID. The ESID Registry is based on contributions from the following national registries: CEREDIH (France), REDIP (Spain), PID-NET (Germany), UKPIN (UK), IPINET (Italy), AGPI (Austria), the Netherlands, Czech Republic. Additional contributions are received from the following countries: Turkey, Poland, Ireland, Portugal, Belgium, Switzerland, Slovakia, Sweden, Slovenia, Croatia, Serbia, Greece, Belarus, Russia, Hungary, Romania, Ukraine, Estonia, Lithuania, Egypt, Israel. In 2014, the technical backbone and user interface have been overhauled. All patients are now documented once per year and a three level registration concept has been implemented: Level 1 is mandatory for all centers participating in the registry project and aims at basic epidemiological features with yearly updates on survival and treatment. A genetics module will be implemented to be filled in by the genetics laboratories for consistent terminology. Level 2 foresees more detailed clinical and laboratory information and centers can choose to participate in certain disease categories according to their resources for documentation and scientific interests. Level 3 provides a platform for projects targeting individual diseases in even more detail. Level 3 studies have a defined endpoint (number of patients and/or period of observation) and offer opportunities for industry collaborations. Criteria for the clinical diagnosis of PID with unknown genetic cause have been elaborated and have to be confirmed for patients at registration. Built-in checks now validate all fields for consistency and completeness, and users are guided through the data entry process. Additional datasets are being programmed, data links to the Spanish and Italian registries have to be created, and the software will be “rolled out” to the UKPID and LASID registries. Importantly, data output for the centres will be extended, including an automatized annual report with benchmarking figures of the centre relative to national and European figures.

RESULTS

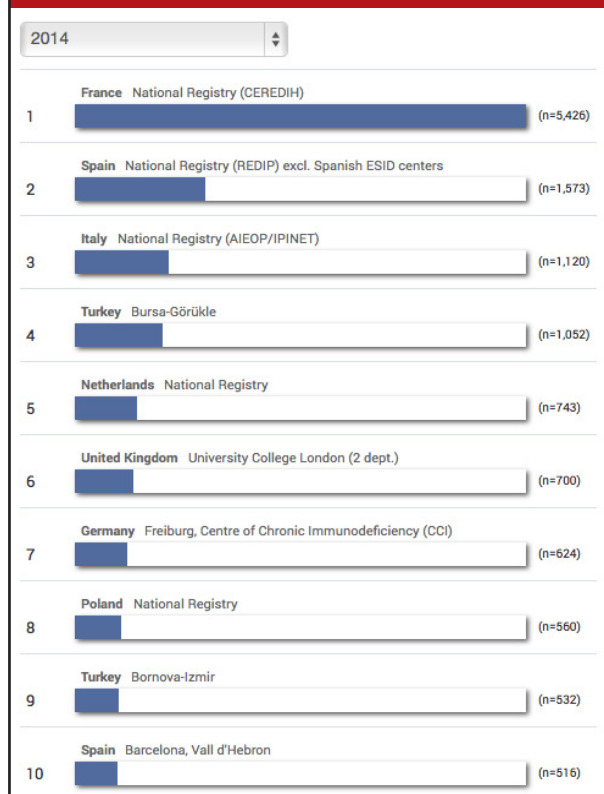
As of May 2014, the ESID Registry is the largest registry worldwide with 19,366 patients (both children and adults, see **Fig 1a and 1b**). Clinical diagnostic criteria have been developed for patients lacking a genetic diagnosis allowing an increased level of data quality. Data transfer from the original system to the new revised registry platform requires individual validation of these criteria.

Data on PID diagnosis both clinical and genetic, familial cases, consanguinity, presenting symptoms, diagnostic delay, type of treatments received (allowing a prospective data entry and follow-up), date of last news, clinical status... are available. Level 2 includes biological data for quality control (consistency of diagnosis with laboratory abnormalities), data monitoring and follow-up. The registry also encompasses data on therapy; especially on Ig replacement therapy, which is a lifelong maintained therapy for a majority of patients (see **Fig 1c**).

In a recently published study (1), registry analysis allowed to identify factors affecting the clinical presentation, association between clinical features, and differences and effects of immunoglobulin treatment in Europe in the most important group of PIDs (CVID, Common Variable ImmunoDeficiency). The data showed that and how patients with CVID are being managed differently throughout Europe, affecting various outcome measures.

PIDs are recognised as rare conditions and data on epidemiology of PIDs is scarce, although many countries across the EU and worldwide have implemented registries for PIDs. An example is the national registry established in France in 2005; the Reference Centre for PIDs (CEREDIH) runs the largest national PID registry worldwide, with dedicated and highly trained staff. It is based on a tight network of all university teaching hospitals, with 130 clinicians and at least 30 diagnostic immunology laboratories. National registries are important tools for assessing the proportion of affected individuals among the general population (prevalence) as well as measuring the number of new cases diagnosed each year (incidence), detection of areas of low diagnosis rates and provision of insights on diagnostic delay associated with increased morbidity and mortality. The registry also provides in-

Fig. 1a. Number of patients entered in the ESID Registry as of Jun. 25th, 2014 (only the first 10 centers are displayed, for more information, please visit www.esid.org)



formation that is helpful to governments regarding estimates of those not diagnosed to aid planning of educational programs and provision of treatments and their costs. Presentation of this data to pharmaceutical industries helps to ensure that the supply of medical products meets demand. Thus a national registry is an important tool for health policy makers, stakeholders and health insurers, enabling plans for allocation of therapies and the development of innovative treatments, as also demonstrated in the UK Demand Management Plan. Prevalence of PIDs is at least 6 in 100,000 inhabitants although data provided by the ESID Registry shows variability most likely linked to lack of data entry is several countries (due to lack of manpower and money dedicated to data registration). Minimal incidence is still not accurately known but might be close to 1:3000 to 1:4000/year. These key indicators are useful especially in setting the frame for a pan-European newborn screening for Severe Combined ImmunoDeficiencies (including health economics).

CONCLUSION

Based on the ESID registry, more registries (local, regional or national) have been implemented in Europe and abroad, showing wider interest in the field and in this approach in trying to address clinical and scientific questions, suggesting that registries for rare diseases are widely considered as a valuable part of the toolbox to increase knowledge in the field (2).

REFERENCES

1. Gathmann B, Mahlaoui N; CEREDIH, Gérard L, Oksenhendler E, Warnatz K, Schulze I, Kindle G, Kuijpers TW; Dutch WID, van Beem RT, Guzman D, Workman S, Soler-Palacín P, De Gracia J, Witte T, Schmidt RE, Litzman J, Hlavackova E, Thon V, Borte M, Borte S, Kumararatne D, Feighery C, Longhurst H, Helbert M, Szaflarska A, Sediva A, Belohradsky BH, Jones A, Baumann U, Meyts I, Kutukculer N, Wågström P, Galal NM, Roesler J, Farmaki E, Zinovieva N, Ciznar P, Papadopoulou-Alataki E, Bienemann K, Velbri S, Panahloo Z, Grimbacher B; European Society for Immunodeficiencies Registry Working Party. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014 Jul;134(1):116-26. doi: 10.1016/j.jaci.2013.12.1077. Epub 2014 Feb 28. PubMed PMID: 24582312.
2. Kindle G, Gathmann B, Grimbacher B. The use of databases in primary immunodeficiencies. *Curr Opin Allergy Clin Immunol*. 2014 Dec;14(6):501-8. doi:10.1097/ACI.0000000000000113. PubMed PMID: 25225780.

Fig. 1b. PID main diagnostic categories of patients entered in the ESID Registry as of Nov. 15th, 2014.

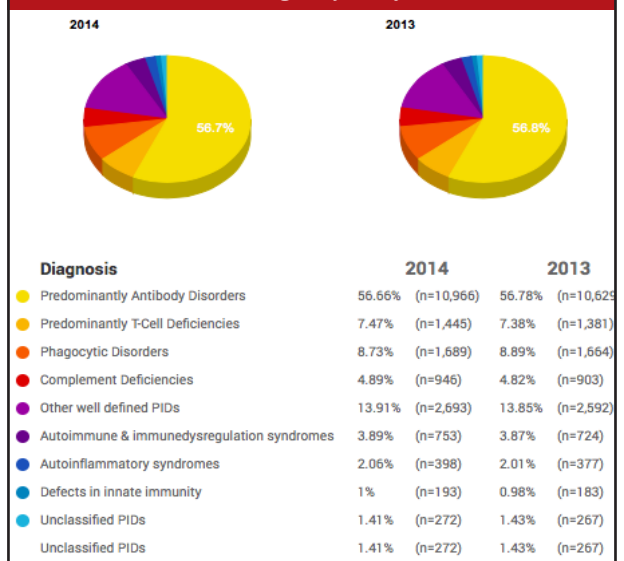
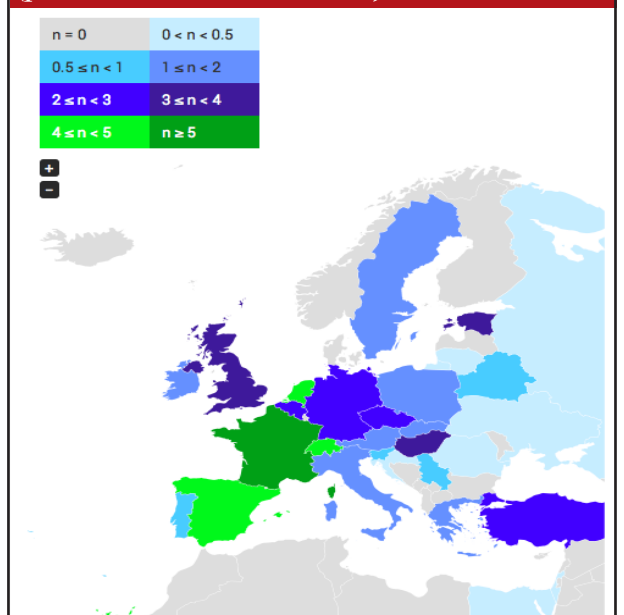


Fig. 1c. Frequency of Immunoglobulin replacement therapy (including route of administration) in the ESID Registry as of Jun. 25th, 2014.

2014	
Additional statistics:	2014
How many alive patients** overall are on Ig replacement?	(n=6,476) 50.36%
... alive patients** on IVIG	(n=4,239) 32.96%
... alive patients** on SCIG	(n=2,181) 16.96%
... alive patients** on IMIG	(n=22) 0.17%
Total number of alive patients**:	(n=12,860) 100%
**Alive patients with no information on therapy are excluded from this evaluation.	

