6th International Conference on Rare Diseases and Orphan Drugs

Global Approaches to Research and Patients Access to Diagnosis, Information and Care, And the Common Issues with Neglected Diseases in Developing Countries.

Program and Abstract Book

March 18-20, 2010

Buenos Aires – Argentina

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Member-at-Large	**Kerstin Westermark**	**Sweden**

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Anna-Lisa Trama **Italy**

Barbara Wuebbels **USA**

ICORD Mission and Aims

Mission

The ICORD mission is to improve the welfare of patients with rare diseases and their families world-wide through better knowledge, research, care, information, education and awareness.

ICORD is an International Society for all individuals active in rare diseases and/or orphan drugs, including health care, research, academic, industry, patient organizations, regulatory authorities, health authorities, and public policy professionals

In order to achieve our aims, ICORD organizes annual International Conferences

Aims

* To organize International Conferences on Rare Diseases and Orphan Drugs (ICORD)

* To promote research, ethics, policies and actions on rare diseases and orphan products in all regions of the world

* To facilitate and provide a global forum for all stakeholders for effective communication, formation of opinion and public debate, concerning rare diseases and orphan products

* To enhance international discussion, cooperation and coordination of research, policies and actions of all bodies active in the field of rare diseases and orphan products

* To exchange best practices between existing bodies and develop international approaches and tools to address common issues in rare diseases and orphan products

VI ICORD, Buenos Aires 2010, Supports and official declarations of importance.

The following official institution supports VI ICORD, Buenos Aires:

* Pan American Health Organization (WHO)

* National Ministry of Health, Argentina

* National Ministry of Science, Technology, and Productive Innovation

* Ministry of Health, Government of the City of Buenos Aires.

* Embassy of the United States of America

* Embassy of the Kingdom of Sweden

*COPIDIS (Comisión para la plena participación e inclusión de las personas con discapacidad), Argentina

VI ICORD, Buenos Aires, has been declared of:

* National Importance by the General Secretary of the Presidency, Argentina

* Educational Importance by the National Ministry of Education, Argentina

* Legislative Importance by the Congress of the Province of Buenos Aires.

Academia Support

* Argentinean Academy of Pharmacy and Biochemistry

* Argentinean Society of Cardiology (SAC)

* Argentinean Society of Clinical research (SAIC)

* Argentinean Society of Dermatology

* Argentinean Soc. of Osteology and Mineral Metabolism (AAOMM)

* Argentinean Society of Pharmaceutical Medicine (SAMEFA)

* Argentinean Society of Rheumatology (SAR)

* Ibero-American Society of Scientific Information (SIIC)

* Institute Leloir

* Latin American Soc. of Med. Research in Rare Diseases (SLADIMER)

Patient Organizations Support

* EURORDIS, European Organization for Rare Diseases.

* GEISER Foundation (Latin America & Caribbean)

* NORD, National Organization of Rare Diseases, (USA)

* NZORD, New Zealand Organization of Rare Diseases

6th International Conference on Rare Diseases and Orphan Drugs

Global Approaches to Research and Patients Access to Diagnosis, Information and Care, And the Common Issues with Neglected Diseases in Developing Countries.

Programme

March 18-20, 2010

Buenos Aires - Argentina

Thursday, March 18
Palais Rouge
Calle Salguero 1441 – Buenos Aires

07:30 **REGISTRATION – BREAKFAST**
Mattisse Ballroom

08:30 **SESSION I: Introduction and Welcome.**
Doré ballroom **Stephen C. Groft**, president ICORD
Virginia A. Llera, Congress Chairwoman
Vilma Martinez. U.S. Ambassador to Argentina.
and Government Authorities.

09:00 **SESSION II. Inaugural Conference.**
Doré ballroom Coordinator: **Kerstin Westermark (**COMP**,** Denmark**).**
Stephen C. Groft (Office of Rare Diseases Research, NIH, USA), Actions on Rare Diseases from a Pioneer Country Toward the Rest of the World. A Vision of Globalization.

9:30 **SESSION III. Rare Diseases: Turning them into an international**
Doré ballroom **Public Health Priority.**
Coordinators: **Catarina Edfjäll** (Celgene Int., Switzerland).
Yann Le Cam (EURORDIS, EU), Presentation of the Draft ICORDs Position Statement.
Virginia A. Llera (GEISER Foundation, LA&C), Including the Developing Countries into the International Scenario of RD and OD.
Timothy Cote (FDA, USA**),** FDA Foreign Offices and its Impact in the Orphan Drugs Field.
Segolene Aymé (EU Rare Diseases Task Force, EU), Review of the International Classification of Diseases.

11:00 **COFFEE BREAK.**
Mattisse ballroom

11:20 **SESSION IV. Initiatives from the Public Institutions to Research**
Doré ballroom **and Patients Access.**
Coordinators: **Ana Maria Martins** (IGEIM, Brazil), and **Erik Tambuyzer** (Gemzyme Corporation, Belgium)
Sophie Koutouzov (GIS, France**)** European Programme on research on rare diseases.
Domenica Taruscio (ISS, Italy), EU Project EUROPLAN Guidelines for National Plans, Strategies on Rare Diseases.
Marlene E. **Haffner** (USA)

12:30 **LUNCH.**
Mattisse ballroom

13:30 **SESSION V. Research on Rare Diseases at Academia and in Industry.**
Doré ballroom
Coordinators: **Desireé Gavhed** (Karolinska Institute, Sweden), and **Alessandro Ferreira Do Nascimiento** (ANVISA, Brazil).
Bernardo Fantini (University of Geneve, Switzerland), International Network on History, Philosophy and Social Medical Issues of Rare Diseases.
Jan-Inge Henter (Karolinska Institute, Sweden)
Erick Tambuyzer (Genzyme Corp., Belgium), Business Models.

14:30 **SESSION VI. Patients and Family Care Models of Accessibility.**
Doré ballroom
Coordinators: **Peter Saltonstall** (NORD, USA), and **Tomas Pulido Zamudio** (Inst. Nac. de Cardiologia I. Chavez, Mexico).
Miguel Angel Ruiz Carabias (CREER, Spain)
Ana María Martins (IGEIM, Brazil)

15:30 **COFFEE BREAK.**
Mattisse ballroom

15:50 **SESSION VII. Insights from Key Stakeholders on Best Practices in the Approval of Orphan Products: A Practical Panel Discussion.**
Doré ballroom
Coordinator: **Penny Oakley** (Simpson Healthcare Executives, USA) and **Marlene Haffner** (USA)
Opening Remarks: Top Ten Learning from Orphan Drug Launches in the Past 3 years. **Penny Oakley** (Simpson Healthcare Executives, USA) and **Marlene Haffner** (USA)
Real World Views and Expectations: Patient Advocacy Group, Patient and Healthcare Provider.
Yann Le Cam (EURORDIS, EU)
Blanca Vazquez (USA)
PNH Patient
The Products and Their Commercialization Pathways
Christopher Cheney (Alexion, USA)
Fran Olson and Julie Wilson (Questcor, USA; via videotape)
Karina Brito (Genzyme, Latin America)
Catarina Edjfäll (Celgene, Switzerland)
Getting the Word Out: Tools & Tactics
Penny Oakley (Simpson Healthcare Executives, USA)
Kurt Kleefeld, (The France Foundation, USA)

18:00 **GEISER Foundation invitation to Rare Diseases Latin American and Caribbean Meeting (ER2010LA).**
Mattise ballroom
Free admission carrying ICORD´s badge. Sessions will be in Spanish language with simultaneous translation to English (Keep your earphone equipment or ask for one at the fist floor).
Conferences will be printed in the post-congress book

20:30 **SLADIMER invitation to Fun & Football evening.**
A relax time for tasting good local food and beverages at the Buenos Aires Velez Sarsfield Club. Av J.B.Justo 9200. Free admission carrying ICORD´s badge. Bring your sport shoes, players will receive a black or a white commemorative soccer shirt. Courtesy Buses available for transportation will be available at the entrance of the Palais Rouge. Courtesy Transportation will be available to Hotel Areas (Downtown and Palermo) after the end of the show.

Friday, March 19
Palais Rouge
Calle Salguero 1441, Buenos Aires

07:30 **REGISTRATION – BREAKFAST.**
Mattisse ballroom

08:30 **SESSION VIII. Bioethics in vulnerable populations.**
Doré ballroom Coordinators: **Jan-Inge Henter** (Karolinska Inst., Sweden), and **Manuel Posadas** (Instituto de Salud Carlos III, Spain)
Luis Alejandro Barrera (University Javeriana, Colombia)
Xiao Mei Zhai (Center for Bioethics/Basic Medicine, China)

09:20 **SESSION IX. Linking needs from neglected diseases.**
Doré ballroom Coordinators: **Virginia Llera** (GEISER, LA&C), and **Carlos Correa** (CILFA, WHO, Argentina)
Olga Pleguezuelos (Pep-t-cell, UK), New Strategies for Developing Vaccines.
Terry Sharon (Genetic Alliance, USA)
Maria Laura Tinelli (Medicos sin Fronteras, Argentina)
Alberto Mantovani (ISS, Italy), Food and Birth Defects: Risks and Benefits**.**

10:40 **COFFEE BREAK.**
Mattisse ballroom

11:00 **SESSION X. Exploring Strategies for a Better Accessibility to**
Doré ballroom **Diagnosis and Therapies.**
Coordinators: **Emilio J. A. Roldán** (SLADIMER, Argentina), and **Howard H Yuwen,** Shire Human Genetics Therapies**, USA)**
Analía Porras (PAHO/WHO, USA), Strategy and Action Plan on Public Health, Innovation and Intellectual Property.
Sonia van Weely (Dutch Steering Committee on Orphan Drugs; Netherlands) Differences and similarities between orphan drug regulation and national plans. Alternatives for Affordable Orphan Products.
Carlos Correa (UBA, WHO, Argentina), Intellectual Property and Needs for the Development of Neglected Medications.
Wilson Caparrós Wanderley (Pep-T-Cell, UK) Specific strategies from the Industry, re-profiling of drugs.

12:30 **LUNCH.**
Mattisse ballroom
12:30 **ICORD Executive Board meeting II.**
Molliere room

13:30 **SESSION XI. POSTERS SESSION.**
Matisse ballroom Coordinators: **Desireé Gavhed** (Inst Karolinska, Sweden), **Alejandra Menéndez** (GEISER, Argentina), and **Virgina Fano** (Garrahan Hospital, Argentina).
Group A, posters P01 to P15; group B, posters P16 to P30; Group C Posters P31 to P46.

14:50 **SESSION XII. International Initiatives on Rare Diseases and Orphan Drugs**
Doré Ballroom
Coordinators: **Virginia A. Llera** (GEISER, LA&C), and **Stephen C. Groft** (NIH, USA)
Argentina**: Emilio J. A. Roldán,** (SLADIMER)
Chile: **Marco Antonio Nuñez Lozano,** (Diputado Comité Parlamentario)
China: **Xiao Mei Zhai** (Center for Bioethics)
Columbia: **Luis Guillermo Velez,** (President of High Cost account in the Ministry of Health)
Japan: **Yukiko Nishimura** (University of Tokyo, Japan)
Mexico**: Luis Carbajal ,** (President Mexican Pediatric Society)
Spain: **Verónica García** and **Francesc Palau** (CIBERER)

17:30 **COFFEE BREAK.**
Mattisse ballroom

18:00 **GENERAL ASSEMBLY MEMBERSHIP MEETING.**
Doré ballroom
Chair: **Stephen C. Groft (**ORDR, NIH, USA)
Secretary: **Domenica Taruscio** (ISS, Italy)

20:00 **GEISER Foundation invitation to the Night of Awards and Tango Show.**

Gala Dinner at Café los Angelitos, Av. Rivadavia 2100 y Rincón, Buenos Aires. **Admission is free for ICORD´s registered, but due to limited availability of seats invitation ticket will be required (Claim yours at Secretary on the basis of first come first served).**
Courtesy Buses will be available for transportation at the entrance of Palais Rouge.
Courtesy Transportation will be available to Hotel Areas (Downtown and Palermo) after the end of the show.

The prize: A blue transparent replica sculptures made by Raquel Sarangello, Argentinean plastic artist, represents the logo-figure of GEISER, the human expression of Latin America and Caribbean search for equity in health.

Saturday, March 20
Palais Rouge
Calle Salguero 1441, Buenos Aires

08:30 **REGISTRATION – BREAKFAST**
Mattisse ballroom

09:00 **WORKING GROUPS.**
Doré ballroom General Coordination: **To be designated**
Summary of previous meetings **(Washington 2008 and Rome 2009).**

Working Group A - Regulatory Needs.
Doré ballroom Coordinators: **Timothy Coté** (OOPD, FDA), and **Kerstin Westermark**
Front part (COMP, EU)

Working group B - Research Collaborations.
Doré ballroom Coordinators: **Barbara Wuebbels** (BioMarin, USA), and **Karina**
Back part **Brito** (Genzyme, Latin America).

Working group C - Patient/Family Needs, Disease Awareness, and Informational Needs.
Matisse ballroom Coordinators: **Peter Salstonstall** (NORD, USA), and **Cecilia**
Front part **Micheletti** (IGEIM, Brazil)

Working group D - Obtaining the Diagnosis of Rare Diseases.
Matisse ballroom Coordinators: **Domenica Taruscio** (CNMR, ISS, Italy), and **Sharon F.**
Back part **Terry** (Genetic Alliance, USA)

Working Group E - Access to Therapy, in Countries With or Without Orphan
To be designated **Drug Legislation.**
Coordinators: **Erik Tambuyzer** (Genzyme, Belgium), and **Yann Le Cam** (EURORDIS, EU)

10:15 **COFFEE BREAK**
Mattisse ballroom

10:30 **SESSION XIII. Plenary Conferences, development of information in Rare Diseases and orphan products**
Coordinator: **Manuel Posadas** (Instituto de Salud Carlos III, Spain)
Segolene Aymé (EU Rare Diseases Task Force, EU)
Sharon F. Terry (Genetic Alliance, USA)

11:20 **SESSION XIV. Conclusions from Working Groups**
Doré ballroom Coordinators: to be designated

12:15 **SESSION XV. Open Discussions**
Doré ballroom Coordinators: **Stephen C. Groft** (NIH, USA), and **Domenica Taruscio** (ISS, Italy)

12:40 **SESSION XVI. Closing session – Summary of Meeting – next steps**
Doré ballroom **Stephen C. Groft**, (ORDR-NIH, USA)
Domenica Taruscio, (ISS, Italy)
Virginia A. Llera, (Fundación GEISER, LA&C)

13:00 **Adjourn**

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Abstract Book

March 18-20, 2010

Buenos Aires - Argentina

Authors	Posters

P01 -VI ICORD 2010

QUALITY OF THE RARE DISEASES DATA FILED AT HEALTH INSTITUTIONS OF ARGENTINA.