Fig. 2. Minimal prevalence map of PIDs in Europe (prevalence/100,000 inhabitants)



OP-01. Activities of the National Registry of Hemolytic Uremic Syndrome (HUS) in Italy, 1988-2014

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Introduction & objectives: HUS is a common cause of acute renal failure in children. In Italy, a national Registry of pediatric HUS was established since 1988 by the Italian Pediatric Nephrology Society, in cooperation with the National Reference Laboratory for E.coli. The aims were to carry out surveillance of HUS, to estimate the burden of the disease in the population and to monitor the associated infections with Verocytotoxin (VT)-producing E.coli (VTEC).

MATERIALS & METHODS

The population under surveillance included children < 15 years of age and a case of HUS was defined as a patient with acute renal failure and microangiopathic hemolytic anemia (Hb<10 g/L) or thrombocytopenia Plt<100.000 mL). Clinical and epidemiological information were collected, together with stool and blood samples. Laboratory diagnosis of VTEC infection was based on the isolation of VTEC strains, the detection of free VT in stools and the detection of serum antibodies to the lipopolysaccharide (LPS) of the most important serogroups. A subset of patients was also examined for the presence of VT in their circulating polymorphonuclear cells (PMN).

RESULTS

Up to September 2014, 914 cases have been identified, accounting for a mean annual incidence of 0.38 x10⁻⁵ (0.91 x10⁻⁵ in children of 0-4 years of age). The incidence rate was higher in the northern regions of Italy. Several epidemic outbreaks, involving a number of cases ranging from 2 to 23 cases, were observed. The mean age of the patients was 38 months (median 24), and most of them were in the age group 0-4 years. Prodromal diarrhea was observed in 710 cases (84.6%) of those having the information available. Clinical samples were obtained from 741 cases and the laboratory assays provided evidence of VTEC infection for 535 of them (72.1%). The VTEC serogroups involved were O26 (31.8%), O157 (30.3%), O111 (10.1%), O145 (8.2%), and O103 (6.7%). Other 11 serogroups, including O121, O55, accounted for 5.0% of cases. Cases associated with VTEC non-O157 infections, particularly O26 and O145, increased over time, and in the decade 1998-2007 outnumbered those associated with VTEC O157. Patients with VTEC non-O157 infections were younger (median: 22 mo) than those with VTEC O157 (median: 32 mo). A more clear summer pattern was observed for VTEC O157 infections. Atypical HUS cases, for whom no prodromal diarrhea nor diagnosis of VTEC infection were reported, were 55, representing the 8.0% of the 685 cases with information on both characteristics available.

CONCLUSION

Registry data suggest that the incidence of HUS in Italy is lower than those reported for other industrialized countries and that VTEC non-O157 in particular O26 have an important role in its etiology. This highlights the need for a comprehensive laboratory approach to the diagnosis of VTEC infection.

OP-02. Medicines for paediatric rare diseases in EU and US

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Introduction: Registries and databases are key tools to increase knowledge on rare diseases and facilitate research. EuOrphan is one of the few existing databases which collects and catalogues information on drugs for rare diseases in Europe and the United States, the two regions in the world in which an Orphan Drug (OD) Regulation has been well-established. Using EuOrphan data, we depicted the status of drugs in development or already available for paediatric patients affected by rare diseases in Europe, and we compared these data with US ODs.

METHODS

The following drugs have been investigated: i. ODs designated in Europe; ii. Medicinal products approved for a rare condition through the European centralised procedure (including approved ODs, ‘orphan-like drugs’, and non-Orphan medicinal products approved for a rare condition before Regulation (EC) 141/2000 entered into force); iii. ODs designated and approved by FDA.

We also analysed the advantages resulting if the designations and the approvals would be merged between the two territories, by standardising names and terms of active substances and conditions.

RESULTS

Up to December, 31st 2013, 722/969 (74,5%) orphan designations resulting in the European Orphan Drugs Register refer to a paediatric condition. Similarly, this ratio results 1587/2087 (76,0%) in the FDA register. With reference to marketed drugs, if we consider the conditions affecting children, about half of drugs approved in EU and US for a rare disease affecting children does not have a paediatric indication: 49/102 (48,0%) in EU and 139/348 (39,9%) in US. This lack of medicines is even more evident for younger children: in EU 26 and 24 indications are approved for preterm and term newborn infants respectively; in US the number of indications approved for preterm and term newborn infants is almost twice higher than in EU (59 and 55 respectively) ($P < 0.001$). If we merge the efforts of the two agencies, both would advantage of a greater number of approvals. Conclusions Our results show that in Europe, notwithstanding the incentives issued by the OD Regulation, paediatric patients affected by rare diseases have still access to a lower number of drugs than in the United States. More efforts and more cooperation between Europe and United States seem necessary to advance the availability of medicines in the field of rare diseases. OD registries could be of help in focusing these efforts in the right way.

REFERENCES:

European Parliament and of the Council Regulation (EC) 141/2000 of 16 December 1999 on Orphan Medicinal Products. OJL 018/1, 22.01.2000; Ceci A, Catapano M, Manfredi C, Wong I, Orlu-Gul M, Meneguz M, Baiardi P, Della Pasqua O, Iolascon A, Scarpa M, Neubert A. Changes in Research and Development of Medicinal Products since the Paediatric Regulation. Chris Rundfeldt (ed): Drug Development - A Case Study Based Insight into Modern Strategies. InTech, 2011 Dec: 585-638. Eurordis (2005) Medicines for children: better, more and faster. Eurordis position paper on the proposal for a regulation on medicinal products for paediatric use. [www.eurordis.org]. 2005 Jan. Available from: http://www.eurordis.org/IMG/pdf/eurordis_position_medicines_children_31jan05.pdf

OP-03. Characterization of high-quality Rare Disease Registries by using a data mining approach

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Introduction: Rare Diseases Registries (RDRs) are important epidemiological tools for health policy makers and researchers working in the field of low prevalence diseases. The quality of procedures used when a RDR is defined and also during the first steps of their development sets the basis for its success and it is at the same time the best way to guarantee the long-term sustainability. Therefore the quality of RDRs is one of the key questions to be assured and designed during the first steps of their design.

AIM OF THE STUDY

To provide information useful to characterize high-quality RDRs by using an analytical approach

METHODS

At first, a score of quality was defined by choosing a small set of variables derived by the EPIRARE Survey and related to quality assurance, quality control and quality assessment. In a second step, the random forest (RF) method was applied to the Survey data, so that, starting from the entire set of 223 variables, a subset of variables can be identified as the most informative to afford a reliable characterization of different levels of quality. In the third step, the presence of statistically significant associations between each variable identified by RF and the indicator of quality of RDR were checked with a Chi-square or Fisher exact test. Then the Cochran-Armitage test was also carried out to identify the presence of a linear trend.

RESULTS

Out of the 223 variables RF identified a subset of 47 informative variables. Statistically significant associations are identified between 44 variables (out of 47) and the indicator of quality. A significant linear trend is observed for 43 variables, most of them showing a strong evidence ($p < 0.001$). This set of variables was useful to characterize high-quality RDRs that seem to pay much attention to: ethical and legal issues (protocol approved by Ethical Committee), governance (Main Governing Board executing all the main functions and composed by internal members and external experts), communication of the activities (scientific meetings, scientific journals, website), access to data and security, sustainability. These findings are in line with the results of similar researches on disease registries [1], highlighting that quality is usually associated with a good oversight and governance mechanism and would benefit from a support in organization and management, information technology, epidemiology, and statistics.

REFERENCES:

Black N, Barker M, Payne M, Cross sectional survey of multicentre clinical databases in the United Kingdom, *BMJ*. 2004 Jun 19; 328(7454):1478-82.

OP-04. EUROCAT surveillance: Making Congenital Anomalies Preventable Rare Diseases

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EUROCAT is a European network of geographically defined population-based registries (representing the unselected experience of all who live in the population) for epidemiologic surveillance of congenital anomalies (CA). Started in 1979, EUROCAT currently surveys over 1.7 million births per year in Europe (31% of all EU births), via 37 registries in 21 countries. The DG Sanco Public Health Programme has funded EUROCAT from 2008-2013 as a Joint Action (JA) of the EU and Member States (MS) and as an Operating Grant for 2014.

CA are a major cause of perinatal mortality, childhood morbidity and disability, with a total prevalence of 2.5% of births. Most CA are Rare Diseases (<5 per 10,000 population). The live birth prevalence of rare CA in 2010 was 96.2 per 10,000 births, extrapolating to approx 4.7M affected persons in the EU, 12-15% of the total estimated persons affected by Rare Diseases.

EUROCAT's mission is to support the primary prevention of CA and the provision of appropriate services to pregnant women, affected children and their families by the ongoing collection, analysis, interpretation and dissemination of population-based epidemiologic data. Epidemiologic surveillance should reduce teratogenic and life style risks preconceptionally and in early pregnancy, inform policies and interventions in order to secure high quality diagnostics, treatment and counseling and to reduce the size of, and inequalities in, the public health burden of CA.

Many CA are potentially preventable, nevertheless the prevalence of CA has remained stable in recent decades, despite growing knowledge regarding prevention. As part of the EUROCAT JA (www.eurocat-network.eu) a working group was created in collaboration with EUROPLAN (European Project for Rare Diseases National Plans Development, www.europlanproject.eu) to establish policy recommendations on primary prevention of CA to be implemented in National Plans or Strategies for Rare Diseases. The recommendations were developed and shared through a multistep process.

A preliminary phase covered collection and analysis of relevant literature to define the main evidence-supported risk factors for CA followed by identification of public health actions for the primary prevention of CA in themed working groups (i.e. medicinal drugs or folic acid). A consensus draft was elaborated jointly by the EUROCAT JA working groups and EUROPLAN, and presented to and subsequently endorsed by EUCERD (European Union Committee of Experts on Rare Diseases).

Areas for policy actions are specified in the field of medicinal drugs, food/nutrition and lifestyle, health service, and environmental pollution including the workplace. Levels of preventive action include advice to future parents by health professionals during individual preconceptional and early pregnancy consultations tailored for high and low risk couples; health education campaigns targeted to potential future parents; regulatory actions which affect risk factors at source such as medicines, foods, tobacco and alcohol and other recreational drugs; surveillance, research and evaluation generating evidence for the initiation or updating of primary preventive measures.

The recommendations represent a first step towards an integrative prevention strategy. Their implementation in National Plans will be further monitored by EUROCAT and EUROPLAN.

OP-05. Guidelines for optimal use of registries in trial design for small populations

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Introduction: Development of effective therapies in rare diseases is limited due to low prevalence and heterogeneity in phenotype. Increasing the efficiency of the available research sources is one way to approach this problem. In this case, a rare disease registry focusing on outcome measures can be a valuable tool for supporting the development of clinical research. In October 2013, the ASTERIX consortium has started working on the development of new trial designs in rare diseases (www.asterix-fp7.eu). One topic is to explore in what way a rare disease registry can be informative for trial design. The aim is to develop guidelines for optimal use of these patient registries to inform clinical trial design for small populations.

METHODS

First, we have conducted an environmental scan in literature and on internet to find information on what type of rare disease registries have been developed, and what is incorporated in registries with a scientific goal.

DISCUSSIONS

With statisticians will be held on requirements for trial design. Furthermore, interviews with different stakeholders will give insight in the possible gaps regarding registries and possibilities how to resolve them.

RESULTS

Results will become available in 2015.

PPa-01. The EPIRARE data set for the registration of patients in Europe

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B **ackground:** The European Commission has stated that its strategic objective is the creation of the European Platform for RD patient registration (RDR), providing common services and tools for the existing (and future) rare disease registries in the EU [1]. The EU co-funded EPIRARE project (“Building Consensus and Synergies for the EU Registration of Rare Disease Patients”), studied a model for this platform[2].

METHODS

A reference list of registry-based indicators was defined, building on previous projects [3, 4] and the results of the surveys and consultations carried out during the EPIRARE activities[2].

RESULTS

The variables, which are necessary to calculate these indicators, have been considered for inclusion in the set of Common Data Elements. Among them, some variables have a particular importance for the best use of registry data. These comprise variables for the unambiguous universal patient coding; for analysis by diagnosis, geographic location of the patient and health care services; or variables allowing the ethical processing of patient data, including his/her willingness to participate in research. Consistently, a Minimum Data Set was defined, which is made of data which are in the knowledge of the patient (or their family) and which can be entered without the involvement of physicians or the health services. A second group of variables refers to health determinants and services and collect information on the genetics, history of diagnosis, different treatments and donation of biological material. Registries may select the variables in this group according to their aims and scope. The third group of variables is focused on outcome assessment. It consists of data of patient death, health-related quality of life (HRQoL), education level attained and occupational status; and of co-morbidity and other observed symptoms. In spite that they are not in the usual interest of pathology registries, the proposed variables allow an integrated outcome assessment, which can serve many purposes, from patient-centered description of the disease course, to monitoring the impact of policies and best practices, to provide a basis for patient advocacy actions and to assessments cutting across all diseases, such as equitable decisions based on the burden of disease. Therefore, a registry aiming at collecting outcome data should collect the full set of CDE indicated in this last group. Conclusions: The definition of a set of CDE for the European RDR Platform is the first step in the promotion of the use of common tools for the collection of comparable data of RD patients.

REFERENCES:

1. European Commission: Supporting rare diseases registries and providing a European Platform for rare diseases registration. [http://ec.europa.eu/health/rare_diseases/policy/registries/index_en.htm] (accessed June 18, 2013).
2. All documents referred to EPIRARE are available at the project web site: www.epirare.eu.
3. European Project for Rare Diseases National Plans Development (EUROPLAN): Selecting indicators to evaluate the achievements of RD initiatives. 2011, [http://www.europlanproject.eu/newsite_986989/Resources/docs/2008-2011_3.EuroplanIndicators.pdf] (accessed September 2013).
4. EU Rare Disease Task Force: Health Indicators for Rare Diseases: I - Conceptual Framework and Development of Indicators from Existing Sources. [http://www.eucerd.eu/post_type=document&p=1211] (accessed on 22 September 2013).

PPa-02. The Global FKRP Registry – the international registry for patients with FKRP-related muscle diseases

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Patient registries constitute a vital role in establishing clinical research in rare diseases, providing longitudinal natural history data and benchmarks by which to design clinical trials. The Global FKRP Registry is an international registry for patients with conditions caused by mutations in the FKRP gene and aims to ready the patient population for future clinical trials as well as develop a better understanding of the natural history and prevalence of FKRP-related muscular dystrophies. The conditions that fall under this description are a form of limb girdle muscular dystrophy, LGMD2I, and at the more severe end of the clinical spectrum are the congenital muscular dystrophies, MDC1C, Muscle Eye Brain Disease and Walker-Warburg Syndrome. The conditions are most prevalent in countries such as Norway, Sweden and Denmark due to the founder mutation being of Scandinavian origin, making these countries very important to the Registry. The Global FKRP Registry is a patient driven registry, whereby patients register and consent themselves online, with data reported by both patients and their healthcare professionals. The clinical dataset that is collected focuses on the inclusion criteria required for clinical trials in these rare conditions and includes motor function and muscle strength, respiratory and cardiac function, with information on the underlying genetic mutations. The registry is contributing to the RD-Connect platform(2) as part of the Core Implementation Group for Registries to ensure that national and international registries are interoperable with the platform and contributing data to the rare disease research community. There are currently 293 patients (55% female : 45% male) from 30 countries (30.7% Germany; 26.6% USA; 13.3% UK) represented in the Global FKRP Registry. The age range of patients is 2 to 74 years with a mean age of 34 years, with diagnoses reported as being LGMD2I (89.4%), MDC1C (4.1%), other FKRP-related MDs (0.4%), unspecified (6.1%). 74.4% of patients are reported as being ambulant with 21.5% non-ambulant. The proportion of mutations reported within the Registry are 64.3% homozygous for the common mutation (c.826C>A), 28.7% heterozygous for the common mutation, 7.0% (4.4% heterozygous, 2.6% homozygous) have a mutation other than c.826C>A. The average age of onset for the whole population is 15 years with the average age of diagnosis being 28 years. Bi-annual newsletters are sent out to all registered patients allowing the registry to keep an open line of communication with all patients and keep them informed about developments in research specifically relating to their condition.

REFERENCES:

1. Global FKRP Registry website. Available from: www.fkrp-registry.org
2. Thompson R, Johnston L, Taruscio D, Monaco L, Beroud C, Gut IG, *et al.* RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. *J Gen Intern Med.* 2014 Aug;29 Suppl 3:S780-7.

PPa-03. The Italian National Rare Diseases Registry

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The Italian National Rare Diseases Registry (RNMR) is established by law since 2001 (Ministerial Decree 279/2001) with the main objective of producing epidemiologic evidence on rare diseases (RD), of supporting policy making and health service planning and of monitoring exemptions from diagnosis and care costs. RNMR, situated at National Centre for Rare Diseases, Istituto Superiore di Sanità, is as a network of regional/interregional registries (RRs). These last are fed by clinicians working at Centers of expertise officially designated to diagnose and care patients with rare diseases in each Italian region. RNMR achieved full coverage of the national territory in 2011. The establishment of the RRs resulted in a significant increase of the cases communicated to the central database, which now contains 110841 valid records. RNMR is a population-based and it is clear that this registry must work with other database in order to ensure the interoperability and to improve the data completeness. The linkage with Italian Health Information System, such as mortality data and the ministerial flow of “Monitoring the health care assistance” is a priority action. On the other hand RNMR is also supporting the clinical research. In fact there is a growing need for clinicians to participate in specific RD registries for clinical research purposes. In particular the Registry participate actively in a collaborative effort to combine its data with other specific RD registries such as Emoglobinuria parossistica notturna, Primary immunodeficiency. Standardization of data in order to exchange of information across registries is necessary. The experience of RNMR show that a population based and multi-disease registry with a public health aim provides information not only for public health service assessment, but also for assessing priorities for clinical research registry. The legally mandatory involvement of governmental bodies (the Regional Health Authorities in the decentralized Italian National Health System scenario) in the setup and maintenance of rare disease monitoring systems guarantees the long-term sustainability of the registration process because it is the first step in the provision of patient care. The registry backed by health authorities for health services assessment and planning, can provide the legal, infrastructural, technological and economic support necessary also to research registries. Registry initiatives for rare diseases will be a focus of the future Italian National Plan for Rare Diseases.

REFERENCES:

1. Italian Ministry of Health. Decreto 18 maggio 2001, n. 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124. (GU n. 160 del 12-7-2001- Suppl. Ordinario n.180/L) (in Italian). Available at: <http://www.iss.it/binary/cnmr/cont/DM279-2001.1205943575.pdf>. Accessed on 11/10/2014.
2. Registries for Evaluating Patient Outcomes: A User's Guide. 3rd ed. AHRQ Publication No. TBD. Rockville, MD: Agency for Healthcare Research and Quality. September 2012.

PPa-04. Italian Registry for bleeding disorders

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Congenital bleeding disorders are rare inherited diseases, caused by a defect of proteins involved in the coagulation system. In 2005 a specific pathology registry has been activated at the Istituto Superiore di Sanità (ISS): the National Registry of Congenital Coagulopathies (RNCC), as recommended by the World Federation of Hemophilia (1). The RNCC supplies epidemiological data on the Italian prevalence of the different congenital bleeding disorders (Haemophilia A HA, Haemophilia B HB, von Willebrand disease, deficiency of fibrinogen, Factor II, V, VII, X, XI, XII, XIII), on therapy complications (infections and inhibitor antibodies) and on needs/consumptions of drugs for treatment therapy (2). Data are collected in collaboration with the Italian Association of Hemophilia Centers, through a web-based data flow, on voluntary basis, with the 54 Italian Hemophilia Treatment Centers (HTC). The elaborated data are published in an annual technical report and on the ISS website. In 2013 HTC participating to RNCC are 51/54. The total of patients recorded is 9,469, 40% with HA, about half with the severe form, 24% with von Willebrand disease, 8% with HB and 18% with other rare deficiencies (40% with Factor VII deficiency). The remaining 10% is represented by haemophilia carriers and patients with platelet disorders. The prevalence/100,000 inhabitants of HA and HB is 6.2 and 1.2 respectively. In the analyzed patients, 260 are indicated HIV+ and 1,546 HCV+; respectively 66% and 47% represented by patients with severe HA. Actually the development of inhibitor antibodies represents the most relevant adverse event during the HA therapy. In 2013 total patients recorded positive to inhibitor antibodies are 411, 86% with HA, 18% of the total severe HA patients. Inherited bleeding disorders require wide-ranging care and effective management within a multidisciplinary team setting. The modern treatments of inherited bleeding disorders are now remarkably effective, although expensive. The estimated amount of Factor VIII utilized in the HA therapy and Factor IX for the HB therapy was 478x106 International Units (IU) and 70x106 IU respectively; in both cases 80% in recombinant form. The availability of a specific pathology Registry at national level improves the knowledge of the disease in terms of epidemiology, correlated diseases, care requirements, resources and new therapeutic strategies and could represent an important tool in regional and national health organization. The NRCC, realized by the experience of different actors (institutions, physicians, patients and their associations) could represent a model for surveillance and management of information relative also to other rare diseases.

REFERENCES:

1. Evatt BL. The natural evolution of haemophilia care: developing and sustaining comprehensive care globally. *Haemophilia* 2002; 12:13-21.
2. Abbonizio F, Giampaolo A, Arcieri R, Hassan HJ, Associazione Italiana Centri Emofilia (AICE). Registro nazionale delle Coagulopatie Congenite. Rapporto 2012. Roma: Istituto Superiore di Sanità 2012. (Rapporti ISTISAN 14/12).