Feldman S., Chacón C., Roldán E.J.A., Fanco-Alanis F., Llera V.A.
GEISER Foundation, fundgeiser@yahoo.com.ar

Rare diseases (RDs) are mostly neglected in health and educative programs due to the lack of interest, availability of resources to diagnosis and treat, and/or priority given to the more prevalent conditions. Consequently we suggest that the currently available retrospective epidemiological data must undervalue the magnitude of RD impact in our health system. In order to quantify the fact we made a survey in 36 institutions of Rosario, Mendoza and Buenos Aires city, which are 3 main urban centers of the country, working with a statistical power of 0.80 to discriminate 20% differences, with a $p<0.05$ (Fisher test). A form of 111 items was designed and filled by practitioners, 67% having experience with RDs, and being 32% head of their Departments. Of the participant institutions 48% were main hospitals well equipped, including own genetic and psychological support. All the participants gave their written consent and comply with regulatory norms of clinical research. The survey was approved by an independent ethical committee. In 86% of the institutions, the clinical records are made in a pre-formatted form, following SOPs in 79%, and under internal audits in 71%, but in 91% the responsible of maintenance is a low experienced resident. Apart from the current condition, data on patient performance was available only in 60% of the institutions, psychological data in 50%, and quality of life variables in only 11%. Disease qualification by ATC is made only in 6%. Only 42% ask for signed consent to allow the use of data in scientific studies. Although complexity, the derivation due to RD is not ruled in the institutions, around 38% has some method, independently of institution size (Pearson, $r = 0.63$; $p<0.05$). Regarding reports, only 34% of the institutions perform it regularly, being the figure for RD of 23%. Half of the institutions perform internal education, but only 20% includes RD issues within it. In only 14%, their members attend meetings devoted to RDs. These figures are lower for non medical health staff. Our statistical analysis is not concluded yet, being the average sum of factors not calculated. Nevertheless, it is possible to realize that the accumulation of deficiencies will reduced more the overall quality of the files. We conclude with this preliminary information that current institutional files has a number of deficiencies, even in well equipped institutions, which in turn may sub-valuate the number and impact on health of affected by RDs. This observation contributes to explain in part the observed invisibility and lack of priority of RDs in many health programs. The sample is not country representative but it belongs to urban centers, so the conditions may be worst in regions with less economical resources. Health professionals should be better connected to RDs networks, and education in these conditions enhanced at all institutional levels. The filling of quality of life data, as well as psychological support is needed. Finally norms and SOPs methodology should be harmonized in order to make feasible the collection of RDs data, under GCP, and within a controllable set of bias. Under the current circumstances the RDs retrospective data collection at our health institutions is not recommended.

This study was supported in part by grants from the National Ministry of Health, and GEISER foundation (2008-2009).

P02 -VI ICORD 2010

HOW WELL ARE RARE DISEASES INFORMATION CENTRES KNOWN WITHIN HEALTH INSTITUTIONS OF URBAN CENTERS OF ARGENTINA?

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Rare diseases (RDs) and Orphan Drugs (ODs) information centers are currently considered essential tools to guide practitioners to updated diagnosis and therapies for those conditions not frequently seen in practice. Information centers and networks can be easily approached through internet, and basic information as well as scientific evidences can be downloaded on demand. Nevertheless in our media such centers are not well promoted within the health system, academic educational programs, or any other mean. Consequently it is observed that practitioners approach them very late, or not at all, or when the informed patient introduces the link. In addition, most data appears written in foreign languages, being that a barrier. The lack of accessible net of consultants in the region, and/or of diagnosis know-how and resources, made them not much attractive for the daily practice. We wanted to know well know are some forums of information on RDs and ODs within the doctors working in health institutions of Buenos Aires, Mendoza and Rosario, three of the most populated cities of Argentina. The present data was part of a more ample survey performed at 36 health institutions, working with a statistical power of 0.80 to discriminate 20% differences, with a $p<0.05$ (Fisher test). Participants were requested about their perception of RDs frequency, and on their interaction with international information centers available at internet or through the national health system, being the latter a dummy set of question as there is no active RDs information forum at present. All the participants gave their written consent and comply with regulatory norms of clinical research. The survey was approved by an independent ethical committee. Among the 36 participants, 67% declare to have own experience with RDs (mean RD diagnosed in the last year 8.2± 10.6 diagnosed in the last year), but only 26% judge to be confident in the management of ODs. 32% were head of their Departments and 72% count with internal consultation with pediatricians, 50% with genetic services, and around 42-50% with other specialist in RDs available at hand. It is observed in this sample of practitioners having diagnosed a pool of 295 RDs (immunologic, bone metabolism and neuro-pediatric conditions) within a year, that 53% define adequately the prevalence to consider a diseases rare (1/2,000), but only 7% realize the extra-pooled figure of total RDs expected in the country (3 millions), and 15% of them realize that 8% of an average consult at a general hospital can be one RD. 42% declare to have interacted with GEISER Foundation (the supporter of the survey), 18% acknowledge the data base at NIH website, being other forum less recognized ad sources of information in our environment. Surprisingly 24% mentions services at the National Health System, not actually offered, hence this responses are interpreted as having solve some needs within non specialized institutions of the system. We conclude with this preliminary information that practitioners working at health institutions of big cities in the country have a modest interaction and access to information data base. As such is a cheap mode of managing RDs, campaigns to promote them should be encouraged in our media.

This study was supported in part by grants from the National Ministry of Health, and GEISER foundation (2008-2009).

P03 -VI ICORD 2010

THE ROLE OF PATIENT & PARENT ORGANIZATIONS IN PREVENTION AND TREATMENT OF GENETIC AND RARE DISEASES – LESSONS LEARNED IN BRAZIL

Carvalho, MMSLBS.
Brazilian Genetic Alliance – President**;** International Genetic Alliance – Vice President, Latin America. slscarvalho@linkway.com.br

Objective: This presentation will provide a framework of the role Patient and Parent Organizations play in making easier for individuals and families affected by genetic and rare diseases to get diagnosis, genetic counseling and treatment in Brazil.
Methods: The Brazilian Genetic Alliance – BGA (Aliança Brasileira de Genética), a non-profit organization founded in 2005, brings together 36 patient and parent organizations to establish collaborative efforts seeking improvement in the quality of life for families living with genetic and rare diseases in Brazil. Working as an umbrella organization BGA provides support groups with information and resources to be most effective and to create opportunity for them to share common issues, to identify emerging problems, to learn from each other, and to find creative solutions. BGA proactively collaborates with researchers, industry and policymakers discussing public policies concerning the prevention and treatment of genetic and rare diseases.
Results: Building up a network, BGA promotes awareness about genetic conditions, serves as a contact center for advocacy organizations, and address ethical, legal and social issues related to genetic and rare diseases. Planning and holding or even attending meetings, BGA has given the unique perspective patients and parents have about the impact genetic and rare diseases have in their lives, in the community and in the society. Being invited to debate health insurance coverage with the National Supplementary Health Agency (Agência Nacional de Saúde Suplementar – ANS) BGA succeeded in having private health insurance companies covering DNA tests for investigation and treatment of genetic diseases. Acting in conjunction with the Brazilian Society of Medical Genetics (Sociedade Brasileira de Genética Médica - SBGM), BGA is restless struggling to have genetic services included in the Unified Health System (Sistema Único de Saúde - SUS), the public healthcare system in Brazil.
Conclusions: Genetic and rare diseases affect people all over the world and their consequences are devastating for individuals, their families and also for the society. In developing countries like Brazil, the impact of those conditions is dramatically aggravated by the lack of education, resources and appropriate public policies. Parent and patient organizations, not wanting to be part of the problems but part of the solutions, play a crucial role in this process, identifying barriers and misconceptions about prevention and treatment, providing strategies to address them, and protecting families from additional distress.
Over the past four years, the Brazilian Genetic Alliance has actively contributed to leverage the voices of people living with genetic and rare diseases in Brazil.

P04 -VI ICORD 2010

WORKING WITH PATIENTS TO IMPROVE THE QUALITY OF GENETIC TESTING-THE GENETIC TESTING REFERENCE MATERIAL COORDINATION PROGRAM (GeT-RM)

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Reference and quality control (QC) materials are essential for many aspects of genetic testing. These materials, which are tested alongside patient samples, allow the laboratories to detect errors due to test system failure or operator error. In addition, reference materials are needed for test development and validation, and for proficiency testing/external quality assessment programs. Over 1500 genetic tests are currently offered in clinical laboratories; however, for the vast majority of these tests, no publicly available characterized reference or QC materials are available. In the absence of such publicly available materials, laboratories must improvise to obtain these reagents and, in some cases, develop and run assays without adequate controls. Often, DNA derived from left over patient specimens, which are not easily available or renewable, is used as a reference material. The Centers for Disease Control and Prevention (CDC), in partnership with the genetics community, has established the Genetic Testing Reference Material Coordination Program (GeT-RM). This program works with the genetics community to develop appropriate, well characterized and renewable cell line-based genomic DNA reference materials for clinical genetic testing. Although the GeT-RM Program is coordinated by the CDC, all of the actual work, including decisions about reference material priorities, specimen collection, material development and characterization occurs through voluntary collaborations with laboratories and others in the genetics community.

The GeT-RM program utilizes cell lines from the National Institute of General Medical Science (NIGMS) Repository at the Coriell Cell Repositories to make reference materials. Although this repository has over 10,000 cell lines, the collection does not include all clinically significant genotypes for each genetic disorder, and many genetic disorders are not represented. In the absence of appropriate cell lines for reference material development, the GeT-RM has formed successful collaborations with patient advocacy groups and registries, including DuchenneConnects and the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members to collect blood samples from consented patients for cell line development by the NIGMS Repository. Cell lines created from the collaboration with the DuchenneConnects registry are currently being characterized. Through this collaborative effort the necessary documents for IRB submission have been developed and can be adapted for future use, including consent forms and letters to patients and families of patients and medical providers regarding blood collection. We have also establishing mechanisms for submission of clinical data while protecting the privacy of the subjects. The newly created cell lines will be used to develop reference materials for genetic testing and will also serve as a useful and publicly available resource for continued rare disease research. This poster describes the GeT-RM program, the process used to develop reference materials, completed and current reference material development projects as well as efforts to establish collaborations with the patient community to improve the quality of clinical genetic testing.

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REPORT OF FIVE CASES OF MUCOPOLYSACCHARIDOSIS IN CARTAGENA DE INDIAS, COLOMBIA.

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Introduction: The mucopolysaccharidoses (MPS) are a group of rare diseases, caused by a deficiency of a lysosomal enzyme required for the degradation of glycosaminoglycans (GAGs). The MPS are progressive diseases that present a wide spectrum of clinical manifestations, both physical and mental. Seven types of MPS are recognized, all autosomal recessive inherited, except one, which is sex-linked.
Objective: To report and show the experience of the Academic Unit of Biochemistry, University of Cartagena, Colombia, five cases of MPS, detected during the period 2002-2005, through screening tests in urine and its correlation with clinical manifestations.
Methods: 172 patients were referred based on the clinical impression of physicians. When a MPS is suspected, the following two assays were performed in urine: albumin acid and cetilpiridinium chloride testing. When these tests were found positive, GAGs electrophoresis was performed, and eventually was also determined the activity of L-iduronidase, with external collaboration.
Results: We diagnosed five MPS, three males and two females, aged 4 to 12 years. Common signs are: short neck, broad hands and macro-glossia. No consanguinity was presented.
Conclusions: Within clinically suspected cases, the estimated prevalence of MPS in our city is 2.8%, which justifies the realization of screenings and more specific tests that will lead to accurate diagnosis of MPS types, so that patients can benefit from available treatments and improve their quality of life.

P06 -VI ICORD 2010

RARE DISEASES: CHALLENGES FOR THE PUBLIC HEALTH SECTOR IN BRAZIL

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Introduction: The disease profile in Brazil and all over the world is changing. Brazil adopts the international estimates to establish the rarity of a disease. Life expectancy for patients with rare diseases is usually significantly reduced due to many factors, among them are the rarity, the gravity and the diversity of the disease, the lack of research and investigation; all these are motives for little interest in interventions from the public health sector. These factors also make new studies and research related to them less attractive. In Brazil, as in other countries, we still don't have an integrated and specific epidemic surveillance of some rare diseases, in terms of incidence, prevalence, repercussion about the mortality, morbidity, quality of the patient's life with some rare diseases, what also makes it difficult to have trustworthy epidemic data. *Objective:* To analyze the lack of effective public policies in Brazil that includes patients with rare diseases. Material and Methods: It is a bibliographical revision, the Database consulted were the BVS and the ORPHANET, manuals of national programs were used, in a period ranging from 2000 to 2009.

Discussion: the Brazilian public policies have a great challenge which is the inclusion of rare diseases in the public health programs. Associations of patients and their relatives, and the group of Rare Diseases recently established in São Paulo have been struggling to have the government authorities elaborate public policies directed to the rare disease group and put them in their priorities list. Even though they reach a minority, they need specialized care and qualified professionals in order to change the profile of these diseases in Brazil and in the world, every time they are diagnosed. The lack of public policies for rare diseases in Brazil place the patients and their families in undesirable situations, especially with regards to medications, since most of the medication used for the treatment is very expensive the relatives can not afford a parallel treatment; however, lawsuits, with the objective of having the government pay for the drug treatment and for patient's care, are becoming ever more common; however, besides these problematic situations there are other problematic situations such as in hospital service where there are no protocols or guidelines for most rare diseases; thus, when assisting patients with rare diseases the doctors are disorganized, therefore they end up not following any guideline, but only complying to judicial orders. Brazil has already started to include rare diseases in their public health programs. In November of 2009 in Brazil there was another important landmark in the public policies for rare diseases, the 1st Brazilian Congress of Rare Diseases organized by GEISER In this congress ministers, representatives of associations, representatives of the Public Health sector and of the pharmaceutical companies met to discuss the improvement of the well being of patients with rare diseases and their families, to give support to research, to discuss public policies and to improve international cooperation. *Conclusion*: The lack of available care for patients with rare diseases in Brazil is related to the economy and education and it affects the rights of this affected minority. Therefore, it is necessary to overcome such challenges, encouraging investigations and studies about rare diseases, what would make it possible for those who have these diseases to have longer longevity with better quality of life and health care and appropriate therapy.

P07 -VI ICORD 2010

GENETIC TESTING IN EUROPE: TRANSBORDER TESTING IS A NECESSITY.

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Genetic tests are now offered internationally, through both public and private sector genetic testing services. Physicians prescribing these tests and biologists receiving the samples need to know which tests are available, where they are performed and whether the identified laboratories meet quality standards. To fulfill this need, www.orpha.net was launched thirteen years ago to set up a database of clinical laboratories in the field of rare diseases. Data was collected in 1 country in 1997, 15 in 2003, 26 in 2006 and 38 in 2010. This major effort was enabled thanks to resources from the EC DG for Public Health. In collaboration with the EuroGentest Network of Excellence, information on quality management has been added to the Orphanet database over the past four years. To obtain information on genetic testing in Orphanet, it is possible to search by disease name or by gene (symbol or name in English) in addition to the traditional search by name of laboratory or professional. The information provided on laboratories includes data on quality management. Currently, 956 laboratories offering tests for 1,559 genes are registered in the Orphanet database. The test offer differs greatly from one large country to another: Germany

(1,141 genes), France (874 genes), Italy (625 genes), Spain (582 genes), UK (414 genes). Medium and small-sized countries have a test offer ranging from 1 to 233 genes. This situation explains the large cross-border flow of specimens and underlines the need to provide access to services in other countries when necessary, especially for very rare diseases. Testing for Cystic fibrosis is the only service which is provided by every country. The distribution of this test offer will be presented.

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MOLECULAR BASIS OF THALASSEMIA IN SERBIA. **Pavlovic S[1], Radmilovic M[1], Zukic B[1], Krivokapic-Dokmanovic L[2], Janic D[2], Cvorkov-Drazic M[3] , Bunjevacki G[3]**
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Thalassemia is a hereditary disorder, generally caused by mutations in globins genes, resulting in reduced amount of globins produced. Thalassemia is a rare disease in Serbia. The overall frequency of thalassemia in Serbia is 1.9%. Serbia is one of the Balkan countries, a part of former Yugoslavia. It is situated in the southeast of Europe. Mostly, the population consists of Serbs, Slavs by origin. There are two hospitals in Serbia with genetic counseling activity, where thalassemia patients are recruited: University Children's Hospital, Belgrade and Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic", Belgrade. After hematological and biochemical analysis, patients are referred to the Institute of Molecular Genetics and Genetic Engineering for the confirmation of diagnosis at the molecular level. This study is a report of the molecular characterization of thalassemia mutations in Serbia. Molecular detection of the mutations was carried out by reverse dot blot (RDB) or ARMS analysis (amplification refractory mutation system) and, for the rare mutations, direct sequencing of polymerase chain reaction (PCR) products was performed. Hemoglobin (Hb) Lepore, thalassemic Hb variant, is the most common cause of thalassemia phenotype in the population of Serbia, (26.2%). Ten different β-thalassemia mutations were identified (codon 39 (C>T), IVS-I-110 (G>A), IVS-II-745 (C>G), codon 44 (-C), -87 (C>G), IVS-II-1 (G>A), IVS-I-6 (T>C), IVS I-1 (G>A), Codon 5 (-CT), IVS-I-5 (G>C)) in 130 patients (68 unrelated families). Three mutations (Hb Lepore, codon 39, IVS-I-110) (Hb lepore, IVS-II-745, Codon 39, IVS-I-110) accounted for up to 80%. Furthermore, α thalassemia and a rare unstable β-chain variant, Hb Sabine, were detected.
Additionally, we have studied the β-globin gene cluster haplotypes and their association with most common mutations using PCR-RFLP analysis (restriction fragment length polymorphism). Nine haplotypes, characteristic for Mediterranean population, were detected, the most frequent being haplotype I (43.75%). In addition, haplotype analysis revealed a novel haplotype associated with Hb Lepore Boston Washington gene. These results support the hypothesis of multicenter origin of this mutation. Also, our results have suggested that common Mediterranean mutations had probably been introduced into population of Serbia through historically documented migrations and settlements.
The characterization of the most common thalassemia mutations in Serbia has created the basis for screening, counseling and first trimester prenatal diagnosis program that has started in the year of 2000 in our country.

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GEDR – RARE DISEASES STUDY GROUP – BRAZIL.
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Introduction: The Brazilian Rare diseases Study Group began its activities on July 04, 2009. The date marked the beginning of a study project on rare diseases; this project was suggested by the group coordinator and was based on diagnostic difficulties, inexistence of public policies and lack of information on this subject for the society. The symbol of the group is a four-leaf clover, reinforcing the rarity subject. The volunteers' group, in its current structure, is composed of professionals and students from the Health Area, totaling 45 volunteers. The center of interest of this group is to study rare diseases and orphan drugs and everything related to them. However, it develops many other activities related to the health area that are not related to those diseases, but are informative, educational and divulgational in nature, such as prevention campaigns against non-communicable chronic diseases, organ and marrow transplants, among other of similar importance.
Objective: To disclose what are rare diseases to the civil society, trying to strengthen it in the following aspects: citizenship, rights and dignity of the carriers of those diseases, propitiating the social inclusion; To lay claim to the government on implementation and regulation of public policies for genetic services in the Brazilian Single Health System (SUS),and the supply of free drugs; To perform the exchange between the society and the associations created with the objective of supplying the multidisciplinary support to the carriers of rare diseases and their relatives and caretakers; To promote the scientific study of the rare diseases.
Material and methods: The group meets once or twice a month. The meetings consist of clinical discussions about rare diseases, event planning such as Seminars, Congresses, Walks, and Campaigns, all related to rare diseases. All research, lectures, event organization and event logistics are under the responsibility of the group with the coordinator's orientations. Results: Since July /2009, the group, with the current structure, has obtained only positive results in our proposals, which were: Public Events, Lectures, Conferences, Seminars and The 1st. Brazilian Congress of Rare Diseases and Orphan Drugs, Promoted by the GEISER foundation (Bond, Investigation and Support Group for Rare Diseases in Latin America),non governmental Latin American organization and mutual member of European Organization for Rare Diseases (EURORDIS) and of the National Organization for Rare Disease (NORD), and carried out by the Institute of Genetics and Innate Metabolism Errors (IGEIM), together with the CANGURU Institute and, also, for the Rare Disease Study Group.
Conclusion: Based on all of the activities promoted by the group and by the renowned supporting entities, in this short period of time and mainly in the 1st Brazilian Congress of Rare Diseases, we concluded that we took an important and inedited step with the elaboration of the document from the 1st Congress. This document is fundamental to have an effective popularization of the subject. And this document is the starting point for the Brazilian participation in International Conferences for Rare Diseases and Orphan Drugs (ICORD 2010).The Rare Disease Brazilian Study Group knows that there is a lot to be done; thus, we will continue our activities and discussions in order to reach, together with other partner entities, the elaboration of public health policies in favor of the longings and the needs of the patients with rare diseases and in favor of the civil society.

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ORPHAN DRUGS AND THE BRAZILIAN LEGISLATION.

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Introduction: Twenty five years ago President Ronald Reagan signed the Orphan Drug Act (ODA) of the United States of America. Ever since, it became one of the most important current health legislations. The ODA represents a change point in the history of public health policies because without it the drugs to treat rare diseases would not exist. It was responsible for attracting the interest of the pharmaceutical industry to the development of drugs for rare diseases by offering incentives for the companies which investigate and develop new drugs or new indications for the ones that already exist. These incentives came in the form of financial benefits and of government incentives. *Objective:* To propose the elaboration of a law (similar to the one adopted by the USA - Orphan Drug Act) that will offer fiscal incentives to the pharmaceutical industries when developing orphan drugs; Marketing exclusivity for the commercialization during a certain period of time and Assistance in designing clinical study. Material and methods: It is a bibliographical revision.
Discussion: In Brazil, some initiatives were taken by the government to ensure access to drugs for rare diseases. The CEME (Central of Drugs) proposed a government action to make available essential drugs, among them orphan products, which are difficult to acquire in the international market due to low profitability of its production or due to the rare use of the drug in the producing countries. In spite CEME always having the objective of producing critical drugs, the official laboratories didn't develop production technologies for exceptional drugs to break the dependency in the area. CEME was one of the government efforts, maybe the most important to act in the critical points of the government policies for the pharmaceutical sector, which are: production expansion of domestic raw materials for the production of essential drugs and the potential growth of the government market, allowing greater access to those drugs for the population. After the extinction of CEME, in 1997, its duties were scattered among several agencies of the Ministry of Health. Important decisions have been made in the area, In spite of those investments, Brazil didn't advance in the production of those drugs, and today it is dependent on the importation of drugs of high costs. Regarding Brazil, the discussion should be greater, because besides not producing the drugs it needs (most are imported), there are still the criteria for standardization of the drugs listed in the program.
Conclusion : The adaptations proposed in the American law would be the following: Instead of developing reference drugs, whose costs are very high and whose costs we cannot afford, we could establish partnerships with developed countries in order to obtain production authorization for their generic in Brazil, which could be a production and distribution center for Latin America; In order to grant the market exclusivity for orphan drugs, we can create a breach in the law granting commercialization exclusivity rights only for this type of drug, since few drugs used for the treatment of common diseases are used for treatment of rare diseases, according to the lists of drugs now available in the government programs (exceptional drugs, right dosage, popular drugstore and strategic drugs) and To propose tax exemption for the registration of orphan drugs in the ANVISA

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MARKET EXCLUSIVITY AS AN INCENTIVE FOR THE DEVELOPMENT AND MARKETING OF ORPHAN DRUGS.

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Objectives: To analyze the market exclusivity incentive, whereby approval of similar drugs is not permitted during a certain period of time, as an effective tool to fight against Rare Diseases (RD) and Neglected Diseases (ND) – or diseases of poverty. To take into account and compare the success of the laws that promotes Orphan Drugs (OD) by means of this type of incentive: The Orphan Drug Act (ODA, US) and Regulation 141 (R141, EU). To review the institutional and regulatory context of drug registration, both at the domestic and at the international levels. To identify the range of problems associated with RD, ND, and OD. Finally, to suggest lines of actions to be followed locally.
Method: Analysis of documents. Among the documents selected to be analyzed, there are laws, executive orders, regulations, administrative decisions, reports, newspapers, press releases, scientific papers, and other documents concerning both the national and the international spheres.
Results: A wide array of problems in connection with OD was detected, among which are: Need of specific pharmaceutical laws, scarce regulation of clinical research on RD, absence of valid biomarkers, inadequate or non-existent diagnosis systems, absence of economic and financial incentives, lack of access to a correct diagnosis and appropriate drug treatments, social consequences, high prices, obstacles to property rights, non-inclusion of the notion of RD and OD in the curricula of university courses (Medicine, Pharmacy, etc), lack of information and of continuous training of professionals, among others. The incentives that the ODA and the R141 establish have successfully encouraged the research and development of OD, market exclusivity being the most remarkable one.
Conclusion: We have confirmed our hypothesis that this mechanism, if applied at the national level, would encourage the availability of drugs to satisfy the health needs of the population. Also, we suggest the following initiatives: Need of specific laws on the topic, drafting of an RD National Program by different parties, need of defining the term OD, creation of an RD and OD National Program, creation of an OD National Program, establishing a mechanism of designation/approval of OD, special considerations for registration such as market exclusivity. It would also be convenient to consider additional encouragement, such as tax credits, grants, fast-track review, fee waivers, protocol assistance, and written recommendations. The incentive under examination could be used to satisfy priority local needs including, not only RD, but also ND, which affect a great part of the Argentine population and the population of other developing countries which markets do not naturally offer enough incentives either.

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FOOD COMPONENTS AND RARE BIRTH DEFECTS.

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Maternal diet is critical to prevent an inadequate and/or unbalanced embryonic nutrition, as well as the transfer of contaminants to the conceptus during the organo-genesis. Diet is a complex matrix, influenced by the environment and lifestyles, containing macronutrients (e.g., proteins, lipids) and micronutrients (vitamins, trace elements), as

well as non-essential bioactive and/or undesirable compounds (myco-toxins, heavy metals, man-made contaminants). The term "nutrients" does not imply that "the more the better": as pointed out also by the European Food Safety Authority (http://www.efsa.europa.eu/), both deficiency and excess of specific essential nutrients may lead to adverse effects (e.g., selenium, vitamin A). Last but not least, natural diet components and xenobiotics may interact in diverse ways, still to be clarified in many cases (database EDID at http://www.iss.it/inte homepage; Baldi and Mantovani, 2008, *Ann Ist Super.Sanità*). The many implications of food wholesomeness have supported the new concept of "sustainable food safety" pivoting on risk prevention and health promotion of the generation to come (Frazzoli et al., 2009, *Ann Ist Super.Sanità*). It is therefore of no surprise that the scientific literature indicates the role of a range of food components (from nutrients to contaminants) in the pathogenesis of rare birth defects. The most well-known example is the major preventive effect of an adequate intake of *folic acid* towards neural tube defects (NTDs). However it is interesting to note that several other factors may impinge on NTD pathogenesis, such as inositol deficiency, glucose unbalances, zinc deficiency or some contaminants (arsenic, the mycotoxin fumonison B1) which interfere with folate metabolism. Thus such factors might be involved in NTDs (between 30%-50% in different areas) that are not preventable by folic acid-targeted periconceptional supplementation. Among *trace elements*, zinc appears rather critical for embryonic health. Interestingly, zinc metabolism and utilization may be impaired by high exposures to toxic or non-essential metals (such as cadmium or tin); conversely zinc dietary intake modulates the production of metallo-thioneins, which are a major protective mechanism against toxic heavy metals. Zinc metabolism is impaired also by the excess or deficiency of other essential elements (copper, iron) as well as to *diet-related metabolic disturbances*, such as diabetes and hypertension. Overall, diabetes, obesity, and the excess of food sugars or fats, have been signaled by several papers as risk factors for rare malformations, such as holoprosencephaly, gastroschisis and omphalocoele. Among *vitamins,* an adequate intake of folic acid is a protective factor towards several birth defects, even though the effect on individual conditions is less marked than on NTDs; there are is also evidence for protective roles of, e.g., vitamin C and E toward gastroschisis, choline and group B vitamins toward diaphragmatic hernia. On the other hand, the excess of retinoic acid is a rather unique case of teratogen agent; retinoids have a major, as well as complex, role in differentiation, since relevant nuclear receptors and transport proteins are differentially expressed in specific ectoderm- and mesoderm-derived embryonic tissues. It might be also noteworthy that some widespread, persistent food contaminants appear to disrupt retinoid metabolism, although the possible consequences on vulnerable organisms have still to be understood; one example are polybrominated flame retardants, exposure occurring mainly through seafood and dairy products. In conclusion, when Countries overcome the problem of food security, nutritional deficiencies may change markedly their patterns: *secondary deficiencies* may appear, elicited by the interaction of such factors as i) suboptimal intakes of nutrients, related to food consumption or lifestyle patterns; ii) interference by other factors, such as excess of other nutrients (e.g., through il-aimed supplements) or exposures to pollutants; iii) the multi-faceted range of genetic susceptibility within a population. Although many knowledge gaps do exist, the available evidence can already pinpoint possible priority issues for the prevention of rare birth defects such as ensuring adequate intakes of zinc and vitamin A as well as prevention of obesity; such actions will be both of general public health interest as well as of specific relevance for reducing the malformation burden.

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WHO INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) REVISION PROCESS: INCORPORATING RARE DISEASES INTO THE CLASSIFICATION SCHEME: STATE OF ART.

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WHO has established various Topic Advisory Groups to serve as planning and coordinating advisory bodies in the update and revision process for specific areas of the ICD. A Revision Steering Group oversees the overall revision process. Working groups organised by the Topic Advisory Groups (TAG) review the proposals. A TAG for rare diseases was established in April 2007 as rare diseases should now be traceable in mortality and morbidity information systems. The production of the basic information needed to establish an Alpha draft of the classification of rare diseases has been assigned to Orphanet and may serve as a template for the whole revision process as rare diseases are present in all areas of medicine. Currently, the Orphanet database includes over 6,000 distinct phenotypes which are classified according to published classifications. These classification systems are mainly based on scientific grounds (aetiology and mechanism). To complement these classifications, Orphanet has developed a strictly clinical in-house classification to meet the needs of clinicians. All these classifications can be viewed on the Orphanet website. They now serve to elaborate a proposal for the ICD revision. The first revised chapters currently circulating among experts and expert groups for review are Haematology, Endocrinology, Nutrition, Metabolism and Immunology. The next chapters to be considered are Neurology, Malformation and Multi-systemic diseases. Input from the Rare Disease Community is expected. It is the responsibility of TAG members to contact experts from their region of the world to ensure the widest possible consultation. The alpha draft of the chapters which have already been revised will be published in April 2010 and the beta draft, for field testing, is planned for 2011.The budget of the working group on coding and classification of rare diseases is currently provided by a grant of the European Commission supporting the activities of the Scientific Secretariat of the Rare Disease Task Force.

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PROTOCOL FOR THE HARMONIZED AND COMPREHENSIVE TREATMENT OF THE HETEROTOPIC OSSIFICATIONS: A PROPOSAL.