PPa-05. Italian database for the collection of clinical and epidemiological data of Paroxysmal Nocturnal Hemoglobinuria

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A national database is the instrument scientifically more appropriate, given the limited number of cases, to deep inside the epidemiological and clinical knowledge on paroxysmal nocturnal hemoglobinuria, analysing data of patients from all centers for diagnosis and treatment in the National area. The collection of data at a public institution such as the Istituto Superiore di Sanità (the Italian National Institute of Public Health) has, for the community of hematologists involved, the guarantee of impartiality, fairness and adherence to institutional rules and laws. The project is shared by hematologists actively engaged in research, diagnosis and treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH). All centers of research, diagnosis and treatment of PNH in Italy can participate in the database by entering the data related to their own patients. The PNH database, through the collection of more than 100 variables, is aimed to:

- improve detailed epidemiological information of the disease in our country through the evaluation of the incidence of diseases associated with the PNH
- study the impact of different therapeutic approaches on the natural history of the disease, the life expectancy, the incidence of associated diseases and the quality of life of patients.

This is an eminently scientific project and is not intended to replace or compete with regional and national organizations collecting data of PNH. In addition, the PNH database interface with the National Registry for Rare Diseases, an important tool for evaluating the impact of RD on health services (health planning) and on the general population (surveillance). This Database shares a well defined common data set with the Italian National Registry for Rare Diseases, established by National regulation at the Italian Centre for Rare Diseases. Therefore the two registries can be linked each other. For this reason, the PNH database can be a effective support by integrating epidemiological data in the National Registry for Rare Diseases; currently the database contains data on 112 PNH patients of which 79 are in common with the National Registry. The database runs on an electronic platform specially designed and based at the National Institute of Health. Every physician, authorized by the Istituto Superiore di Sanità data entry is identified with a username and password strictly personal and unique released by the National Centre for Rare Diseases technical arrangements already widely tested for the National Registry of Rare Diseases.

PPa-06. Italian cystic fibrosis registry (ICFR): web platform and website

Cirilli N. (1), Ferrari G. (2) on behalf of ICFR Scientific Committee, Italian CF centres

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B **ackground:** The Italian cystic fibrosis registry (ICFR) restarted its activities in 2009, the year in which CF centers stipulated a cooperation agreements with the Istituto Superiore di Sanità (ISS), which manages the ICFR. To ensure the correct flow of data from CF centers to ISS and then to European cystic fibrosis patient registry (ECFSPR), a web platform was created at ISS. A dedicated website was also created to give visibility to the activities of the ICFR and to create a privileged communication channel with CF centers and with institutional stakeholders. **WEB PLATFORM** The ICFR web platform is a user friendly tool created in accordance with security and confidentiality Italian and European regulations for data protection. Each accredited user is allowed to do the following actions: - consult the documents regarding data quality assessment (QA) activities (Definitions of Variables, Data Export Rules, minutes of meetings, etc.) - read/download an Excel report with the errors reported by the ECFRPR and relative to the last submission of data - read/download its own data QA report (sections data completeness and insights) - input/change identification data of the CF centre (contact person, email, tel, fax, WEB SITE. The ICFR website is under construction. The site will be resident at the portal of the ISS and will contain different sections on the RIFC and Italian regulations about the disease. Specifically: - ICFR annual reports and publications - Italian regulations about the disease - ICFR data in an aggregated form - ECFSPR last news - CF patients and families news

CONCLUSIONS

The ICFR web platform is a user friendly tool that allows interaction between ISS and CF centers to improve the quality of ICFR data. This tool is continuously enriched with topics, as well as the website, which will allow the immediate and rapid dissemination of the results obtained from ICFR, not only to scientists but also to patients and their families, as well as to institutional stakeholders and no-profit organizations.

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PPa-07. Italian cystic fibrosis registry (ICFR) data quality assessment: CF therapies and complications

Cirilli N.¹, Ferrari G.² on behalf of ICFR Scientific Committee, Italian CF centres

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Objective: Identify errors in the ICFR database RIFC with regard to therapies and complications in order to improve data quality.

METHODS

ICFR data quality control started in August 2012 and was performed by one informatics and one CF specialist. For the current study 2010 CF patients' clinical and laboratory data were considered. Therapies and complications data are the same requested by European CF registry.

RESULTS

25 Italian CF Centres contributed to the ICFR database. In 2010 3388 CF patients were treated in these CF care centres. In this analysis only missing data affected therapies and complications: - for therapies 9/25 (36%) CF centres had missing data for one or more variables (range: 0.5%-4.7%) - for complications 12/25 (48%) CF centres had missing data for one or more variables (range: 0.3%-17.7%). **DISCUSSION** 36% of CF centres had missing data in therapies section, while 48% of CF centres had missing data in the complications section. Due to limitations in the extraction of data (data are extracted per year) it was not possible to analyse the coherence of data.

CONCLUSIONS

Data contained in therapies and complications sections are the same requested by the ECFS registry so a good quality of data entry is essential to reduce the risk of data rejected at national and European levels. The only type of error was data missing, so we need to retrain operators at CF centres on the criteria for data entry. We also need to change data extraction mode to analyse the coherence of data.

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PPa-08. Italian cystic fibrosis registry (ICFR) data quality assessment: CF pregnancy, paternity and transplant

Cirilli N.¹, Ferrari G.² on behalf of ICFR Scientific Committee, Italian CF centres

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Objective: Identify errors in the ICFR database RIFC with regard to pregnancy, paternity and transplant in order to improve data quality.

METHODS

ICFR data quality control started in August 2012 and was performed by one informatics and one CF specialist. For the current study 2010 CF patients' clinical and laboratory data were considered.

RESULTS

25 Italian CF Centres contributed to the ICFR database. In 2010 3388 CF patients were treated in these CF care centres. In this analysis the following types of errors affected pregnancy data: - error type A: incomplete data. 8/25 (32%) CF centres are affected by this type of error (range: 0.5-4.1%) - error type B: incoherent data. 5/25 (20%) CF centres are affected by this type of error Paternity section didn't show any type of error. Transplant section showed incomplete data: 21/25 (84%) CF centres are affected by this type of error.

DISCUSSION

The analysis of these three sections of the ICFR highlighted mainly missing data. Paternity section didn't show any type of error, may be because it's easy to fill in. Transplant section showed the highest percentage of missing data that we think may be due to the fact that the patient, after transplantation, is followed up by the transplant centre.

CONCLUSION

The high percentage of missing data especially in the transplant section highlights the need to modify the data extraction, not by year but as a whole. To retrieve all the data related to transplants we also need to think about making a merge with the data from transplant centres that co-manages the patient waiting for transplant or transplanted.

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PPa-09. Italian cystic fibrosis registry (ICFR) data quality assessment: CF microbiology

Cirilli N.¹, Ferrari G.² on behalf of ICFR Scientific Committee, Italian CF centres

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Objective: Identify errors in the ICFR database RIFC with regard to microbiology in order to improve data quality.

METHODS

ICFR data quality control started in August 2012 and was performed by one informatics and one CF specialist. For the current study 2010 CF patients' clinical and laboratory data were considered.

RESULTS

25 Italian CF Centres contributed to the ICFR database. In 2010 3388 CF patients were treated in these CF care centres. In this analysis the following types of errors affected microbiology data: - error type A: missing data (range: 0-100%) - error type B: incomplete data. 15/25 (60%) CF centres are affected by this type of error.

DISCUSSION

Data quality assessment of microbiology section was difficult because these data are distributed in 3 different sections, and CF centres can choose to input data in 2 of them, depending if they use the software as a medical record or a registry database, while one section is mandatory for all CF centres. Due to limitations in data extraction it was also difficult to analyse the coherence of data regarding for example the date of intermittent or chronic colonization.

CONCLUSION

We need to change extraction mode of data and to retrain operators at CF centres on the criteria for data entry.

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The authors would like to thank all participants from the 25 Italian CF centres who contributed data.

SUPPORT STATEMENT

The study was supported by Lega Italiana Fibrosi Cistica - onlus

PPa-10. Italian cystic fibrosis registry (ICFR) data quality assessment: CF centres participation

Cirilli N.¹, Ferrari G.² on behalf of ICFR Scientific Committee, Italian CF centres

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Objective: Check for cystic fibrosis (CF) centres participation to Italian Cystic Fibrosis Registry (ICFS) data quality assessment (QA).

METHODS

ICFR data quality control started in August 2012 and ended in August 2013. Data quality assessment was performed by one informatics and one CF specialist. For the current study 2010 CF patients' clinical and laboratory data were considered. CF centres were asked to answer to queries after a first check in October 2012 and after a second check in June 2013. Each CF centre can check its errors connecting to a web platform (a red symbol states for errors present and a green symbol states for no errors). We compared the quality of the data received after the first check and after the second check and we evaluated both the number of errors still remaining (red symbols) and the number of patients imputed by each CF centre.

RESULTS

In October 2012 25/27 centers submitted data to ICFR (3388 patients in total); in June 2013 26/27 centers submitted data to ICFR (4314 patients in total). In June 2013 14 (53.8%) CF centers registered new patients; 8 (30.8%) CF centers did not change the number of patients; the remaining 4 (15.4%) CF centers registered less patients.

IN SUMMARY

- 2 sections are always without errors: diagnosis and paternity - CF centres n° 16, 20, 22 corrected all errors - CF centres 6, 15, 19, 23 didn't correct all errors.

DISCUSSION

In October 2012 all CF centres showed errors in all ICFR sections. In June 2013 only 3 CF centres corrected all errors, while 4 CF centres didn't correct any error. More than half CF centres increased the number of registered patients.

CONCLUSIONS

This analysis showed that CF centres participation in the ICFR data QA was poor. This weak performance could be due to different organizational or economic reasons. The ICFR Scientific Committee in collaboration with Lega Italiana Fibrosi Cistica should understand these reasons and do any possible effort to help CF centres improving their participation in ICFR data QA.

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PPa-11. Surveillance of congenital malformations in Calabria

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The Congenital Malformations (MC) defects are characterized by an abnormality in the shape or structure of a body part. Taken together affect approximately 3-5% of all births and are associated with situations that, immediately after the birth or long term, lead to situations of more or less serious handicap. Congenital diseases identified so far are thousands and are the leading cause of mortality in the first year of a child's life. It was necessary to organize a regional level observation tools more reliable and better quality to ensure appropriate monitoring, able to promptly identify any population groups at higher risk for species related exposures to environmental pollutants, through the review of models of survey in order to match international standards. In order to contribute to the improvement of qualitative and quantitative characteristics of previous surveillance system, including coverage, accuracy, timeliness and completeness, the Department of Health Protection of the Calabria Region has adopted a modern discovery protocol that provides for the integration with new information sources current (SDO, Cedap and IVG). With Decree n. 3713 of 01.04.2014 "Registro Regionale delle Malformazioni Congenite (RRMC)_integrazione fonti informative", was established the new surveillance system. It was reorganized network notification consists of all points of time, from the TIN, by neonatology, pediatrics and pediatric surgery. The survey is based on a computer platform via the web. The main strengths of the new system are the detection of cases diagnosed from birth to the first year of life, the possibility of integration with the regional information system (improving coverage) and data entry via web form (improving timeliness).

PPa-12. The EPIRARE Registry Platform. A standard for RD registry vendors to build on and enhance.

George Reynolds

OpenApp, Dublin, Ireland

OpenApp Ltd of Dublin Ireland has been providing bespoke open source based solutions for health care analytics for over 10 years. In the last few years we have developed our skills to include health care data collection in general and Rare Disease registry software in particular. For example our Cystic Fibrosis software is used in 26 countries in Europe.

OpenApp Registry™ uses an enhanced Common Data Element set based on the NIH model registry ORDR data set and follows the EPIRARE guidelines for GUID definitions. This can be customized by adding disease specific elements. This will be updated to support JRC minimum CDEs when they become available. OpenApp Registry™ encourages immediate European wide interoperability and data reusability.

Most patient organizations have to date developed bespoke RD registries. These are difficult to update and provide little opportunities to share data. The EPIRARE recommendations will set a standard that patient organizations can use to design new registries. This is a welcome development for patient organizations and for RD registry vendors like OpenApp. Registry vendors like us can act as expert stakeholders in assisting the Joint Research Centre (JRC) to specify the European RD Platform and in developing open source IT tools. We outline below three areas that EPIRARE might wish to issue recommendations:

The registry should offer patient secure online login to allow patients to review lab results and update data to include PROM quality of life surveys and to act as a hub for mHealth data integration. Clinicians can spend more time reviewing patient entered data and less time asking basic clerical questions.

A patient portal can also be used to create a dynamic consent model which could address concerns about the forthcoming Personal Data Protection Legislation where explicit consent is required for secondary uses.

The biggest single improvement in data quality can be achieved by removing paper from data collection. Disease centres should be provided with low cost network enabled tablets that can: (1) reduce bad on missing data entry (2) provide data validation (3) bypass restrictive hospital data protection and ICT policies and (4) provide patients with real time variance reporting against the natural history of the disease.

PPa-13. The International IAHCRC Consortium for the research on Alternating Hemiplegia of Childhood (AHC): a successful Registry-based model for the progress of the collaborative research on this rare disease

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Alternating Hemiplegia of Childhood (AHC) is a very rare neurological disease (one affected individual in a million). The International Consortium for the Research on AHC IAHCRC was formed in 2012 to carry out a collaborative research that led to the identification of the ATP1A3 gene as the main cause of AHC. The Consortium involves clinicians, geneticists and researchers working at University centers in Europe, USA and Australia; it works in close collaboration with health professionals and patient organizations, most of whom were already involved in the EU-funded projects “ENRAH for SMEs” (FP6, 2005-2007) and nEUroped (PH, 2008-2011). In 2013 the Consortium launched a new collaborative study aimed to identify possible correlations between the clinical phenotype associated with AHC and mutations in the ATP1A3 gene, with the goal to investigate whether different mutations can be responsible for the clinical heterogeneity observed in the disease. The data were collected from the largest international cohort of AHC patients to date (155 patients), and the results of their analysis are now under publication. Further collaborative studies, clinical, genetic and molecular, are currently in execution by the centers of the Consortium. The Consortium is based on a network of Clinical Registries, most of them with a linked biobank, developed in compliance to the ENRAH and nEUroped organizational and data management models; its key features are a set of clear rules, included in a charter, for the sharing of the patient data and of the research information, and a set of common formats and procedures for the data assessment, collection and keeping in the Registries, to be usable for all the collaborative studies of the Consortium. This model can easily include any new centers and registries in the network, thus allowing a fast and ethic involvement of a larger and larger number of patients, and a fast and efficient sharing of their data for both retrospective and prospective studies; in the future, they could also be effectively used for therapeutic trials. Furthermore, with its clinical reference centers working together with the research labs according to this model, any new research results and knowledge acquired on the disease can easily and quickly be translated into the clinical practice, so that the Consortium can be considered as an international reference network both for the progress of the research of an effective treatment for AHC and the development of a better health care of the affected patients.

<http://www.nature.com/ng/journal/v44/n9/full/ng.2358.html>

PPa-14. The registry that changed patients' life

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Thalassemia is a genetic blood disease. The patients can't make normal hemoglobin for producing healthy red blood cells. Regular blood transfusions are the only treatment available to patients with thalassemia. While regular transfusions greatly contribute to the quality and length of life of the patients, they also leave patients with an excess of iron in their bodies. This dangerous side effect, called iron overload, can lead to organ failure or death. To prevent this damage generally two types of medicine are used for removal (chelation) of iron: - Deferoxamine - a liquid medicine that's given slowly under the skin, usually with a small portable pump used overnight. This therapy takes time and can be mildly painful. It is negatively accepted especially by the children and patients' compliance is too weak. This should be considered as normal reaction having in mind that pump appliance is connected with a pricking of a needle each couple of days. - Deferasirox is a pill taken once daily. It can be used by patients who are six or more years old. This type of medicine strongly influences the patients' quality of life as it eliminates the negative sides of the pump appliance. As in 2008 Deferasirox was released on the Bulgarian market it became clear that most of the patients can't afford this medicine due to financial issues and the state should support their treatment. The patient organization applied for financial support to the ministry of health. The answer was that there isn't official data regarding the number of patients and the public health authorities are not able to make social planning for financial support. At the end of 2009 started active registration of patients in "The National registry for patients with thalassemia in Bulgaria", initiated and administrated by the Bulgarian Information Center for rare diseases. In March 2010 was released the first official data regarding the number of the patients and was forwarded to the ministry of health. At this point of time only 4.65% of the registrated patients were using Deferasirox. Two years later when the data of the registry was renewed for the last time, already 62.67% of the patients were using the medicine and their treatment was paid by the National health insurance fund as a result of the ministry regulation. Due to the "The National registry for patients with thalassemia" the daily life of many patients was changed for good.

REFERENCES:

1. Miteva Ts., Stefanov R., Kaleva V. et all. National Register of patients with thalassemia in Bulgaria (NRPTB) - initial results of an epidemiological study conducted during January - April 2010. 4th Eastern European conference for rare diseases and orphan drugs – conference proceedings book, 2010: p. 143.
2. <http://www.raredis.org/?p=1296&lang=en>

PPa-15. Italian national registry of subjects affected by ectodermal dysplasias: genotype-phenotype correlation Italian national genetic and clinical registry of subjects affected by hypohidrotic ectodermal dysplasia: genotype-phenotype correlation

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Ectodermal dysplasias (EDs) are a group of genetic disorders characterized by the abnormal development of the ectodermal-derived structures, leading to hypodontia, hypohidrosis, hypotrichosis and characteristic facial features (1), more complex malformations may be present in syndromic forms. The most typical phenotype of is the hypohidrotic ectodermal dysplasia that can be due to mutations of several genes. But, an extreme variability of this syndrome is present also among subjects carrying the same gene mutation so a genotype/phenotype correlation is very difficult. At the Center for the diagnosis and treatment of Ectodermal Dysplasia in the Pediatric Clinic of Luigi Sacco Hospital in Milan, we follow about 150 children and adolescents affected by EDs. With the collaboration of the National Association of families with Ectodermal Dysplasia (ANDE) we have created a national Registry where we collect clinical and genetic data of all our patients. In our knowledge, this is the first Registry of EDs in Italy. All subjects are studied for the main ED-related genes (ED1, EDAR, EDARADD, WNT10A, P63). For each proband we report in the Registry the genetic diagnosis, if available, or every ED-related gene studied, and a detailed evaluation of disease's clinical manifestations. Other family members eventually affected were also reported. The phenotype is characterized by the degree of severity of all major and minor clinical specific disorders evaluated from the same medical operator and expressed with a numerical scale from 0 (if absent) to 2 (completed manifested). The Registry, structured in this way, allows to characterized the phenotype variability among different genes involved. This is very useful for the clinicians, permitting to improve diagnosis and direct clinical care. In particular, recently, we published a study that described in deep the phenotype spectrum and genotype-phenotype correlation of male subjects harboring ED1 gene mutations, the most common X-linked gene defect in this syndrome (2). A next target we want to achieve through the data analysis of our Registry is the study of the phenotype spectrum and genotype-phenotype correlation of subjects harboring the WNT10A gene mutations, a gene recently found as associated to a large number of hypohidrotic ectodermal dysplasia phenotypes (3).

REFERENCES:

1. Visinoni AE, Lisboa-Costa T, Pagnan NA, Chautard-Freire-Maia EA. Ectodermal dysplasias: clinical and molecular review. *Am J Med Genet A* 2009; 149A: 1980-2002.
2. Guazzarotti L, Tadini G, Mancini GE, Giglio S, Willoughby CE, Callea M, Sani I, Nannini P, Mameli C, Tenconi AA, Bottero A, Caimi A, Morelli M and Zuccotti GV. Phenotypic heterogeneity and mutational spectrum in a cohort of 45 Italian male subjects with X-linked ectodermal dysplasia. *Clin Genet* 2014; Apr 12.
3. Bohring A, Stamm T, Spaich C, *et al.* WNT10A mutations are a frequent cause of a broad spectrum of ectodermal dysplasias. *Am J Hum Genet* 2009; 85: 97-105.

PPa-16. The registry project: a European Huntington's disease network longitudinal study of Huntington's disease

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Huntington's disease (HD) is a rare genetic brain disorder leading to abnormal movements, cognitive changes and behavioral disturbances. In order to understand the phenotype better, large cohorts of patients with prospective observational data are needed. Registry, launched in 2004 by the European Huntington's disease Network (EHDN), with the main aims to explore the relationship between clinical characteristics and genetic factors, to expedite identification and recruitment of participants for clinical trials and to develop existing and novel assessment tools to track and predict disease onset and progression. Registry has recruited 13,455 participants (75% manifest HD, 15% pre-manifest, 4% at-risk and 6% control participants) at 159 study sites across 20 countries, with data collected by local clinical centres and stored via an internet portal. An extensive range of clinical assessments and biological data are gathered on a wide spectrum of people affected by HD, ranging from those with a positive genetic test but no symptoms through to those with advanced disease. Much knowledge has been gained by analyzing the data set. A key strength of Registry, a study strongly supported by lay HD organizations, is its collaborative approach, linking clinicians and scientists, and providing an extensive clinical and biological data repository to facilitate international studies that could not otherwise have been possible. The entire Registry database is available for researchers to conduct data mining projects.