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At present there is no guideline for medical intervention to treat heterotopy ossifications (HO). The available clinical studies show a variety of interventions in small sample size trials, being their outcome non conclusive. OH are a group of different diseases having in common the spontaneous or trauma induced calcification of soft tissues, being severity depending on the extension and/or localization of the lesions. Specific decalcifying agents are not yet available hence substances as bisphosphonates, warfarin, corticosteroids and diltiazem had been employed. Data on safety, long term

outcome, impact and quality of life, is also lacking in the medical literature. Aiming to gather more consistent data we propose a common protocol to be used in practice for the acute, protracted and preventive medical management of patients having HO. The guideline includes 6 areas of primary intervention as follow: 1- Medical modulation of phosphor-calcium metabolism, including daily oral bisphosphonates in order to reduce the actual bone active surface (By daily administrations of either pamidronate, alendronate, risedronate or ibandronate upon availability); plus periodic I.V. infusions of etidronate (e.g. cycles of 7.5mg/Kg/day, 3 consecutive days) to decalcify the most recent ossified areas, and prevent the expansion of the hard tissue. 2- Symptomatic medications as diclophenac, indomethacin and/or prednisone, aiming to alleviate symptoms and/or improve functionality. 3- Nutrition and calcium intake adapted to the requirements in each individual. 4- Physical therapy and rehabilitation of the affected areas or critical functions. 5- Surgical intervention. 6- Psycho social support for the affected and for the care givers, aiming to reinforce resilience mechanisms, improve compliance and ameliorate the quality of life. Information on health, social, legal (reimbursement policy, accessibility to diagnosis and treatments) will be updated. Treatment follow-up is suggested by biochemical variables in serum: Calcium, phosphorus, GSR, PTH. 25HOvitD, ß cross-laps, alkaline phosphate and its bone specific enzyme, osteocalcine; urinary: Ca/creat ratio, and renal and hepatic functional test each 3 months. Image monitoring includes – spine x-rays, bone mineral absorptiometry, bone sctingraphy, TAC and RMN depending on localization of the calcified tissue. In this scheme, intravenous etidronate is considered and orphan drug, not available in all the countries, and perhaps the limiting step of the intervention. Therefore, to develop compliance the guidelines will be distributed together with the etidronate ampoules and upon request. In this way our group plan to gather valuable information, and to progressively accumulate it in seek of statistical definition regarding the risk/benefit ratio of this intervention in real world conditions. Data will be periodically clustered and reported in scientific means. Further guides in other skeletal and mineral metabolism rare disorders, not having clear or definite diagnosis and therapies, are being outlined by our group.

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LANGERHANS CELL HISTIOCYTOSIS– A RARE DISEASE WITH MANY FACES.

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Background. Langerhans Cell Histiocytosis (LCH) is a rare disorder with highly variable clinical presentation and biological behaviour and of unknown aetiology. Almost any organ may be involved, but the most common manifestations are skin and bone. The pathogenesis of LCH is poorly understood. The disorder may be divided in two general groups: patients with symptoms present in only one organ system, "single-system" LCH (SS-LCH) and patients with symptoms in more than one system "multisystem" LCH (MS-LCH), such as bone, skin, lymph nodes, lungs, liver and spleen, central nervous system including endocrine organs.

The course in the individual patient is unpredictable upon diagnosis. It ranges from spontaneous regression to multiple bouts of disease activity over many years, to rapid deterioration with lethal outcome within weeks. Patients with MS disease with involvement/dysfunction of critical organs (e.g. liver, spleen, hematopoietic system) have a significant risk of mortality, particularly those that do not respond to systemic

therapy. LCH may be associated with CNS dysfunction. Progressive CNS neurodegeneration (CNS-LCH) may result in cognitive and motor dysfunctions that may be severe. Detection of CNS-LCH early and to evaluate the potential efficacy of therapeutic interventions is important.

Some common problems for many rare disorders -Some of the symptoms at onset of single LCH, e.g. skin rash, eczema, external otitis, skeletal pain, endocrine deficiencies (that later may develop to a progressive multi-systemic disease) may be difficult to differentiate from other more common disorders. Remittance to a specialist may therefore be neglected and the accurate diagnosis delayed. Awareness of the different "faces" of multisystemic disease may lead to an earlier diagnose and treatment.-Patients with multisystemic disease may experience poor coordination between the different specialist clinics. A holistic view of the patient may lessen the burden of the parents and patients themselves.- Treatment in current use for LCH is chemotherapy, originally not developed for LCH, but rather empirical. The main cause for this is that the biological cause for the disease is not known. Further, no cure for LCH-CNS exists.

Good examples for acquiring scientific knowledge and medical information about a rare disorder-Patient organisations (Histiocytosis Association of America, Histiocytosis Association of Canada and others) not only support patients but also cooperate with researchers/doctors to prepare clinical trials and they support both clinical trials and scientific research as well as education about the disease and related disorders.-Annual Histiocyte Society meetings are held to spread scientific results to doctors, patient groups and scientists around the world. Such conferences dedicated to a limited group of related disorders are of great value to push the frontline of knowledge forward in a certain field.-Research on LCH (and other histiocytoses) has been set up on international basis to increase the study population, which is an excellent way to learn about the disease and also is a basis to spread knowledge about it.

Recent research findings and further needs. At the Astrid Lindgren's Children's Hospital about 10 children with LCH and neurological signs have been studied. The results of neuropsychological tests indicate a specific, uneven neuropsychological profile in children affected by CNS-LCH, with a decline particularly on perceptual tasks, whereas the verbal performance was not as negatively influenced. Furthermore, verbal and visual memory functions were below normal for their age in most of the studied children. It is important that these cognitive dysfunctions are recognized in order to provide adequate advice and support. Finally, it is a medical challenge to find a treatment reducing this unfortunate neuropsychological development. By MR investigations of LCH patients at the hospital, the incidence of neurodegeneration in LCH was shown to be higher than previously appreciated and estimated to affect 20%-25% of all LCH patients. Since the development of CNS disease in LCH is slow, it has become important to detect and evaluate evidence of neurodegeneration. Moreover, it is particularly important to be able to assess the degree of the ongoing neurodegenerative process in order to be able to evaluate the potential efficacy of therapeutic interventions. We studied biomarkers in the cerebrospinal fluid and found that neurofilament protein and tau protein could be valuable markers of neurodegeneration in CNS-LCH.

In conclusion, without knowledge about the presentation, the cause and the course of the LCH-CNS disease patients may be misdiagnosed, misunderstood and get inadequate treatment and psychological support. More research for finding the cause of LCH (and other rare diseases), would lead more efficient treatment and education about the disease would benefit the patients and their relatives.

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RARE DISEASES RESEARCH IN EUROPE: AN OVERVIEW BASED ON DATA FROM THE ORPHANET DATA BASE.

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Orphanet "Research & trials" is the only database which compiles and presents in a structured fashion information from a multitude of European sources, specifically on rare diseases, concerning European Commission and Member State-funded research projects, on-going and terminated clinical trials, the license offers of the main biomedical research institutions' technology transfer offices and sources of data and materials. Information concerning more than 6 500 research activities is easily retrievable thanks to a multitude of free-access multiple-criteria search engines. The information collected has been analyzed in order to provide an overview of on-going research on rare diseases in Europe, especially in the field of therapy development. This analysis is intended to identify areas in need of collaborative research projects and to target future calls for proposals. The analysis was carried out using the Orphanet database content in November 2009: the classifications of ~ 6 400 RD, the epidemiological data of ~ 2 000 RD, the Orphan drugs database (~600 products) and the ~6 000 research projects, trials and patient registries were cross referenced and analyzed using Excel. The analysis of the distribution of number of diseases by number of treatments in development (estimated through orphan designations or through on-going clinical trials) showed that most RD (276, representing 6 M people affected by RD) have no more than 3 orphan designations, whereas 53 RD have over three orphan designations (representing 2.2 M people affected). Similar results were obtained when the clinical trials, the marketed drugs, the patient registries and the preclinical/epidemiological/basic research were analyzed. Some of the diseases over-represented upstream in the process of R&D (with a treatment on the market or drugs in development) are also well represented regarding the ongoing research, like Cystic fibrosis, pulmonary arterial hypertension and some rare cancers. It is anticipated that the diseases with more treatments in development are those with a higher prevalence, an assumption which is not backed up by our data analysis. The best represented medical domain in terms of percentage of diseases with MA and OD is Rare tumors, followed by Systematic and Rheumatologic diseases, Respiratory diseases, Immunological diseases, Metabolic diseases and Hematologic diseases. It seems that the most mature fields keep on investing in research and are also the strongest ones regarding the products in development and even in basic research for some of them. Other fields, however, like Neurology, seem to be essentially in development, since the percentage of diseases with MA is low compared to other domains and to the percentage of neurologic diseases with OD, clinical trials and research. The absence of orphan designations for some medical domains, like Cardiology, could be explained by the fact that the Cardiology rare diseases (mainly cardiomyopathies and rhythm diseases) benefit from treatments already available for common forms of these diseases. This work was supported by the Rare Disease Platform contract (RDPlatform), a three-year support action project of the European Union's Seventh Framework Programme (HEALTH-F2-2008-201230), which began in May 2008.

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CIBERER: A MODEL OF COOPERATIVE RESEARCH ON RARE DISEASES.

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The CIBERER is one of the nine public consortiums set up at the initiative of the Carlos III Health Institute (ISCIII) to act as a reference, coordinate and foster research into Rare Diseases in Spain. The centre is made up of sixty-one research groups, linked to thirty institutions which form the consortium. The research groups are organized into five scientific areas: Mitochondrial Pathology; Inherited Metabolic and Endocrine Diseases; Neurogenetics; Clinical Genetics and Birth Defects; and Genetic Instability and Predisposition to Cancer. These scientific groups are formed by over seven hundred persons. Most of the staff are basic and clinical biomedical researchers, but also there are technical researchers and management personnel. With this innovative network structure, the CIBERER provides strategic coordination, human resources and materials as well as a collaborative environment where synergy proper to high multidisciplinary and complementary research potential can be developed. CIBERER's main objective is to become an international reference centre for research into the causes and mechanisms of Rare Diseases, with emphasis on translational research. The scientific knowledge generated by the research groups in the CIBERER is intended to be applied in clinical practice in the patient's benefit. CIBERER Programmes & Platforms are the tools used for tackling strategic objectives: strengthening the research groups, giving them more resources and fostering scientific, technical and clinical cooperation, with advance training and knowledge flow in the field of Rare Diseases. These Programmes include: Human Resources Programme, Intramural Research Projects Programme, Training Programme, Programme of Support for Scientific Areas, Equipment Programme and Programme for Special High-Cost Actions. To complete this support, the CIBERER offers 2 platforms services: the CIBERER Biobank (non-profit-making biobank) and the SEFALer (platform which characterize the phenotype of animal models of Rare Diseases). Actually, the CIBERER research groups have more than 1200 Rare Diseases in study, some of them are: Friedreich ataxia, Wolfman sindrome, Gaucher disease, Lafora disease, Fanconi's Anaemia, Congenital dyskeratosis, Hirschsprung's disease, etc. During its 3 years of existence, the CIBERER has allowed increasing the research capacity of its scientific groups and has improved the knowledge about Rare Diseases, always promoting traslational and cooperative research. CIBERER Programmes have jointed and augmented the cooperation between basic and clinical units, increasing the research on Rare Diseases and disseminated the activities of the groups. The CIBERER has launched 77 collaborative research projects with the Intramural Research Projects Programme, fostering new research lines, exploring new fields of knowledge and developing new applications of the knowledge generated. The center has also organized 19 workshops and 26 therapeutic conferences, grouping the best professionals and collaborating with the patients´ associations and the productive sector. Nowadays, 90% of Rare Diseases publications in Spain are led by the CIBERER research groups, with 534 publications in 2008. These facts prove that the CIBERER is a successful model of cooperative research on Rare Diseases.

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THE IMPORTANCE OF DIAGNOSING AMYLOID DISEASES.

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Amyloidoses are diseases characterized by tissue involvement of insoluble fibrillar protein aggregates, so called amyloid. Amyloid is formed as a consequence of protein destabilization, which can be the result of for example mutation, excess protein production and reduced chaperone activity. To date 28 different proteins are known to form amyloid in man, the best known one being the Aβ protein in Alzheimer's disease. The pathology of amyloid depends on the amounts of amyloid that is deposited (sometimes kilograms) as well as on the toxicity of amyloid or preamyloid aggregates that has been observed in surrounding tissues. The amyloidoses include rare diseases such as familial amyloid polyneuropathy (FAP), immunoglobulin light chain derived amyloidosis (AL) and serum amyloid A derived amyloidosis (AA). These three diseases are all systemic amyloidoses, which means that amyloid may deposit in any organ, thereby making it complicated for the clinician to make a correct diagnosis since the symptoms may be very different depending on what organs that are affected. They are all life-threatening diseases and it is crucial that a diagnosis is made in time for an efficient treatment. Amyloidosis can be confirmed by Congo-staining of amyloid-laden tissue. However, as the therapies differ for the various amyloidoses it is of great importance to determine the identity of the specific protein involved in the amyloid deposit and not just settle for the diagnosis "amyloidosis". In AA amyloidosis anti-inflammatory drugs are used to suppress the precursor protein, which is an acute phase protein. On the other hand, FAP patients require liver transplantation and AL patients need chemotherapy to arrest the production of amyloidogenic proteins. Identifying the amyloid protein is most commonly done on amyloid-containing biopsies with protein-specific antibodies in different applications (Western blot, immuno-histochemistry or ELISA). Even though treatments exist for these diseases they are in most cases not curative. Fortunately research efforts in the last decades have resulted in new treatments being developed and evaluated in clinical trials.

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PRELIMINARY EFFORTS AND STRATEGIES DEVELOPED IN CHILE FOR THE WELFARE OF PATIENTS WITH RARE DISEASES.

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Objectives: Our goal is to achieve a better and integral management of patients affected with rare diseases and their families.
Introduction: The law 19.284 for social integration of people with disabilities exists in Chile since January 1994 and further changes have promoted equal opportunities, social inclusion, housing and city planning regulations, assisted voting and others.
FONADIS www.fonadis.cl (Fondo Nacional de Discapacidad) has the mission to promote social inclusion and the effective exercise of the rights of people with

disabilities, through integration and territorial implementation of public policies on disability.
Methods: With all clinical geneticists in Chile, in 2003 we implemented an online system for clinical consultations that serve urban and rural hospitals; Telegenética in Spain began simultaneously. Interchange of technical support financed by Agencia de Cooperación Iberoamericana allowed collaboration and improvement. We have used this site also as a postgraduate learning tool for Clinical Genetics from Latin America. *Contact:teledismorfologia@redclinicauchile.cl* During 2005 we developed a pilot course "Online Education in Clinical Genetics for Health Professionals" for those working in the registry of congenital birth defects in the Maule Region. In 2006, 2007, 2008 we offered the program through www.medichi.cl , a net of digital learning from the Faculty of Medicine Universidad de Chile, and are planning the fourth version 2010, starting in June. The Hospital Clínico Universidad de Chile has created CEMINER: *Centro de Manejo Integral de Enfermedades Raras*, with the goal of increasing the availability of the full capacities of the hospital in professional and technical resources for clinical care, research and teaching, as well as for promoting meeting other patients, sharing information and helping the creation and future activities of patients´ support groups. This is Network of medical and social aid that allows contact with a multidisciplinary medical team in order to achieve a rapid and accurate diagnosis, prognosis, management and recommendations for follow-up of the patients. *CEMINER consultations: ceminer@redclinicauchile.cl*
Challenges: The consultations and the course should improve care for patients and their families by helping primary health care professionals understand genetic influences on illness, and recognize and manage more effectively the most common genetic problems, thus improving the identification and the correct referral for care of children affected by birth defects. Another challenge is facilitating the creation of patients´support groups of rare diseases at a national level, which will reveal the needs of the patients and their support groups; implementing access to the media, the policymakers and the health systems. We struggle for the connection and interchange through an Ibero-American network of these alliances in each country.

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CLINICAL FEATURES OF 28 PATIENTS WITH PROTEUS AND PROTEUS-LIKE SYNDROME.

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Proteus Syndrome is an extremely rare disease characterized by progressive asymmetric overgrowth of limbs, hands and/or feet, connective tissue nevi, epidermal nevi, vascular and lymphatic malformations and skull hyperostosis. It is thought that a dominant lethal gene mosaic distribution would be responsible for local deregulation of growth. We carried out a casuistic study of 28 patients attending our Growth Clinic at Hospital Garrahan.
The objective of this study was to compare clinical, anthropometric measurements and complications of 10 patients with Proteus syndrome and 18 patients with Proteus-like syndrome. Patients and Methods: Medical records of patients were reviewed and divided into two groups: those who met all clinical criteria of Proteus syndrome and those who only met some of them (Proteus-like). Results: Sex ratio (1:1) and median age at last visit (7.37, range: 1.37 to 16.5 years) were similar in both groups. At the time of birth all patients showed symptoms, the most frequent were limb overgrowth

and vascular malformation. Connective nevi and epidermal nevi were present only in the Proteus group. The most common vascular malformation was mixed low flow. All patients showed limb overgrowth, with the right side most frequently affected. Scoliosis and hyperostosis of the skull was more common in Proteus syndrome. Visceral overgrowth (20%) and cystic lung alterations (42.8%) were present only in the Proteus group. Both groups required surgery, the most common reason was macrodactylia. Scoliosis and splenomegaly required surgery only in the Proteus group. Post surgical complications (pneumonia and death) were present only in the Proteus group. Thirty three per cent Proteus and 18% of Proteus-like had developmental delay. Growth in height was normal; only one patient of the Proteus group had macrocephaly. *Conclusions:* epidermal nevi, connective tissue nevi, splenomegaly and cystic lung were present only in the group of patients diagnosed as Proteus Syndrome. The causes of surgery interventions and their frequency were similar in both groups but the postsurgical complications were present only in the Proteus group. We believe that both groups of patients should be followed by a multidisciplinary team, complete Proteus is at higher risk of surgical complications. The team should be aware of the risk of postoperative complications.

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COPD: NEW LESSONS FROM ALPHA-1 ANTITRYPSIN DEFICIENCY?.

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Approximately 6% of the population has COPD, and COPD has become the fourth leading cause of death in the United States. Although the awareness of COPD as a global health problem is growing, our understanding of the pathogenetic mechanisms underlying this highly prevalent disease remains fragmentary. As a result, disease-modifying treatment is still elusive. The lung disease of patients with α_1-antitrypsin (AAT) deficiency resembles COPD. However, in contrast to COPD, the genetic defect and the biology of the structurally and functionally defective AAT protein that is linked to lung disease have been well characterized in persons with AAT deficiency. In this sense, AAT research has had it easier than generic COPD research, and this is exemplified by the advances that have been made in our understanding of the physio-pathologic consequences of the misfolded and polymeric AAT protein, the basic defect that is responsible for both the liver and lung disease of AAT deficiency. For example, the unfolded, polymeric AAT protein that accumulates in the endoplasmic reticulum of hepatocytes and lung epithelial cells initiates a brisk unfolded protein response that involves caspase-3 and apoptosis. Apoptosis of lung epithelial cells has been shown to participate not only in the pathogenesis of the lung disease associated with AAT deficiency but also in the pathogenesis of COPD in general. Since tobacco smoke can interfere with protein folding and induce the unfolded protein response, the pro-apoptotic pathways that have been identified in AAT deficiency could shed light on the development of COPD as well. There are other pathogenetic links between AAT deficiency associated and common COPD. From a scientific perspective, it therefore may no longer be acceptable to think of AAT deficiency as a rare disease that is of little interest to investigators studying COPD, to COPD research funding agencies, to the pharmaceutical industry, and ultimately to patients with COPD.

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NEW FUNCTIONALITIES IN ORPHANET FOR ORPHAN DRUGS, R&D AND MARKETING AUTHORISATIONS TO BETTER SERVE THE RARE DISEASES COMMUNITY.

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The data contained in the Orphanet "Orphan Drugs" database is extracted from official sources. This data includes a list of all substances which have been granted an orphan designation for a disease(s) considered as rare in Europe, whether further developed to become drugs with marketing authorization (MA) or not. The Orphanet database also includes drugs without an orphan designation as long as they have been granted a MA with a specific indication for a rare disease. Orphanet also publishes a quarterly report ("Orphanet Report Series") listing orphan drugs on the European market with or without prior orphan designation. In order to improve access to Orphanet's rich database of information and resources, the search engine has been recalibrated to render data more accessible. In addition to existing search options (by drug or disease), four new sub-tabs improve the visibility of information pertaining to orphan drugs, allowing users to search by a wider range of criteria. Several alphabetical lists of designated products, orphan-designated products with MA, substances and drug trade names are now available. New advanced search options allow users to refine their search by sponsor, MA holder and ATC (Anatomic, Therapeutic, Chemical) category. Substances are now clearly separated from trade names in the results pages: trade names are used solely for products granted MA, whereas substances with orphan designation status (prior to MA) are referred to by their active molecule. Additionally, each substance or trade name is linked to the "Clinical trials" sub-tab of the "Research and trials" tab. Users can retrieve clinical trial(s) that are (or have been) performed for a particular drug. These can also be searched by a wider range of criteria (disease concerned, principal investigator by country, sponsor or clinical trial category). These features are available in all five languages of the Orphanet website.

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RARE DISEASE INFANT BOTULISM. ITALY-ARGENTINA A NEW SCIENTIFIC COLLABORATION BASED ON PREVIOUS EXPERIENCE.

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Infant botulism (IB) is a rare disease originally recognized in USA in 1976. Although IB has been detected on almost all continents, reports of cases have been distributed unevenly. Other than USA, where the IB is the most frequent form of botulism (2614 cases within 1976-2008; average incidence: 2.1 cases/100,000 live births), Argentina has reported the largest number of cases in the American continent and in the world

(507 cases within 1982-2008; average incidence: 2.2 cases/100,000 live births). In the other hand, Italy has reported the larger number of cases in Europe (30 cases within 1984-2009; average incidence: 0.2 cases/100,000 live births). The perceived incidence of the IB remains more a reflection of physician awareness and access to diagnostic testing than of the actual occurrence of disease. The knowledge of the different aspects of the disease is the first step for early diagnosis and prompt treatment of patients. Human botulism immunoglobulin BabyBIG® is the antitoxin of choice for specific treatment. However, its high cost severely limits its use in many countries. Equine botulinum antitoxin might be considered as an alternative with a strict therapeutic protocol considering the particular age of patients. Epidemiological data indicate that a higher number of cases have been reported in countries that have: (1) developed scientific knowledge on IB; (2) a central surveillance system on botulism, particularly in IB; (3) a specific program on IB (e.g. Infant Botulism Treatment and Prevention Program in California). In Argentina, since 1982, and in Italy, since 1984, when the first cases were diagnosed and a national surveillance system was started, a large number of data were collected and several research projects were performed. Based on the experience of both Italy and Argentina on IB, collaborative studies should be very useful to improve and disseminate information worldwide. These scientific activities will be also developed and supported within the European project NECOBELAC (*www.necobelac.eu*). NECOBELAC, as reported during ICORD 2009 meeting in Rome, intends to spread know-how in scientific writing and open access publishing both among researchers and the general public for the safeguarding of public health. At the same time this project also aims to develop or strengthen a network of scientific collaboration between Europe and Latin America. In this framework, the first goal of Italy-Argentina collaboration on IB is to publish a paper in an Open Access journal on a comparison of the different experiences related to clinical, microbiological, and epidemiological characteristics of reported cases of IB. This will help to spread important information on IB, to strengthen research collaborations and to make this information freely available online for all interested parties. Publication of case reports and surveillance summaries will enhance knowledge of the global epidemiology of IB and enable its improved diagnosis, treatment, and prevention.

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LANGERHANS CELL HISTIOCYTOSIS IN ARGENTINA (1991-2010): NATIONAL AND INTERNATIONAL STUDY GROUPS.

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Langerhans cell Histiocytosis (LCH) is a rare disease considered “orphan”, its etiology is unknown, and its clinical pattern is variable (i.e., spontaneous regression, chronic outcome with high incidence of sequelae, or progressive and frequently fatal disease). At Hospital Garrahan (1991) we started working within a multidisciplinary study group focused in this disease (services of Pediatrics, Hematology/Oncology, Pathology, Radiology, ENT and Dermatology), following the Histiocyte Society (HS) diagnostic and therapeutic criteria. Since 1992 till now, we had presented every year our experience in the HS Annual Meetings. Years ago our LCH study group (Garrahan, Gutierrez and Ludovica children hospitals) started performing monthly meetings in order to jointly evaluate patients and chemotherapeutical protocols. Since 1995, we had included patients, from many pediatric institutions of Argentina, in the HS international protocols

of treatment aside other European and North American countries. Thereafter, we became members of the Study groups referred in those protocols. We had also participated in the HS Education and Board Committees. Sixteen manuscripts from our group (some of them in collaboration with other HS scientific centers) were published in international Hematology/Oncology and research journals. We also became LCH reviewers in Pediatric Blood and Cancer, Pediatrics, and in other international journals. The International Annual Meeting of Histiocytosis was organized in Buenos Aires (2006) in collaboration with the HS. Further, we coordinate (Hospital Garrahan) together with the St Jude Pediatric Childrens Hospital (Memphis, USA) monthly meetings by internet and in network with other Pediatric hospitals of Argentina, rest of Latin-America and Spain, presenting patients having this disease. We receive consultations from the doctors, or the parents of the affected, from different cities of Argentina, Latin-America and in some cases from North America, Europe and Australia. We gave conferences in different pediatric hospitals in Argentina, Columbia, Mexico and USA. We also collaborated with the successive parents of Histiocytosis Associations, who are very important for the support of research projects, and to improve the knowledge of the disease within the population. The aim of our group is to continue and to improve our work in this complex disease; nevertheless, to achieve adequate economical support will be essential to reach it.

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MOLECULAR BASIS OF INBORN METABOLIC DISEASES IN SERBIA.

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The first and the only inborn metabolic disease that has been analysed at the molecular level in Serbia is phenylketonuria (PKU). PKU is a rare disease with the incidence of 1/10000 in Caucasians and 1/12300 in Serbian population. PKU is caused by mutations in the phenylalanine hydroxylase gene (*PAH*) that change structure and decrease activity of the enzyme involved in the conversion of phenylalanine to tyrosine in the liver. Although the neonatal screening of PKU in Serbia has been conducted since 1980, the first study on molecular characterization of mutations in the *PAH* gene started in 2004. In total, 34 unrelated patients were analysed. According to pre-treatment serum phenylalanine level, patients were assigned to classical PKU (65%) and mild PKU (35%). By combining PCR-RFLP and PCR-ACRS with multiplex 'broad range' DGGE/DNA sequencing analysis, we reached mutation detection rate of 97% and identified 19 disease-causing mutations. The most frequent mutations were: L48S (21%), R408W (18%), P281L (9%), E390G (7%) and R261Q (6%), accounting for 60% of all mutant alleles. The remaining mutations detected in Serbian population (R158Q, I306V, IVS12+1G>A, Q20X, R111X, V177L, P225T, R261X, L15/S16fsCTdel, S231F, R252Q, R297H, IVS10-11G>A and R413P) occurred at frequency less then 5%. Consequently, calculated homozygosity value of the *PAH* locus (0.10) was low and indicated that molecular basis of PKU in Serbian population is heterogeneous. In order to elucidate origins of frequent mutations: L48S, P281L, E390G (more frequent than in other European populations) and R408W (less frequent than in other Slavic populations), we conducted haplotype analysis. We performed PCR-RFLP on six polymorphic sites (*Bgl*II, *Pvu*II*a*, *Pvu*II*b*, *EcoR*I, *Msp*I and *Xmn*I) and identified VNTRs by PCR analysis. We found that R408W was associated with only one haplotype. On

the contrary, two different haplotypes previously described in European populations were associated with frequent L48S, P281L and E390G mutations. Therefore, we concluded that these 3 mutations had been imported from populations with different genetic backgrounds and propagated afterwards by mechanisms of founder effect or genetic drift. Furthermore, on the basis of the genotype-phenotype correlation (studied in homozygous and functionally hemizygous patients) we analyzed the effect of 9 PKU mutations. For 3 rare mutations (P225T, R413P, R297H), the effect in a patient was described for the first time. Effects of the majority of the remaining mutations (R252Q, R261Q, E390G, I306V, V177L) were in concordance with the previous data. However, for the L48S mutation, previously described as mutation that causes different effects in patients, we observed consistently severe effect in Serbian population. Finally, we made preliminary estimation of the potential benefit of tetrahydrobiopterin supplementation therapy in Serbia. Total frequency of mutations (L48S, E390G, R261Q, R158Q and R413P) which could have positive response to tetrahydobiopterin is 40.2% for the Serbian population. As a result, implemented molecular diagnostics has application in precise diagnostics, genetic counselling and creates possibility to select patients that could benefit from tetrahydrobiopterin therapy.

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A TOOL FOR ACHIEVING STANDARD QUESTIONS FOR PATIENT REGISTRIES: PRISM (PATIENT REGISTRY ITEM SPECIFICATIONS AND METADATA).

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Project Summary: The objective of this NIH-funded project is to develop a library of standardized questions for rare disease patient registries. Questions in the library are structured for consistency, and the underlying data elements will be encoded using controlled terminologies for reliable and consistent retrieval, usage, and analysis. Domain experts from rare diseases research communities are collaborating with programmers and informatics staff to develop a coded question library with relevance to a broader research community. Flexible and scalable technologies enable question re-use and data sharing. The questions will be used in demonstrations of the content and utility of the question library to support new patient registries in several rare diseases including those from rheumatology, hematology, neurology, and metabolic disorders.

Description of the Problem Addressed: Patient registries are an important first step in estimating the impact and understanding the etiology of rare diseases – requisites for the development of new diagnostics and therapeutics. The inability to access existing standardized registry questions results in lengthy and resource-intensive registry development efforts and limits opportunities for data sharing. A standardized library of registry questions will speed the development and deployment of patient registries and allow registries to share and receive data from other registries or data sources. In addition, a library of standardized registry questions will enable cross-indication and

cross-disease analyses, facilitate collaboration, and generate more meaningful results for rare disease patients, physicians, and researchers.

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INFORMATION ON RARE DISEASES: DO FAMILIES HAVE THE ONE THEY NEED? RESULTS OF A STUDY IN ARGENTINA.