PPa-17. Cystic fibrosis mortality trend in Italy from 1970 to 2011

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B **ackground:** Cystic fibrosis (CF) is a recessive disorder caused by mutations of the CF Transmembrane Conductance Regulator (CFTR) gene. Typical symptoms vary according to the severity of CFTR mutations and include salty sweat, persistent cough and excessive sputum, frequent lung infections, bacterial sinusitis, nasal polyps, poor growth and nutritional status due to pancreatic insufficiency and fat malabsorption. The clinical picture of the disease is even more complex when CF-related complications occur, such as diabetes and liver disease. Since the cloning of the gene in 1989, many advances have been made in diagnosis and treatment of CF. Survival has substantially improved, but some evidence suggests the existence of a female-gender disadvantage (1-3).

OBJECTIVES

The purpose of this research was to carry out a study on mortality due to CF in Italy based on the analysis of death certificates. Specific aims of the study were to describe mortality trend due to CF from 1970 to 2011, to verify the female disadvantage in mortality, and to compare the comorbidities reported in death certificates of CF subjects with those of the general population.

METHODS

Mortality data were extracted from the database of underlying cause of death (1970-2011) and multiple causes of death (2003-2011) of the Italian National Institute of Statistics. Age-standardized mortality ratio (SMR) was calculated to compare the mortality between genders. Moreover, we explored if the distribution of a given condition differed from that of the general population by calculating the age- and gender-adjusted Proportionate Mortality Ratio (PMR).

RESULTS

During the study period, 1947 death certificates reported CF as the underlying cause of death. Mortality rate due to CF decreased in newborns and children and by the end of the 1990s also in adolescents and young adults. Adult mortality started to increase in the early 1990s. Over the whole period an excess in mortality was observed in young CF females (1-29 years). The multiple causes of death database included 531 certificates with CF listed as cause of death. Pneumonia, chronic lower respiratory diseases, pulmonary heart disease and diseases of pulmonary circulation, aspergillosis, sepsis, renal failure, diabetes, malnutrition and amyloidosis were more frequently reported in CF death certificates compared to those of the general population (PMR>1).

CONCLUSIONS

This mortality trend provides evidence of a consistent improvement in survival, although the excess female-mortality persists despite aggressive treatment of CF lung disease. Several extra-pulmonary conditions associated with CF contributed to the morbidity leading to death.

REFERENCES:

1. Buzzetti R, Salvatore D, Baldo E, *et al.* An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. *J Cyst Fibros.* 2009;8:229-37.
2. Colombo C, Littlewood J. The implementation of standards of care in Europe: state of the art. *J Cyst Fibros.* 2011;10:S7-15.
3. McIntyre K. Gender and survival in cystic fibrosis. *Curr Opin Pulm Med.* 2013;19:692-7.

PPa-18. A multicenter EGFR CA-SSR-1 microsatellite study with clinical relevance in thymic epithelial tumors

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Multidisciplinary, multicenter networking in rare tumors proved to be successful in collecting wide case series to be investigated for immunohistochemical (1) or molecular biological (2) biomarkers relevant in the pathogenesis of Thymic Epithelial Tumors (TET). Patients affected by these rare tumors often migrate and visit different Institutions facing their surgical or autoimmune or oncological problems. Our well established multicenter multidisciplinary databases (DB) offer a fundamental resource to our long standing engagement in TET diagnosis, therapy and research. Therefore we shared clinically annotated case series among institutions with different recruitment specificities allowing the integrated study of tumors with different clinical profiles and genetic signatures. In the last years the role played by the EGFR (Epidermal Growth Factor Receptor) gene in TET has been investigated. Very rarely EGFR mutations have been reported in TET, although several reports showed EGFR protein overexpression by immunohistochemistry. **Methods-** We used both sequencing and egfr-fluorescence in situ hybridization to genotype 43 thymomas for polymorphisms and somatic loss of heterozygosity of the non-coding EGFR CA simple sequence repeat 1 [CA-SSR-1] microsatellite and for EGFR gene copy number changes. **Results-** Our thymoma series showed two prevalent CA-SSR-1 genotypes: a homozygous 16 CA repeat and a heterozygous genotype, bearing alleles with 16 and 20 CA repeats. The average combined allele length was correlated with tumor subtype, the shorter sequences being significantly associated with the more aggressive WHO histotype group including B2/B3, B3 and B3/C thymoma. Four out of 29 informative cases analysed for somatic CA-SSR-1 loss of heterozygosity showed allelic imbalance (AI), 3/4 with loss of the longer allele. By egfr-FISH analysis, 9 out of 33 cases (6/9 of B subtype) were FISH positive. Moreover, the two integrated techniques demonstrated that 3 out of 4 CA-SSR-1-AI positive cases with short allele relative prevalence showed significantly low or high chromosome 7 “polysomy”/increased gene copy number by egfr-FISH. **Conclusions-** Our data indicated that CA-SSR-1-Allelic Imbalance with short allele relative prevalence significantly associated with increased EGFR Gene Copy Number, with advanced stage and with relapsing/metastatic behaviour in thymomas.

REFERENCES:

1. Lattanzio R, La Sorda R, Facciolo F, Sioletic S, Lauriola L, Martucci R, Gallo E, Palmieri G, Evoli A, Alessandrini G, Ruco L, Rendina EA, Truini M, Chiarle R, Barreca A, Pich A, Ascani S, Remotti D, Tunesi G, Granone P, Ratto GB, Puma F, Pescarmona E, Piantelli M, Marino M, and the Thymic Epithelial Tumor Working Group - Thymic Epithelial Tumors express Vascular Endothelial Growth Factors and their receptors as potential targets of antiangiogenic therapy: a tissue micro array based multicenter study, *Lung Cancer* 2014, 85 (2), 191-196, August 2014.
2. MicroRNAs Expression Profiling of Thymic Epithelial Tumors - Federica Ganci; Carmen Vico; Etlea Korita; Andrea Saccocini; Enzo Gallo; Federica Mori; Annamaria Cambria; Emanuele Russo; Marco Anile; Domenico Vitolo; Edoardo Pescarmona; Rosario Blandino; Francesco Facciolo; Federico Venuta; Giovanni Blandino; Mirella Marino; Francesco Fazi- *Lung Cancer* 85 (2) (2014) 197–204 , August 2014

PPa-19. Patient registry for rare diseases: first steps in Lithuania

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Introduction: The majority of Lithuanian children diagnosed with tuberous sclerosis complex are followed and periodically checked for any likely complications of tuberous sclerosis in the Coordinating Centre for Rare Pediatric Diseases in Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos. In the national level, the lack of legal basis for the creation of registries and biobanks compromises desirable activity in rare diseases area in Lithuania. It is still difficult to produce a database involving more than one hospital in such circumstances so whenever a rare disease patients visits more than one hospital it is impossible to gather all medical data in one center. Despite these drawbacks Coordinating Centre for Rare Pediatric Diseases is working on patients' database to produce at least satisfactory regional data in the field of pediatric rare diseases.

METHODS AND MATERIALS

A brief data analysis of patients with tuberous sclerosis complex could be a great example of how the registry data can be used for research purposes. We use an electronic data base to collect and store patients' health data which is helpful to develop biomedical research in the field of rare diseases, to improve individual patient care and healthcare planning.

RESULTS

Of 21 affected children there were 4 girls and 17 boys. All of them were referred to university clinics due to epileptic seizures. In 38% of patients epilepsy manifested as epileptic spasms, 14% had focal seizures, 28% had secondarily generalized seizures and in 14% of patients seizures were primarily generalized (other types than spasms). Epilepsy manifested in infancy in 62% of patients. Cutaneous signs were prominent in 80%, renal involvement was observed in 24%, abnormalities in heart ultrasound in 48% of patients. Developmental delay was observed in 62% of patients. None of them have respiratory problems. To the date none of them have genetically confirmed diagnosis.

CONCLUSION

21 patient diagnosed with tuberous sclerosis complex are included in rare diseases registry. Long term patient follow-up data are crucial to develop biomedical research in rare disease area. The most important weakness of database is only regional coverage.

PPa-20. The international thymic malignancy interest group database for the study of thymic epithelial tumors

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B **ackground:** Thymic Epithelial Tumors (TET) have an incidence of 1–5 / million population / year and are therefore classified as a rare “orphan” disease. The International Thymic Malignancies Interest Group (ITMIG) was established in 2009 to enable scientific progress by developing infrastructure and international collaboration, and brought an engaged global thymic community of experts and patients together to achieve this. A series of workshops established an international consensus around definition of terms, forging a foundation for communication and collaboration.

METHODS

An early project was the establishment of a global retrospective database. A collaboration between ITMIG and Purdue University created the data structure built on the HUBzero platform (Purdue University) (<http://ccehub.org>). Once ready, 6097 cases were collected from September 2012 to February 2013 from 45 institutions in 17 countries in Europe, North and South America and Asia (1951–2011). This data set is by far the largest ever established, and is built on the standard definitions developed by ITMIG, the Masaoka /Masaoka-Koga stage classification systems, the World Health Organization histologic classification, and the Myasthenia Gravis (MG) Foundation of America classification of MG severity (1). ITMIG established a statistical core to assist in appropriately structuring studies to address the specific questions and the statistical analyses.

RESULTS

The ITMIG retrospective database is actually being used for analyses on treatment effects, the impact of WHO subtyping of thymoma, and characterization of thymic carcinoma and of thymic neuroendocrine tumors. Moreover, ITMIG established a partnership with the International Association for the Study of Lung Cancer (IASLC) to develop the first ever evidence-based stage classification for thymic malignancies for the 8th edition of the staging manuals. The ITMIG database was augmented with cases from the Japanese Association for Research in Thymus (JART) and from additional cases from the European Society of Thoracic Surgeons; extensive statistical analysis was performed, and results were recently published, representing the ITMIG proposals to the UICC/AJCC for the upcoming TET staging system (2). **Conclusions-** This database serves as a resource for the investigation of clinical issues, including histology, treatment, prognosis, autoimmune disease and second malignancies, with multiple investigations ongoing. Furthermore, ITMIG launched in 2012 a worldwide, prospective, internet-accessible clinicopathological database, including patients diagnosed after 1-1-2012 (3).