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*Introduction***:** The design of appropriate policies to face the particular needs of each country's population affected by rare diseases requires good knowledge of both the specific needs and the institutional, social, economic and cultural framework in which this collective is inserted. Within this approach, *Fundación FOP* is executing a scientific research project which aims to produce information on rare diseases´ situation in Argentina which intends to serve as an input for the development of related policies. This research is supported by the *Agencia de Promoción Científica y Tecnológica*, and two private foundations: *FUNI* and *Gianantonio*. Three tools have been designed in order to collect primary information, namely: (i) a survey destined to families affected by 1 out of 12 selected rare diseases, (ii) a survey of physicians, and (iii) a survey of patients/parents of rare diseases organizations. Part of the preliminary analysis outcomes of the survey of affected families was presented last November 2nd at the National Chamber of Representatives as a contribution for the formulation of a national bill on rare diseases which got the approval of the Lower Chamber in November 25th. This document presents analysis outputs of the survey of families affected by rare diseases in the specific topic "information", which involves all aspects needed to live with the rare disease.
Objectives: To produce statistically significant information on the most relevant aspects regarding situations faced by families with a member affected by a rare disease in Argentina, with the purpose of characterizing them according to, among other determinations, place of residence, socioeconomic status and type of health coverage.
Methods: The survey was carried out amongst a random sample of 322 families affected by one out of 12 selected rare diseases across the country. With respect to the specific issue of perception of availability and quality of information, it shows the level of data families feel to have on various aspects of both the disease and available resources.
Results: Families state their information on different issues is not enough. This general deficit increases in other regions different from the Metropolitan Region of Buenos Aires. Information on their rights to social protection for various aspects of pathologies care is one of the most perceived as deficient.
Conclusions: Availability of appropriate information to families should be one of the critical issues to improve the quality of life for patients and families. Additionally, education of the community about their rights has also proved itself a great need, especially in the interior of Argentina.

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NEURO-SOLUBLE URSODEOXYCHOLIC ACID PREPARATION FOR THE PALLIATIVE TREATMENT OF NEURODEGENERATIVE DISEASES. EXPERIENCE IN AMYOTROPHIC LATERAL SCLEROSIS.

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Amyotrophic Lateral Sclerosis (ALS, Lou Gehrigs Disease, Maladie de Charcot), is a rare condition affecting to 5 per millions inhabitants/year in average. It is a progressive, fatal neurodegenerative conditions affecting the voluntary control of muscles.
Drugs aimed to reduce damage to motor neurons are already approved as riluzole, and some other are in R&D phases. The drug extends the time before the patient requires ventilation support and lengthen survival by several months. Nevertheless not all the forms respond equally and combination of drugs may be desirable. Ursodeoxycholic acid or ursodiol (UDCA) is one of the secondary's bile acids have citoprotective activities shown in experimental Alzheimer and Huntington diseases, retinal degeneration and ischemic stroke. Nevertheless the clinical outcomes had been always poor due to its reduced cerebrospinal fluid penetration. Notwithstanding, patients receiving 15 to 50mg/Kg/day may achieve adequate levels (*Gareth P et al Clin Neuropharmacol, 2010, 33: 17*), A recent formulation made by Yoo (Yoo´s solution), Seoul, Korea has been approved for ALS treatment by KFDA, and made available through compassionate uses in further countries. The formulation consist
UDCA(ursodeoxycholic acid) is a primary constituent of bear bile which has been used as a therapeutic agent in local and systemic febrile diseases for over 3,000 years in Asia.UDCA has cytoprotective, anti-apoptotic, immunomodulatory, and protective properties of mitochondrial integrity. Yoo's solution is the only UDCA product which delivered pure UDCA to CSF and brain tissue efficiently. Prime Pharm Tech successively completed the phase III clinical trial of Yoo's solution for ALS (amyotrophic lateral sclerosis) patients. Yoo's solution significantly delayed disease progression of Korean ALS patients.
Yoo's solution significantly decreased infarct volumes, improved neurological function, suppressed certain events in the cell death pathway in a MCAO(middle cerebral artery occlusion) stroke model, and may be effective in the management of stroke.
The clinical efficacy has been tested in a double blind placebo controlled trial in 144 patients. Results show that patient survival is significantly improved in those taking daily UDCA. Tolerability is good up to 50mg/Kg/day.

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THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES (EUCERD): A NEW COMMITTEE TO HELP THE EUROPEAN COMMISSION ADVANCE IN THE FIELD OF RARE DISEASE POLICY.

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The European Union Committee of Experts on Rare Diseases was formally established via the European Commission decision of 30 November 2009 (2009/872/EC). The EUCERD will aid the European Commission (EC) with the preparation and

implementation of Community activities in the field of rare diseases (RD), in cooperation and consultation with the specialized bodies in Member States, the relevant European authorities in the fields of research and public health action and other relevant stakeholders acting in the field. The EUCERD replaces the EC's Rare Diseases Task Force. Members of the EUCERD include representatives of: each Member State, patient organizations, the pharmaceutical industry, ongoing/past Community projects in the field of RD, ongoing/past RD projects financed by Community Framework Programmes for Research and Technological Development, DG Sanco, DG Research, DG Enterprise, Eurostat, and the ECDC. The EUCERD will foster exchanges of relevant experience, policies and practices between these parties and is charged with the following responsibilities: assisting the EC in the monitoring, evaluating and disseminating the results of measures taken at Community and national level in the field of rare diseases; contributing to the implementation and improvement of Community actions in the field; contributing to the preparation of EC reports on the implementation of the Commission Communication and the Council Recommendation; delivering opinions, recommendations or submit reports to the EC either at the latter's request or on its own initiative; assisting the EC in international cooperation on matters relating to rare diseases; assisting the EC in drawing up guidelines, recommendations and any other action defined in the Commission Communication and in the Council Recommendation; providing an annual report of its activities to the EC. The EUCERD may establish temporary Working Groups including external experts for specific missions. The Scientific Secretariat of the EUCERD is supported by an EC Joint Action.

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A MASTER PLAN FOR THE MANAGEMENT OF PATIENTS HAVING HETEROTOPIC OSSIFICATION IN LATIN AMERICAN COUNTRIES.

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A number of different diseases are known as Heterotopic Ossifications (HO) having in common the abnormal calcification of soft tissues. Prognosis is largely depending on extension and localization of the lesions. Clinical diagnosis is not difficult but sometimes the pathogenesis and specific treatments are not known. Due to the low prevalence of this conditions clinical trials are always small, non conclusive and consequently effective treatments are not available. Etidronate large concentration (by I.V. infusions) at the extra-skeletal space may reduce calcified areas, improving functionality and decreasing symptoms, but no protocol is available. Beyond calcification, a number of quizzes from diagnosis, monitoring tools and adequate variables, long term efficacy and impact on quality of life (QOL) had not been quantified; accordingly physicians do not solve all the inquiries from patients. Taking HO as a model of building master plan for given rare disorders, GEISER and SLADIMER suggest a master plan for HO from research to QOL issues. The program will ne mounted in the Argentinean Republic as a pilot experience, and consists in the making and involvement of: 1-Specific regional patient NGOs, through GEISER Foundation "incubator program". 2-The foundation activates awareness campaign at specialized centers and mass media, 3- enhance its databases; and 4-designs precise supporting services for HO patients in hands of trained teams. 5-The affected and caregivers are educated and organized in order to strength its health and social demand of medical attention, psychological support and family aid, following European

models. In addition SLADIMER: 6- Stimulate a network of HO specialist within the country, and basic/genetic studies, 7- elaborate guidelines for intervention (see poster P14), 8- harmonize data collection and publish scientific data regarding safety, efficacy, monitoring variables, and QOL. 9- Promote awareness campaigns at medical societies and congresses. Both institutions cooperate in order to: 10- check availability and accessibility to diagnosis and treatments, 11- organize meetings seeking for new approaches and enhancement of interest in HO at academies and governments facilities, as well as linking the local needs with the international scenario related to HO issues.
It s expected that the results of this program can be reported yearly, starting in 2011, and that same can be afterwards organized and replicated in further Latin American and Caribbean countries willing to adhere.

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DERMACAMP: NEW BOARDING IN THE ATTENTION TO ADOLESCENTS WITH SEVERE DERMATOSIS

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Naturally complex for those who enjoy good conditions of health, adolescence can become extremely challenging and threatening for youngsters that present some type of physical or mental disturbances. Diseases of skin, frequent in the population, represent important factor of compromise of the quality of life in the adolescent population, especially in function of the great valuation of the appearance and aesthetic models. Based in their experience, authors show highly positive results reached with a new form of intervention and boarding next to adolescents with severe problems of skin, through thematic camps and periodic meetings that use playful and dynamic activities specially planned to promote integration, dealing with diversity and self-knowledge to adolescents that suffer from severe dermatological diseases. This promotes improvement in their self-esteem and their perception on improvement in DLQI. *Objective*: To demonstrate as the participation of the youngsters in the Dermacamp Project contributes for overcoming of the difficulties lived deeply in daily with the other adolescents and population (preconceptions, stigmatization, rejection) in function of its "different" physical appearance; also, as the development of abilities for the personal and collective confrontation of these awkward situations, their organization and pro-activity in the project, training for leadership, monitoring and creativity to act in the project, had contributed on such changes. Method: qualitative study with phenomenological boarding as research trajectory. Carried through by means of interviews, inquiries, analysis of figures, having involved 136 children and adolescents who had been part in 12 camps between 2001 and 2008. *Results*: Interviews carried through after participation in 1 or more camps, after at least 1 year of family's participation, we've detected effective changes in the attitude and way to perceive their condition, to deal with the problem and its treatment. Better integration in the school and community (62%), greater participation in activities (43%), greater confidence in themselves (42%), change in the cares with appearance and clothes (53%). The results of the camps demonstrate that the youngsters feel safer, learn to deal better with its adversities, they make empowerment in the project; give new direction to perspectives and projects of life (73%). *Conclusion*: The implementation of complementary strategies to the medical treatment, proposals for the DERMACAMP

revealed highly positive in the development of the capacity of confrontation of the adolescent ahead of these adverse situations. Also the adherence and continuity of participation of the "former-adolescents", that they had passed as campers in Dermacamp and are today monitors in the project, multiplying next to other children and adolescents the experience for them lived deeply. The confrontation of the chronic illnesses exceeds the establishment of actions focused only on biological aspects. Psychosocial aspects have important meaning and can last lifelong. Simultaneous to treatment we need different ways to deal with the affection, using different strategies in interface between three factors: cycle of the illness, family and subject. DERMACAMP can be one of these strategies.

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PERCEPTION OF BODY IMAGE BY CHILDREN AND ADOLESCENTS WITH CHRONIC PROBLEMS OF SKIN.

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The association between organic affections and psycho emotional manifestations is an emergent field of research, due to its complexity and challenges in its boarding in the practical daily clinic (Gleeson, 2006). Related studies to body image (BI) and corporal dismorphic disturbance (CDD), restricted initially to the field of the neuroscience and psychiatry, evolved forwards the search of new information and new looks, with a more including perspective and to interdisciplinar, due to multiplicity of involved factors with the construction processes, perception and experiences related with the corporal image throughout the life cycle (Cash and Pruzinsky, 2002). Carried through work on the basis of our experience of more than 20 years with children and teen with skin diseases, severe chronic and in its majority, disclosed the feeling, as much of the parents as of the proper young, of constant, preconception and difficulties of acceptance and integration in group activities, as result of alterations in the appearance on account of the skin illnesses (Mandelbaum and col.2007).Ahead of the impact that such feelings caused in these families and face the consequences on the personal, family and social life of these children, we decided to investigate as the construction of the corporal image is perceived by children and adolescent in the validity of problems of skin and how such perception influences in the assistance planning, nursing care and strategies, in order to favor the integration and to raise the level of quality of life of these children (Smolak, 2002).The objectives of this work had been to identify as the children and adolescents with skin problems perceive their BI and how this perception is modified throughout their experience; which elements participate in this process and as they impact on participation in familiar and social activities. The work was carried through with 17 children and teens, age 9 to16 years and with its responsible ones, all participants of a social project developed in a city of the São Paulo state, in the period of July 2007 till December 2008. Qualitative methodology was used, having been applied some free instruments as interviews, drawings, plates with drawings and cartoons. The conceptual base that gave basis to this work was the theory of the speech of the collective citizen (SPC) of Lefévre (2000). The collected in formations were submitted to Qualisoft software; drawings and depositions on the plates and photos had been analyzed on the basis of the program. The research was approved by the ethics committee; a parents' Informed Consent was signed. Results had been divided in three areas: self perception, hetero-perception and perceptive integration, on the basis of the concept of Slade (1994).In this work we are presenting data related to

self-perception, as the children perceive themselves. We identified that the BI of these children and youngsters is strongly influenced by the perception that develops from the form by people deal with illness since first years of life, having strong influence of the perception of these children in relation to the feelings, behaviors and attitudes of the family in relation its problem of skin. It is a subjective experience, which does not depend solely on the diagnosis or the severity of the illness, being much more strong influenced by factors as: personal perception, feelings and the image these children and young make of its body and itself, and of the exterior manifestations and personal experience of each child with the problem in its skin. Such process is dynamic, strongly influenced by the familiar and social context and significantly influences the interpersonal relations of these children, as well as impact on the development of its potentialities and perspectives of future.

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DENTAL COMPLICATIONS OF A BONE RARE DISEASE: PAGET'S DISEASE

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Paget's disease of bone is a condition characterized by a rapid skeletal remodeling. and the development of structurally abnormal bone. It can cause pain, fracture, deformity and more rarely malignancy. The jaws are implicated infrequently in Paget's disease, in about 15% of all cases having Pagetic´s skull involvement. Hence the management of dental issues in combination with abnormal bone metabolism is not well defined and case descriptions are desired. Some of the dental complications that can occur in patients having Pagetic bone involvement of the mandible and maxilla are: malocclusion, loosening of teeth, hypercementosis, root resorption, pulp calcification, dry socket, excessive bleeding on extraction, osteomylelitis and difficulty in fitting dentures.

We describe one case of our casuistic, an 80 year old man suffering Paget's bone disease, diagnosed twenty years ago. The biochemical laboratory tests showed serum alkaline phosphatase: 1,000 U/l, and high spots of scinthigraphic ^{99m}Tc-methylene-disposphonate bone uptake located at the sacrum and at the upper jaw. At the beginning, he started being treated with oral etidronate disodium, available at that time. After this first schedule, he was subjected to four prosthodontic rehabilitation bridges in his upper jaw. Afterwards, he continued receiving treatment, in order to modulate the Pagetic bone metabolism, and in those periods when the serum alkaline phosphatase levels were found supra-normal. Either oral pamidronate or oral olpadronate were administered. The latter, authorized (compassionate use) after the poor outcome with the previous agents.

After 20 years, the patient loss stability of his prosthodontic bridges, and was submitted for an orthodontics consultation. The oral surgeon suggested trying with dental implants and the use of chromium-cobalt for dentures.

The dental complications of Paget's disease receive little attention, and are worthy of a more focused study by basic scientists, and clinicians as well, within the broad field of hard tissue research.

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SACRAL FRACTURES: REPORT OF TWO DIFFERENT CASES

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Sacral fractures are relatively rare and can constitute a debilitating condition causing low back pain. The etiology is diverse: sacral insufficiency type fractures in elder osteoporotic people; fatigue fractures in young active individuals; metastasis and consequent irradiation therapy in gynecological malignancies.
We hereby describe 2 cases: a) A 64-year-old woman suffering osteopenia who is under treatment with calcium tablets. She reported lower back pain and difficulty walking in the absence of trauma. Plain radiographs showed a linear fracture in the alae sacrum, while bone scinthigraphic with ^{99m}Tc-methylene disphosphonate showed a linear pattern uptake, suggesting osteolitic lesion. She had suffered of breast adenocarcinoma fourteen years earlier. We decided to perform bone biopsy and the pathology exam diagnosed metastasis of adenocarcinoma at the affected location.
b) An 82-year old female patient, with history of visual disease (macular degeneration). She had been diagnosed with osteopenia, three years ago, and was being treated with oral alendronate. At presentation, she reported moderate back pain, and a sacral fracture was detected by computerized tomography at the emergency room. Bone biopsy was carried out trying to detect possible metastasis or primary tumor. The anatomo-pathology examination reported no cellular malignancy; hence the injury is interpreted as a fracture by insufficiency (structure). Afterwards, we realized that she had previously had high serum alkaline phosphatase. The biopsy was reviewed, and it revealed Paget's disease of bone.
The first patient improved after receiving radiotherapy in the fracture site and pamidronate at 90 mg i.v. doses. In the second case we advised resting and oral pamidronate intake, the patient also improved.

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NF1 MICRODELETION SYNDROME: CLINICAL AND CYTOGENETIC CHARACTERIZATION OF A FAMILIAL DELETION.

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Neurofibromatosis type 1(NF1 MIM 162200) is an autosomal dominant disorder caused by deletion or point mutations of NF1, a tumor suppressor gene located to17q11.2 with marked variation in expression, affecting approximately 1/3,500 individuals. The main clinical features are *café au lait* spots, axillaries and inguinal freckling, cutaneous neurofibromas, hamartomas of the iris (Lisch nodules) and an increased risk of benign and malignant tumors, optic glioma, neurofibrosarcoma, malignant peripheral nerve sheath tumors and childhood myeloid leukemia. Additional complications include central nervous system tumors, scoliosis, plexiform neurofibromas, learning difficulties, and epilepsy. Approximately 5-20% of all NF1 patients carry a heterozygous deletion of

usually 1.5Mb involving the NF1 gene and contiguous genes lying in the flanking regions resulted by unequal homologous recombination during the meiosis. The “NF1 microdeletion syndrome” is often characterized by a more severe phenotype than that observed in the classical group. NF1 microdeleted patients show variable facial dimorphism, mental retardation, developmental delay and an excessive number of neurofibromas for age. The severity may be explained by variations in the expression of the genes involved in the rearrangement caused by different mechanisms such as gene interruptions or position effects with a decreased gene dosage. In this report we present three-generations on a large pedigree with 3 patients, mother, sister and son whose clinical and laboratory data are characteristic of the NF1 microdeletion. The patients show a large number of cutaneous neurofibromas, facial anomalies, large hands and head, and developmental impairment. The 4-year-old sister present plexiform neurofibromas and learning disability. At 10 months of age she showed 13 *café au lait* spots. The 2-year-old boy presents renal malformations and psychomotor retardation. The histology study of both revealed juvenile xanthogranuloma. Furthermore, several other relatives of the patients have been affected with NF1 as well tumors, cardiac anomalies, hypertension, and other relatives died in the newborn period or during the young life without diagnosis. Peripheral blood of the three patients was cultured using standard techniques to perform cytogenetic preparations suitable for high resolution analysis. Karyotyping with GTG banding revealed a cytogenetically visible deletion at 17q11.2 sub-band. The deletioned chromosome was shorter than the normal chromosome 17. According to literature data this family shows the most common extra NF1 signs as cardiac anomalies, dimorphism, and learning disability indicating clinical NF1 microdeleted. We conclude the importance to carry out cytogenetic studies, molecular and FISH analysis with locus specific probes to confirm the deletion size at 17q11.2 in patients with suspected clinical “NF1 microdeleted”, such as improving the assessment and the multidiscipline management of the clinical problems in isolated individuals or in families with one or more members affected with this genetic disorder.

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EUROPEAN PROJECT FOR RARE DISEASES NATIONAL PLANS DEVELOPMENT (EUROPLAN)

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EUROPLAN (www.europlanproject.eu) is a three year EU funded project (2008-2011) coordinated by the Italian National Centre for Rare Diseases (Istituto Superiore di Sanità, Italy), which involves 30 Countries and EURORDIS. The Council Recommendation on European Action in the field of Rare Diseases (RD) which was adopted by the EU Council in June 2009, calls upon Member States to adopt National Plans for RD, before the end of 2013. In line with this, EUROPLAN is an operational measure within the European strategy in the field of RD.
The project aims at a) elaborating recommendations on the different steps to develop a national plan or strategy; they will include priority areas and actions of intervention supporting the harmonisation of public health strategies on RD throughout Europe; 2) select indicators for monitoring the implementation and evaluating the impact of national plans or strategies.

In order to turn the Council Recommendation into concrete actions in favour of RD patients at national level, several rare disease patient alliances, coordinated by EURORDIS in conjunction with national authorities, are organizing National Conferences to be held in 16 Countries in 2010. During National Conferences local stakeholders will discuss the EUROPLAN recommendations and the main elements of the European strategy on RD, with the aim to assess their transferability in their own Country.
In conclusion, EUROPLAN is collecting information on EU Member States initiatives contributing to share experiences, data and effective strategies to address RD; is promoting the development of RD plan or strategy trough recommendations and indicators; is increasing awareness on RD and the recommendations will also serve as an important advocacy instrument at policy level. The EUROPLAN outcomes will support and encourage EU MS in developing national health policies to ensure equal access and availability of prevention, diagnosis and treatment for citizens with RD.

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KNOWLEDGE OF THE HEALTH PROFESSIONALS ON CYSTIC FIBROSIS IN BRAZIL AND THE IMPORTANCE OF THIS PATHOLOGY AND PUBLIC HEALTH ISSUE

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Introduction: The cystic fibrosis or mucoviscidosis, is a genetic disease, recessive autosomal, affecting chromosome 7. Cystic Fibrosis belongs to a group of pathologies named DPOC (CHRONIC OBSTRUCTIVE PULMONARY DISEASE) that are characterized by having a chronic obstruction of the airways, diminishing the capacity of ventilation . The first description of cystic fibrosis was done in 1905 by Landsteiner on a newborn passed away in the fifth day of life by meconium ileus ³. From 1930 to 1940 when the cystic fibrosis was identified the survival over the 5 years old was used to be very rare. It's considered as child disease, with 80% of the children affected dying before becoming ten years old. The advancements in the diagnosis and the developed therapeutic strategies on the last years have increased the life expectation of the patients about the disease, but however is difficult to survive after 30 years old and most of to deaths happens before the patient to complete 10 years old According to the entrance number 338 from June 29 of 2005, there are approximately 2,000 patients with CF in Brazil [6]. The diagnosis has been making too late: the average age for the diagnosis of 4.5 years old in Brazil and is about 2.9 years old in the United States [7]. In Brazil, first publication about the disease was in 1949, which reviewed the knowledge about the disease and its methods diagnosis [8]. According to the literature of the institution (IRR), for neonatal screening of cystic fibrosis in Brazil would entail an approximately budget of fifteen thousand *reais* per patient [10]. In addition to these costs for analysis of early diagnosis in institutions, there is also difficulty for the family to continue the treatment, which must be maintained indefinitely, without being sure of cure, or by financial conditions.
Objective: Show the professionals of the health area that the recognition of CF previously detected increases the survival time of patients about the disease, supporting data about the high costs for both institutions and family.
Methodology: This study was carried out from a literature review, from years 2000 to 2009. *Discussion*: the multi-professional team should be deep on the pathos-physiology of the disease, to diagnose it. By this way the early CF diagnosis will be as soon as possible the best way to avoid mortality and longer survival of patients with the disease. According to authors the disease is later identified by lack of health services or lack of sufficient training to diagnose and treat this condition early. For, having success in the therapy of CF it's necessary to have total agreement of the

multidisciplinary team, studies, researches, and an education on health for the family members of that customer continuing the same treatment, resulting in the effectiveness of cares. While there is no cure is possible to have an improve quality of life[11]. *Conclusion*: CF can be a rare disease being diagnosed less than 10% in Brazil becoming it-self more complicated due to the treatment, because of the late diagnosis, the life time of the bearer become without perspective. The Scientific knowledge of the professionals regarding to the standards to be used in procedures, reduce rising costs, length of stay at the hospital and improve quality of life of the CF patients.

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DERMACAMP – A NEW APPROACH TO SEVERE AND RARE SKIN DISEASES
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Since 2001 we promote a special camp, DERMACAMP, for children and adolescents with rare and severe, chronic skin diseases. Through activities dedicated to self-knowledge, sel-steem and dealing with diversity, DERMACAMP promotes changes in quality of life and integrates children in the society.
In this poster we will show several pictures illustrating the activities performed at DERMACAMP.

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A BIOINFORMATICS RESEARCH FOR DRUG TARGETS OF RARE DISEASES USING OPEN SOURCE DATABASES
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The drug development of rare disease has not been actively tackled by industrial companies so far because the market size of each rare disease is too small. There are possibly thousands of different kinds of rare diseases. Many of those have not been established their medical treatments and diagnosis's, and even the mechanisms of the diseases have been unclear. Therefore, basic researches against those are needed for establishing the effective therapies and accelerating the drug developments. There is a possibility that some of the rare diseases would potentially become a *druggable* target by accumulation of basic and clinical researches even though such cases have ignored so far.
We have been organizing a scientific research team, named Collegium for Rare Disease Drug Discovery in Japan (CoRDs Japan) since 2008. In one of our recent activities, we carry on the potalization of knowledge about basic biological and medical researches against rare diseases and orphan drugs using bioinformatics approaches. One of the goals is to find drug-target candidates of rare diseases whose effective drug has not been developed. For this aim, recently, we are developing a bioinformatics approach to collect the literatures which are related to rare diseases, and perform the trend search of those per year, and extract the causal or related protein and gene information by utilizing open source biological, medical and chemo-genomics databases.

In this poster presentation, we will show the results of the preliminary survey for 404 rare diseases whose estimated prevalence are less than 10/10,000 using our approach. As a result, one third of the 404 rare diseases have not been reported by more than 50 published papers. On the other hand, we found that some rare diseases have their causal or related genes which are identical or similar to known drug targets. We believe our approach may provide useful information for a better understanding about rare diseases from a comprehensive stand point. We will also discuss about an importance of potalization of knowledge about rare diseases and orphan drugs, and sharing the knowledge among a wide range of research communities including basic biological researchers, clinical researchers, and drug development researchers.

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EVALUATION OF FOOD DISORDERS IN PATIENTS WITH TYPE I DIABETES MELLITUS

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Introduction: The relationship between Diabetes Mellitus (DM) and Psychiatric Disorders is described at least a century (1,2,3). DM bring to the patients numerous adjustments social, psychological and food necessary for the disease control (1) and compromised of the life's quality (4,5). Many diabetic patients, mainly young, have many complications caused by this disease. Several associated factors should therefore follow a line of treatment to avoid them. (6) The Burdens Food (TA) are psychiatric syndromes associated with the presence of eating disorders and the perception of body image (2,7,8,9). They are multifactorial and are very common in female patients, especially during adolescence. It is estimated that many of these patients with Type 1 Diabetes Mellitus (T1DM) have an Eating Disorder as a result of the restrictions. Adjustments are required for the control of the type 1 diabetes. They also are influenced by individual and external factors (6). The present a TA has been associated with increased clinical complications of type 1 diabetes may be different (1,2,5,25). In Brazil, recent publications show that this correlation, others show no significant samples and limited studies with low power to reveal these differences (1,2,3,7,11).
Methods: The based articles were found in the Base VHL (www.decs.bvs.br), from 1999 to 2009. We interviewed 32 females, from 18 to 30 years old, whose have Type I Diabetes Mellitus attending associations and institutions to support patients with type 1 diabetes, or treated in outpatient of clinics and nutrition treatments, or members of communities of social networking sites, using mechanisms such as analysis of the self-administered questionnaire - Eating Attitudes Test (EAT-26) - Eating Attitudes Test Garner et al, 1982, adapted to the Portuguese language (14,17,18,19,20,22,25) and self-administered questionnaire - Bulimic Investigatory Test Edinburgh (BITE) - Bulimic Investigatory Test Edinburgh Henderson, Freeman, 1987, also validated in the Portuguese language (14,17,18,21,22).
Results: The population evaluated (38 women) were assessed through self-administered questionnaires EAT-26 suggested and 12 other issues in evaluating the state nutritional. The result obtained by the EAT-26 suggests that the anorexic disorder is more than 80% compared to American studies in 2000, which indicate the prevalence of the related disease at rates lower than 5% (from 0.3% to 3.7% (4)). The total score shows that around 80.95% of the women may have bulimic profile, suggesting that for its inquiries. This result is probably overestimated, as the EAT-26,

compared the average prevalence of American studies, within 1.1% to 4% (4) due narrowly interviewed.
Conclusion: It is Essential to identify the frequent episodes of binge eating that hinder the emergence of adequate dietary guidelines prescribed in each treatment or increased concern about the eating habits and the possible weight gain are all factors before (a factor that could have enhanced the psychopathic food) or later (featuring thus predisposed to an event) to insulin therapy. This article has an epidemiological importance because it is a correlation not often explored. It is a great value to business the abidance of the scientific research. Urge extend these studies to the development of specific tools, making an effective processes of intervention and prevention to the population.

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KALLMAN SYNDROME AS A NON FREQUENT DIFFERENTIAL DIAGNOSIS OF OSTEOPOROSIS IN YOUNG WOMEN. REPORT OF A CASE.

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We hereby describe a case of a 38 year old woman suffering osteopenia since her 24 years. In addition, she was taking oral contraceptives from her 17th year age. The laboratory test at her 17 years old was: FSH: 1.0 mIU/ml, LH: 0.8 mIU/ml, estradiol: 35 pg/ml and TSH: 1.8 mIU/ml; bone mineral density (assessed by a Lunar DXA absorptiometer) was:

Bone density	mg/cm^2	T-score	Z-score
Lumbar L1-L4	0.888	-2.4	-2.1
Femur	0.914	-0.5	-0.3

Accordingly she was treated with daily calcium tablets, and weekly alendronate, during the year before. However, she reported primary amenorrhea and two wrist fractures after a low loading trauma. In the current clinical inquiry she revealed anosmia suggestive of the new and actual diagnosis of Kallman syndrome. The magnetic resonance imaging (MRI) verified the absence of her olfactory bulbs. Kallman syndrome (KS) is a genetic disorder that occurs in both, sporadic and inherited forms. Clinically is characterized by a combination of hypo-gonadism features and anosmia. The prevalence of the disease is estimated to be: 1 in 10,000 men, and 1 in 50,000 women. The hyogonadism and anosmia seen in Kallman Syndrome stem from the failure of proper neuronal migration during fetal development. Basically, the olfatory placodes are ectodermal thickenings that develop into an epithelium from which both the gonadotropin releasing hormone (GnRH)-secreting and olfactory neurons differentiate.
In this case, the protracted hypo-estrogenic state also contributed to her decreased bone density, rendering the patient more susceptible to fractures. Kallman Syndrome should therefore be included in the differential diagnosis of a young woman presenting with multiple fractures.