REFERENCES:

1. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, *et al.* Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Ann Thorac Surg* 2000;70:327–334.
2. Detterbeck F, Stratton K, Giroux D, Asamura H, Crowley J, Falkson C, Filosso PL, Frazier AA, Giaccone G, Huang J, Kim J, Kondo K, Lucchi M, Marino M, Marom EM, Nicholson AG, Okumura M, Ruffini E, Van Schil P. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors. *J Thor Oncol* 2014;9, Suppl 2:S65-72.
3. Huang J, Ahmad U, Antonicelli A, Catlin AC, Fang W, Gomez D, Loehrer P, Lucchi M, Marom E, Nicholson A, Ruffini E, Travis W, Van Schil P, Wakelee H, Xiaopan Yao, Detterbeck F on behalf of the International Thymic Malignancy Interest Group International Database Committee and Contributors, *J Thor Oncol*, 2014, in press“

PPa-21. Experience ASL of Bergamo for the management of a patient with Hereditary Angioedema.

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The Reference Centre dell'A.O. L. Sacco of Milan, for the diagnosis and treatment of 'Hereditary Angioedema in the month of April 2014 has provided to the Pharmaceutical Service of Territorial ASL Bergamo (SAF) the treatment plan for a patient suffering from this disease. The Hereditary Angioedema is a rare hereditary disease characterized by the appearance of swelling (edema) of the skin, mucous membranes and internal organs, which can also be fatal in some cases. The SAF has provided over the years to the patient different medications indicated for the treatment of this pathology, that are prescribed with diagnosis and treatment plan and that are classified in group A PHT (Berinert and Cinryze) and in group H (Firazyr). The responsiveness was sooner or later quite poor. The new treatment plan, lasting one year, prescribers' Ruconest 2100 U powd. for soluz. ev 1 flac.', active Conestat ALFA, (ranked in group C, RR recipe - without prior treatment plan), with a dose of two vials / 3v / week. The Ruconest is a recombinant C1 esterase inhibitor that is used in a dose of 50 IU / kg for the treatment of acute angioedema attacks. The reference standard, D.Lvo 279/2001, provides that patients suffering from rare disease also are entitled to the provision of drugs in group C, which can be prescribed by physician on NHS prescription and dispensed by pharmacies territorial. Because it is a high-cost drug (retail price 2,189 Euros per vial) was deemed necessary to carry out the distribution to a careful evaluation of the costs both in the case of direct distribution by the SAF that in the case of supply through pharmacies territorial. Therefore, there has been a request for bids to the company Swedish Orphan by the office of the SAF orders that led to obtaining a price / vial of 995 Euro excluding VAT. The same firm, for a minimum purchase of 20 vials, has integrated the offer at a price of 700 Euro excluding VAT. If the drug was dispensed by a pharmacy territorial, on prescription red of the NHS, it would cost the NHS 1595,61+ VAT at 10%. The patient therefore was contacted, managed directly by the pharmacist of SAF, through scheduled deliveries of 20 vials at a time. She was also informed about how the drug administered. The pharmacist before you place a new order ensures that the patient is not hospitalized or who has not had adverse drug reactions that require discontinuation of therapy.

REFERENCES:

Decreto ministeriale - Ministero della Sanità - 18 maggio 2001, n. 279 "Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie ai sensi dell'articolo 5, comma 1, lettera b) del decreto legislativo 29 aprile 1998, n. 124."

PPa-22. Evaluation of amyotrophic lateral sclerosis in registry rare diseases in Balearic island, 2010-2012.

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Objective: The population based Registry of Rare Diseases of the Balearic Islands (IB-RDR) have collected cases registered in from several sources (mainly the minimum data set of hospital discharges (MDS) and the registry of mortality (RM)). Among them Amyotrophic Lateral Sclerosis (ALS), a chronic and progressive neurodegenerative generally disease of unknown origin characterized by the progressive death of motor neurons, central and peripheral, causing muscle weakness and atrophy that leads to paralysis. The aim of this study is to describe de patients with amyotrophic lateral sclerosis in the IB-RDR and evaluate their diagnoses.

MATERIAL AND METHODS

Descriptive analysis of the cases of ALS detected by the IB-RDR from 2010 up 2012. Revision of the medical records of the cases and further classification of the cases according to the criteria of El Escorial in: Definite, Probable, Possible and Suspected,

RESULTS

The registered cases were 70, 80% collected from the MDS and 20% from the registry of mortality. 58% (41 cases) were men, median age 64 years (35-89), women with a higher median age, 71 years, all them residents in the Balearic Islands, 91% of Spanish nationality, 73% of cases (51) residents in Mallorca. Medical records of 67 cases could be consulted. According to the criteria of El Escorial 81% were definite ALS, 8% probable and 6% suspected. 71% (50) of patients were dead, 43 definite cases, 2 probable and 2 suspected.

CONCLUSIONS

The IB-RDR is highly specific, as 81% of the recorded cases were classified as definite cases. Nevertheless, it is necessary to validate the recorded cases through the revision of the medical records to improve the quality of the registry

REFERENCES:

1. Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler R J, Millul A, et EURALS. Incidence of Amyotrophic Lateral Sclerosis in Europe. *Neurol Neurosurg Psychiatry*. 2010 April; 81(4): 385–390.
2. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial “Clinical limits of amyotrophic lateral sclerosis” workshop contributors. *J Neurol Sci*. 1994 Jul; 124 Suppl:96-107.
3. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial “Clinical limits of amyotrophic lateral sclerosis” workshop contributors. *J Neurol Sci*. 1994 Jul; 124 Suppl: 96-107 Brooks. Diagnostic dilemmas in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* 165 (1999) S1–S9.

PPa-23. Italian cystic fibrosis patient registry: 2010 data

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Italian Cystic Fibrosis Patient Registry (ICFPR) was established in 1988 and from 2009 is managed at the Istituto Superiore di Sanità. The ICFPR collects epidemiological, clinical and molecular data on CF patients from Regional CF Centers and aims at i) supporting and performing research on epidemiological, molecular and genotype/phenotype aspects ii) monitoring diagnostic and therapeutic approaches to improve patients care. All data included in the registry are entered through a dedicated software and Quality Controls have been performed to check the validity and accuracy of specific variables (i.e. data completeness, diagnosis, etc). In 2010, 27 Italian CF Centers sent data to ICFPR and 4159 patients were registered (52% M vs 48% F). Five out the 27 Centers take care of more than 200 patients; 17 have 50 to 200 patients; 5 less than 50 patients. We estimated that the number of patients in charge of a specific Center is often significantly different from the number of patients living in the same Italian Region in which the CF Center is located, being this fact explainable by patient health care migration. Median age (yrs) of all patients included in the registry is 17. As regarding diagnosis it was estimated that median age (in months) at diagnosis was 6 vs 5 (M vs F) and that the number of new diagnosis in 2010 was 169. More than 87% of new CF patients was diagnosed by neonatal screening, indicating the efficacy and the importance of this program in the early identification of CF status. More than 94% of patients were fully characterized from a genetic point of view; for 3956 out of 4159 patients, 2 different mutations were identified and for 32 of them the 3rd mutation was also indicated. F508del (44.41%), N1303K (5.25%) and G542X (4.93%) are the most frequent mutations reported and their frequencies values are in accordance with European ones. Weight for Length and the Length for Age (Z-score) for 0-2 yrs old patients, the BMI (Z-score) for 2-17 yrs patients and the BMI (Z-score) for >18 yrs old patients were calculated. According to Cystic Fibrosis Foundation criteria regarding patients >18 yrs old aged, a good nutritional status was observed in about 36% and 28% of patients (M vs F). As regard mortality 34 patients died in 2010 being death a rare event in CF patients; respiratory insufficiency was the its main cause (74% of patients).

PPa-24. The Italian multi-region thalassaemia registry (HTA-THAL): centres, services and patient population

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B **ackground:** Beta-thalassaemia patients should have access to healthcare services specialised in the management of this disease providing them with regular transfusion therapy, iron chelation treatment, multispecialty care and iron overload monitoring. In Italy, patients are managed in several clinical or transfusion units, but a clear picture of the type of services they offer is not available. This paper report data on 60 centres adhering to the "Multi-regional Network" set up in the context of the HTA-THAL project (1-2) collecting data on 1873 beta-thalassaemia major patients registered in the HTA-THAL registry.

METHODS

A survey has been developed using two electronic Case Report Forms for the collection of data on centres' and patients' characteristics. Results: Out of 60 centres adhering to the Network, 40 correspond to clinical units (22 adults and 18 paediatrics) and 20 to transfusion units. The centres are extremely heterogeneous in terms of: a) dimension (20 centres have in care 1-9 patients, 18 centres 10-29, 17 centres 30-79 and 5 centres > 80); b) patients' age (all centres include paediatrics and adults with a mean percentage of paediatric patients of 32% and 7.5% in paediatric and non-paediatric centres, respectively); c) specialised services and laboratory tests availability (30% of the centres refer their patients elsewhere); d) iron overload monitoring procedures, including biopsy/SQUID cardiac and liver MRI availability (40% of centres refer their patients elsewhere). On a total of 1873 beta-thalassaemia major patients in the registry, the youngest is 50 days-old and the oldest 65 years (mean age:30.21±11.04), 259 patients are paediatrics (8.1% under 12 years), and 108 patients (5.8% out of the total) are > 45 years. All patients were submitted to a regular transfusion and chelation regimens (DFX is the most commonly used, followed by DFP used both as monotherapy and in combination with DFO; DFO remains the commonest chelator > 45 Years). During the one year study-observation 56% and 58.4% of patients received cardiac MRI and hepatic iron monitoring (MRI or SQUID or biopsy), respectively. Percentages differ by age groups.

CONCLUSIONS

Our study confirm the feasibility and the usefulness of patients' data collection in the context of the national registries. We describe the large diffusion in Italy of thalassaemia centres and their characteristics. Critical point are: the lack of appropriate measures for shifting paediatric patients to adults units and the need to identify the appropriate distribution and use of resources to assure adequate care to beta-thalassaemia patients.

REFERENCES:

1. Rete Interregionale per la Thalassaemia: HTA dei percorsi diagnostico-strumentali e terapeutici e monitoraggio dell'accumulo di ferro (HTA-THal), 2008. Rif. nota del Ministero della Salute n. DGRST.4/2760-P/1.9.a.b del 2.05.2007 e DGR Basilicata nn. 1591/07 e 201/08.
2. Ceci A, Mangiarini L, Felisi M, Bartoloni F, Ciancio A, Capra M, D'Ascola D, Cianciulli P, Filosa A. The management of iron chelation therapy: preliminary data from a national registry of thalassaemic patients. *Anemia*, 2011;2011:43568.

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PPa-25. Registration of International Codification as part of medical care: intrinsic improvement.

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Introduction: In 2011 draft guidelines were established by the international Shwachman-Diamond (SDS) community, based on the Medical Home or Chronic Care model. SDS shares features with other chronic and rare conditions such as: pancreas insufficiency with cystic fibrosis; neutropenia with a variety of neutropenic syndromes, and skeletal dysplasias with a number of disabilities which restrict full participation in society. Shwachman Diamond Syndrome Support Holland has developed a model for continuous integrated care and self management (2013, SDS congress Toronto).

IMPLEMENTATION OF GUIDELINE

Features such as steatorrhea (a early sign of pancreas insufficiency) can be provided with a LOINC, the universal code system for tests, measurements, and observations. More than 32,000 people in 162 countries use LOINC to make bridges across their islands of health data (<http://loinc.org/>). Also in Tbilisi, Georgia, the laboratory uses the LOINC. The SNOMED CT (Systematized Nomenclature of Medicine Clinical Terms) is one of the international codifications recommended by the European Commission's Rare Disease Expert Group. As rare diseases are defined by their low prevalence as well as by disabling conditions affecting one or more senses, the ICF (International Classification of Functioning, Disability and Health) is applicable to all. When early signs are (usually) encountered in primary care, elements of the medical care, as well as the disabilities themselves, are linked to one disease code and registered. A self improving healthcare system is thus born.

The Shwachman-Diamond community is small. At present there are many disease-specific international rare disease registries. We wish to emphasise the need for inter-disease collaboration on incorporation of medical care information into registries, with the aims of improving early diagnosis, developing treatment and strengthening social integration of people with a rare disease.

REFERENCES:

Dodge *et al.* The importance of rare diseases: from gene to society. Arch Dis Child. 2011; 96:791-792 (doi: 10.1136/adc.2010.193664)

PPa-26. The clinical, cognitive and motor features in CHARGE syndrome: case study and new tools for diagnostic, therapeutic and rehabilitative management.

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CHARGE Syndrome is an autosomal dominant genetic disorder typically caused by mutations in the Chromodomain helicase DNA-binding protein-7 (CHD7) gene [1]. The incidence is estimated at 1/8,500-12,000 births [2]. The term “CHARGE” is an acronym that denotes the six major clinical features: ocular Coloboma, Heart defects, Atresia of choanae, Retardation of growth and/or development, Genital and/or urinary anomalies, Ear anomalies [3]. CHARGE children are affected by plurisensorial disabilities and therefore they have many medical problems not evaluable by already-known developmental scale. The Pediatric Clinic of the Institute of Maternal-Infantile Sciences in Ancona, Regional Reference Center for Rare Diseases, in collaboration with the Lega del Filo d'Oro in Osimo (An) (non-profit organization for people with multi-sensorial deficiencies) take care of 35 patients with clinical and molecular diagnosis of CHARGE syndrome. Because of the very big number and the wide geographical distribution of our patients, our study can be representative of the Italian population affected by CHARGE syndrome. All patients are examined by a specific protocol of laboratory tests and equipments and in particular by an Italian questionnaire called “Guida ai progressi del bambino” (Progress Guide) using to define the cognitive and motor profiles of these children. The purpose of this article is to delineate the natural history of CHARGE syndrome more thoroughly and further to study and define patients' cognitive and motor disabilities to improve their diagnostic, therapeutic and rehabilitative management. Actually the “Progress Guide” is a tool that can identify, in a simple manner and with a certain flexibility, the behavioural characteristics of multi-disabled children by comparing them with non-disabled children. The tool also makes it possible to identify the areas of strength and weakness of any subject and to monitor the development that takes place during psychoeducational interventions. Statistical analysis showed that our patients have delayed development in all skills with respect to chronological age. In particular, the delay is statistically significant in terms of self-care skills (worse toileting, better washing) and the communication skill (language); on the other hand, the expression skill is still preserved.

REFERENCES:

1. Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, *et al.* Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet.* Sep 2004;36(9):955-7.
2. Issekutz KA, Graham JM Jr, Prasad C, Smith IM, Blake KD. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A.* Mar 15 2005;133A(3):309-17.
3. Pagon RA, Graham Jr JM, Zonana JYSL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981; 99: 223– 227.

PPa-27. Incontinentia pigmenti Genetic Biobank

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Incontinentia pigmenti (IP, MIM308300) is an X-linked dominant neuroectodermal disease associated with skin defects and with extracutaneous manifestations (ocular, dental, hair, nail and central nervous system_CNS defects). In 30% of patients CNS anomalies (seizures, encephalopathy, encephalomyelitis, ischemic stroke) are reported. IP patients carry a mutation in the IKBKG/NEMO gene (IKBKG/Nuclear Factor kappaB, Essential MODulator) that encodes for NEMO/IK-Kgamma regulatory protein of IKK complex, required for the activation of the canonical NF-kB pathway. We describe the content, architecture and future utility of our collection of data related to IP patients to offer molecular and clinical anonymous information to the international scientific community. We have built a database of information related to 386 cases of Incontinentia Pigmenti collected in a thirteen-year activity (2000–2013) at our centre of expertise. The database has been constructed on the basis of a continuous collection of patients (27.6/year), the majority diagnosed as sporadic cases (75.6%). The pedigree and clinical information are available for 308 IP cases, while the genetic data are available for 193 samples, respectively. Clinical and Molecular details will be carefully shown. This activity has generated a rich source of information for future research studies by integrating molecular/clinical data with scientific knowledge.

PPa-28. Web based system for data collection, care and follow up of children with chronic, complex and rare diseases.

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The number of children with rare diseases and disabilities is increasing for the reduction of neonatal mortality and pediatric care improvement. Personal and familial quality of life is affected by the numerous clinical problems, attendance to hospitals and the complexity and multispecialistic aspects of care. Health care providers are often different and not connected between themselves and parents are many times the only link between different institutions and types of care. Children with more severe diseases also suffer for a lack of coordination between hospital and home care.

Abilita has been created to support the standardization of the clinical assistance and make data of patients with disabilities available in real time: it is based on a web platform to allow a safe and easy access to clinical documents, to enable the continuous updating of therapies and to organize the documentation and diagnosis on priority criteria. All this allows the parents to have at their disposal all the documentation of the clinical history of their child, avoiding them to carry big amount of papers and reducing the lack of relevant elements. The web database, which has a direct access through Internet, is being tested at the Department of Pediatrics of the Hospital “Bambino Gesù” in Rome. It allows to whom is registered to enter the information on the patient, to update treatment plans and interactions with the ASL and CAD by computer and / or smartphone, after the parental consent. Depending on the credentials provided by the different profiles (doctor, nurse, assistant, family carer ...) the health care providers can see and / or edit information and treatments. All transactions take place in a safe and protected procedure as needed for confidential and personal data. The parents give to the users the rights (and times span) to insert, update and view the data. One part of public information will be used to update and communicate what may be of interest to professionals and families on rare diseases, new treatment options and care, home assistance, etc. At the end of the trial in half 2015, the program will be made available to all those (hospitals, doctors and patients) who will request it and promoted throughout the Country.

REFERENCES:

http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

PPa-29. UK registries for facioscapulohumeral muscular dystrophy (FSHD) and myotonic dystrophy (DM1), their advanced multi-stakeholder reporting system, and their use in clinical trials.

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The John Walton Muscular Dystrophy Research Centre in Newcastle, UK, is home to a number of neuromuscular patient registries using the same novel multi-stakeholder online reporting system. Here we will focus on the UK registries for myotonic dystrophy (DM) and facioscapulohumeral muscular dystrophy (FSHD). These registries have been set up with the primary aim of accelerating and facilitating research into these conditions. Though online patient driven registries they combine patient reported outcomes with clinically verified details. This is achieved through a portal by which the patient initiates registration themselves and as part of this process nominates a clinical specialist, normally a consultant neurologist. The patient provides basic contact information along with some details of their condition, for example current ambulation status. The nominated specialist is notified automatically that a patient has registered. Using the same online portal the specialist is then able to verify the patient entered data while providing some detailed clinical and genetic items, for example ECG results. This multi-stakeholder approach to registries ensures that the patient is at the centre of the process while not compromising on data accuracy or quality. In addition a curator is in place to further monitor the accuracy and completeness of data. These registries are successfully integrating into the research environment in the United Kingdom and have both identified a significant proportion of the participants recruited into a number of clinical studies, in most cases being responsible for around 50% of recruitment. In addition the DM Registry is providing continued support in the planning and recruitment of international trial OPTIMISTIC (www.optimistic-dm.eu) funded through the 7th framework of the European Commission. We have collected data on over 900 patients across these two disease areas, providing a new insight into these populations in the UK that will be used to inform future research and help develop nationally accredited standards of care. Set up under the umbrella of global network TREAT-NMD the data collected in these registries follow internationally agreed datasets that are shared with other national registries across the world. This will allow for data to be fed into a global database that can be a single point of access for researchers with an international scope. We hope to be at the forefront of any such global developments.

REFERENCES:

1. Thompson R, Schoser B, Monckton DG, Blonsky K, Lochmuller H. Patient Registries and Trial Readiness in Myotonic Dystrophy - TREAT-NMD/Marigold International Workshop Report. *Neuromuscular disorders : NMD*. 19. England2009. p. 860-6.
2. Tawil R, van der Maarel S, Padberg GW, van Engelen BGM. 171st ENMC International Workshop: Standards of care and management of facioscapulohumeral muscular dystrophy. *Neuromuscular Disorders*. 2010;20(7):471-5.

PPa-30. ECFS tracker: new software for the European cystic fibrosis society patient registry

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Introduction: ECFSTracker: new software for the European Cystic Fibrosis Society Patient Registry Introduction The European Cystic Fibrosis Society Patient Registry (ECFSR) collects demographic and clinical data on over 30,000 cystic fibrosis (CF) patients from 22 countries in Europe to increase knowledge of the disease. In order to create a uniform data-collection platform, a multi-purpose, multi-source and multi-national software program has been developed.

RESULT

The ECFSR described the requirements, considerations and wishes the software had to accommodate and discussed and validated the developments with the software company regularly.

The software uses open source technology to allow easy access and meets security and European data protection requirements. Strict rules are defined for de-identification of data and for user management. Different ways of data collection, i.e. manual entry or uploading an Excel/XML file with data, are described. Anonymised data are sent to the European database in a uniform way according to agreed definitions and coding, thereby providing data suitable for statistical analysis and reporting on a European, country and centre level. The software contains a patient encounter form (to collect data at each patient visit in real time), the facility to extract reports on patient, centre, country and European level and offers countries the flexibility to collect additional data. Continuity with data that ECFSR collected in the past is assured through seamless incorporation of existing data. The quality of data is guaranteed by automatic controls and validations rules in the software on different levels. The system allows addition of features and modules for multiple use of the registry, i.e. data-extraction for scientific/political purposes and data-collection for pharmacovigilance.

CONCLUSION

The software is a data-collection tool suitable for different kind of users in the European countries and for various purposes. Although the software is customised to the data collection of CF patients, its structure can easily be adapted for use by other rare disease registries.