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ANAPHYLAXIS AFTER PARENTERAL COLLOIDAL HYDROXY OF IRON THERAPY IN DISTROPHYC EPIDERMOLYSIS BULLOSA (DEB) PATIENT

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Background: Parenteral iron therapy is indicated in patients with iron-deficiency anemia if the patient is unable to receive oral iron or have absorption problems. Epidermolysis bullosa (EB) is a congenital disease characterized by fragility of the skin and mucosa. Blisters and erosions formation are response to a minimal trauma. Most EB patients have malabsorption related to esophageal atresia or lesions that affect the intestinal epithelium. Replacement doses of iron required to replenish iron stores are based on body weight and the observed hemoglobin value. Methods of administering iron dextran include intramuscular and intravenous injections of the undiluted drug, which increases the risk of anaphylactic reactions. *Aim*: To report a fatal anaphylaxis after parenteral iron in EBD patient. Methods: RD, female, 15 years with EBD congenital and was admitted at the hospital with vomiting for 3 days, generalized weakness, dyspnea and fatigue. She had deep lesions that affected 89% of their body surface. The complete blood count (CBC) test showed deep anemia. The patient was receiving hydroxy Iron 100 mg each 24 hours for 3 days. On the second day she started having gastro-intestinal discomfort and a drop in blood pressure. The drug was suspended, but the patient developed respiratory insufficiency and clinical signs of anaphylaxis. *Results*: The overall incidence of adverse reactions associated with the parenteral administration of iron is low; the potential for an anaphylactic reaction in the EB patient should be discussed. Conclusion: Doctors and nurses should be aware of the occurrence of anaphylaxis after the use of parental iron and be able to promptly recognize and treat the asphyxia. Replacement doses of iron required to replenish iron stores are based on body weight and the observed hemoglobin value, if iron supplementation is really required, the benefits of sublingual administration should be discussed.

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BENEFITS OF ANALYSIS OF BLOOD MORPHOLOGY IN THE EVALUATION OF CHILDREN WITH DISTROPHYC EPIDERMOLYSIS BULLOSA (EBD)

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Background: Epidermolysis bullosa (EB) is a congenital disease characterized by fragility of the skin and mucosa. Blisters and erosions formation are response to a minimal trauma. The concern in the assessment of these patients is to establish the diagnosis, implement appropriate skin care and treatment of extra-cutaneous complications in order to ensure the best quality of life for these patients. The relationship between the patient's clinical symptoms and the shifts in peripheral blood as part of a total patient evaluation has been described for researchers in the worldwide as an accurate and cost-effective means of monitoring therapeutic.
Aim: To report benefits of using High Resolution Blood Morphology in assessing the disease condition and treatment follow-up of the patient with EB.

Methods: Sixteen patients (12 m 4 f) were underwent evaluation of a drop of peripheral blood. After collecting of the blood sample, a live and coagulation screening test as well as free-radical oxidative footprints screening test was analyzed through the method of Bradford Research Institute.
Results: High Resolution Blood Morphology allowed us to evaluate and identify blood morphologies correlating with disease states like anemia, metabolic imbalances, malnutrition, oxidative stress, systemic toxicity and hormonal dysfunction. In spite of ours results, we clarify that his assessment is not a diagnostic test but functional assessment.
Conclusion: The analysis enables us, from a drop of peripheral blood, to detect a morphologic alteration which has opened a way for the treatment follow-up of patients with EB thereby facilitating the patient's welfare.

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PORPHYRIAS IN ARGENTINA.
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Porphyrias are disorders of haem metabolism; they are the result of a primary and partial deficiency of one of the seven enzymes in the pathway, after the first and regulatory enzyme ALA-S. As a consequence, precursors, ALA and PBG and/or porphyrins accumulate, leading to the typical clinical signs. Porphyrias are classified, according to the main tissue expressing the disease, in: *Hepatic*, New Acute Porphyria (NAP), Acute Intermittent Porphyria (AIP), Hepatic Coproporphyria (HCP), Variegate Porphyria (VP) and Porphyria Cutanea Tarda (PCT), *Erythropoietic*, Congenital Erythropoietic Porphyria (CEP) and Erythropoietic Protoporphyria (EPP) and *Hepatoerythropoietic Porphyria*, HEP: according to the clinical signs, in: *Cutaneous*, *Mixed and Acute*. We present a brief review of the results of the clinical, biochemical and genetic studies performed during the last 35 years, in about 1700 Argentinean families diagnosed in the CIPYP. *Cutaneous* – PCT: is the most common of all. Characterized by skin photosensitivity, with blistering on light exposed areas, skin fragility, hyperpigmentation, hyperthricosis. Biochemically, the deficient enzyme is URO-D. Highly carboxylated porphyrins (Uro, Hepta) are increased in plasma and urine, Plasma Porphyrin Index (PPI) is also increased (λ 619 nm). Genetics: 100 mutations in URO-D Gene. Argentine: 1437 families. In 32 fam, 14 new, 6 reported mutations. G10insA in 32% families. EPP: Deficient enzyme, Ferrochelatase (Fech). Protoporphyrins ⇑ in plasma, faeces and RBC. PPI ⇑ (λ 630 nm). Genetics: 125 mutations in Fech gene. Argentine, 40 families. In 13 families 7 new, 5 reported. CEP: Deficient enzyme, URO III-S. Infantil and adult cases. Red urine, erythrodontia, haemolitic anaemia, strong photosensitivity, esplenomegalia. Uro I, Copro I ⇑ urine and plasma. PPI ⇑ (λ 619nm). Genetics: 38 mutations in URO-S gene. Argentine:5 families. In 2 families, 2 reported mutations. HEP: Deficient enzyme URO-D (homozygous PCT). Uro, Hepta, Penta, Copro ⇑ in urine. Copro, IsoCopro, Proto ⇑ in faeces. No erythrodontia. Genetics: Argentine 1 family, 2 reported mutations. *Mixed* – VP: Deficient enzyme, Protoporphyrinogen Oxidase (PPox). Photosensitiviy and/or neurological signs. Copro, Proto ⇑ in faeces. Porphyrins ⇑ in urine. ALA, PBG ⇑ urine (crisis). PPI ⇑ (λ 626 nm). Genetics: 150 mutations in Ppox gene. Argentine: 60 families. In 31, 12 new, 6 reported mutations. C1043insT in 42% families. HCP: Deficient enzyme, CPGase. Porphyrins (Copro) ⇑ urine, faeces. PPI ⇑ (λ 619 nm).

Genetics: 41 mutations in the CPGase gene. Argentine, 17 families, in 4, 4 new mutations. *Acute* - AIP: Deficient enzyme, PBG-D. Neurological signs. ALA, PBG, porphyrins ⇑ urine. Genetics: 300 mutations in PBG-D gene. Argentine: 156 families. In 67, 17 new, 14 reported. G111R in 54% families. These studies allowed the identification of 146 latent individuals, emphasizing the importance of molecular techniques for pre-symptomatic diagnosis in these rare diseases to avoid triggering factors and therefore the porphyry manifestation.

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ORAL BOVINE TYPE II COLLAGEN AS A TREATMENT OPTION FOR SYSTEMIC SCLERODERMA.

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Introduction: Scleroderma comprises a series of clinical features characterized by alterations of the vascular system and deposition of collagen fibbers in the skin and internal organs.
Objectives: Our purpose was to see whether the administration of collagen II could induce a reduction in the symptoms of the disease.
Materials and Methods: Eleven patients were enrolled in an open study to receive orally a preparation of 0.6 mg of type II collagen 30 min before breakfast. The time of study was 120 days.
Periodical assessment of skin thickening by modified Rodnan skin score.
Results: 1-The skin core of patients show an improvement around of 38%.
2- The 72% of patients reduce its title of anti-Scl-70 antibody.
3- Raynaud's syndrome remains unchangeable during this period.
4- No secondary effects were seen in our patients.
Conclusions: Collagen II may be an effective immunotherapeutic approach for the skin lesions of Scleroderma. It remains to be established whether there is also some effects on internal organs .

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RARE DISEASE DAY 2010 IN JAPAN: FIRST JAPANESE RARE DISEASE DAY EVENT.

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Rare disease day is a day for raising awareness of rare diseases, and intended to improve living conditions for patients suffering rare diseases thorough better diagnoses and treatments. The day originally started in Sweden in 2008, and in last year, 30 countries have participated in world wide. This year, we organized the first Rare Disease Day 2010 in Japan at Tokyo Midtown hall. The organizer is NPO PRIP Tokyo, and the sponsors are Ministry of Health, Labour and Welfare, Japan Patient Association (JPA: the biggest patient association related to rare diseases in Japan), National Organization for Rare Diseases (NORD), RCAST The

University of Tokyo, The Japan Pharmaceutical Manufacturers Association (JPMA: the association comprising 69 research-oriented pharmaceutical companies in Japan) and Japan Biotech Association. This event is also sponsored by some pharmaceutical companies.

Japanese rare disease day targeted not only to rare disorders but also intractable diseases which face similar issues because of Japan original categorization of diseases. Japanese first rare disease day event consists of several sub-events with “to know, to do, to communicate and to connect” as key words; panel presentation, workshop for making an art work with a Japanese leading artist, stakeholder round table discussion in “world cafe” style, testimonials from patients, message board, playground for children and a free cafe.

In panel presentation, various types of information related to rare and intractable diseases were introduced from definition of the concept of those disorders to state-of-the-art research in orphan drug discovery. And the activities of JPA were also presented.

As the art workshop, an installation named “cassette plant” was made by artist Mr. Yamaguchi Keisuke and all of participants of the rare disease day event. This art work consists of many cassette cases with sealed flowers and natural resin. It implies that the image of an amber and an ark as a vehicle to preserve lives and beautiful things.

World cafe was an open discussion in the form of small forums among patients, physicians, researchers and publics. Topics were raised from conversation at each table. In this style, participants were able to cross-pollinate ardors and feelings, and share the time together.

In patient testimonial, six patients presented their real-life experiences, daily lives, and messages to society, etc. from their own heart.

Message board was shaped as a large seascape. Event participants freely wrote messages to message cards shaped as sea creatures like fish and shellfish and stickled it to the seascape board.

As a results, the number of visitors totaled 300 over the day (40% from related patients and 60% from common people). We would say that this event is of tremendous value to society. Due to the huge success of our first event in Japan, we are hoping to hold a similar event again the next year.

General Information

Venue

All the activities will be developed in Palais Rouge, located in Jeronimo Salguero 1441, Ciudad Autónoma de Buenos Aires, Argentina.
The venue is located in Palermo, one of the most developed urban centers that contain boutique Hotels, many restaurants, alternative fashion centers, craft markets and cultural places. At 20 minutes from the City Center and from Aeroparque, Buenos Aires city Airport.
Who arrives to the International Airport Ministro Pistarini (EZEIZA), the access to the venue would be 60 minutes or more in the rush hour, but if it is necessary, everyone could ask for transport coordination from the airport and during the course of the Congress.

Congress Language

The ICORD 2010 official language is English. During the sessions, equipments for simultaneous translation to Spanish will be available.

Registered and grant

ICORD registered will receive a folder with the official program, abstracts and ICORD related information. They have free access to all the event sessions and activities (see program) if somebody needs simultaneous translation service it is free. Breakfast, coffee and lunch services in the Congress venue are included.

All the registered can participate in the 2nd Latin-American and Caribbean Symposium on Rare Diseases ER2010LA, on March 18, 2010 in Palais Rouge.

GEISER Foundation invites to the Pre-Congress Meeting and Welcome Cocktail on March 17, 2010 in the Auditorium of the Ministry of Health, Government of the City of Buenos Aires (Av Amancio Alcorta and Monasterio, City of Buenos Aires),

and to the GEISER Night of Awards and Tango Show on March 19, 2010 - without charges-. At this event, due potential limitations of seats, priority will be giving by registration on the basis of first come first served. (Café los Angelitos, Av. Rivadavia and Rincón, City of Buenos Aires) Bring your invitation ticket.

The Latin-American Society of Medical Research on Rare Diseases, SLADIMER, invites registered participants to the event Fun & Football evening on March 18, 2010 - without charges too- (do not forget to bring your sport shoes), with tasting of typical menus. (The Buenos Aires Velez Sarsfield Club).

The identification badge is very important to access to all these events.

Congress Secretary

We offer personal attention to government members, civil organizations, scientific organizations, companies, press interested in ICORD 2010. The Congress Secretary will be held in our offices in Buenos Aires and Mendoza.

LATINER S.A. is in charge of the Administrative Management, sponsors, reservations, insurance contract and other issues. LATINER S.A. coordinates with GEISER Foundation and SLADIMER, booth in charge of ICORD peripheral activities.

UBATEC (Technological Links Unit – Buenos Aires University UBA) is in charge of the financial and accountant international business.

Sra. Julieta Campillo- GEISER

Av. Avellaneda 595, Ciudad de Mendoza.
Monday to Friday from 9 to 12 hs. Phone 54-261 4251523
Institutional e-mail: secretaria@icord2010buenosaires.net,
Information e-mail: registration@icord2010buenosaires.net

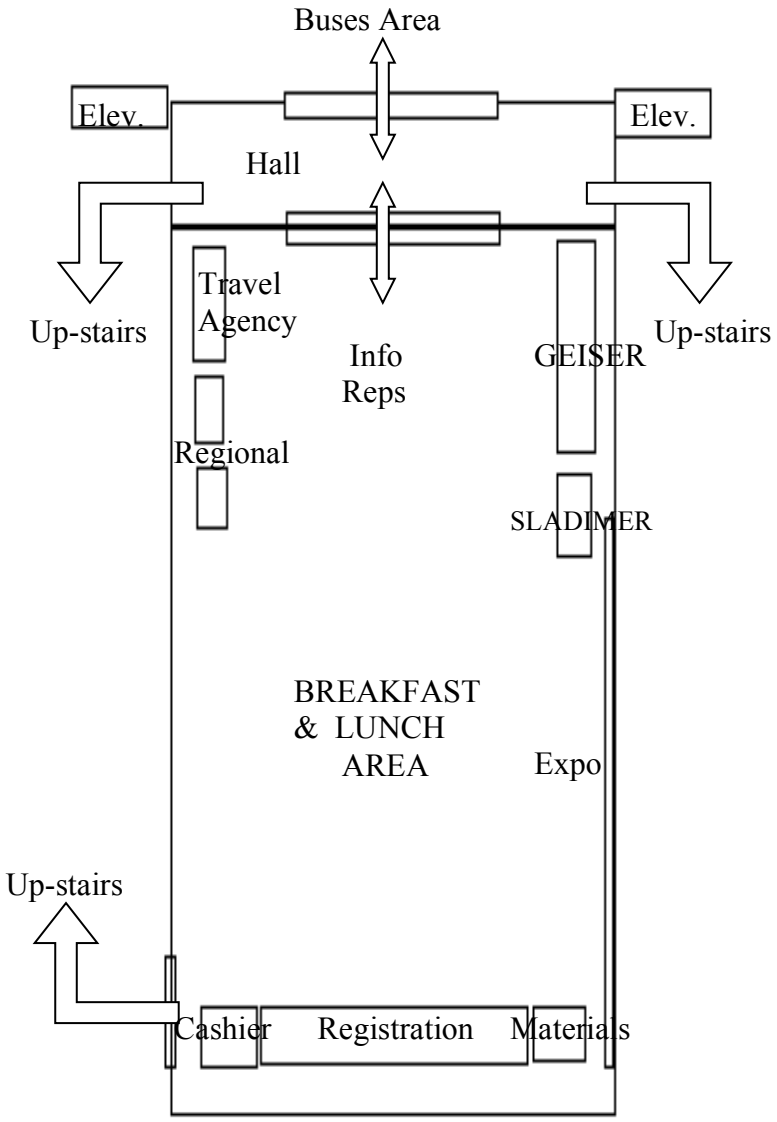
The ICORD Executive organization will be held in GEISER Foundation Auditorium in Buenos Aires, Serrano Street 669, C. A. de Buenos Aires.

Accessibility in Congress venue

The venue have access and toilets for disabled, elevators and inclines are available to go trough all the areas.

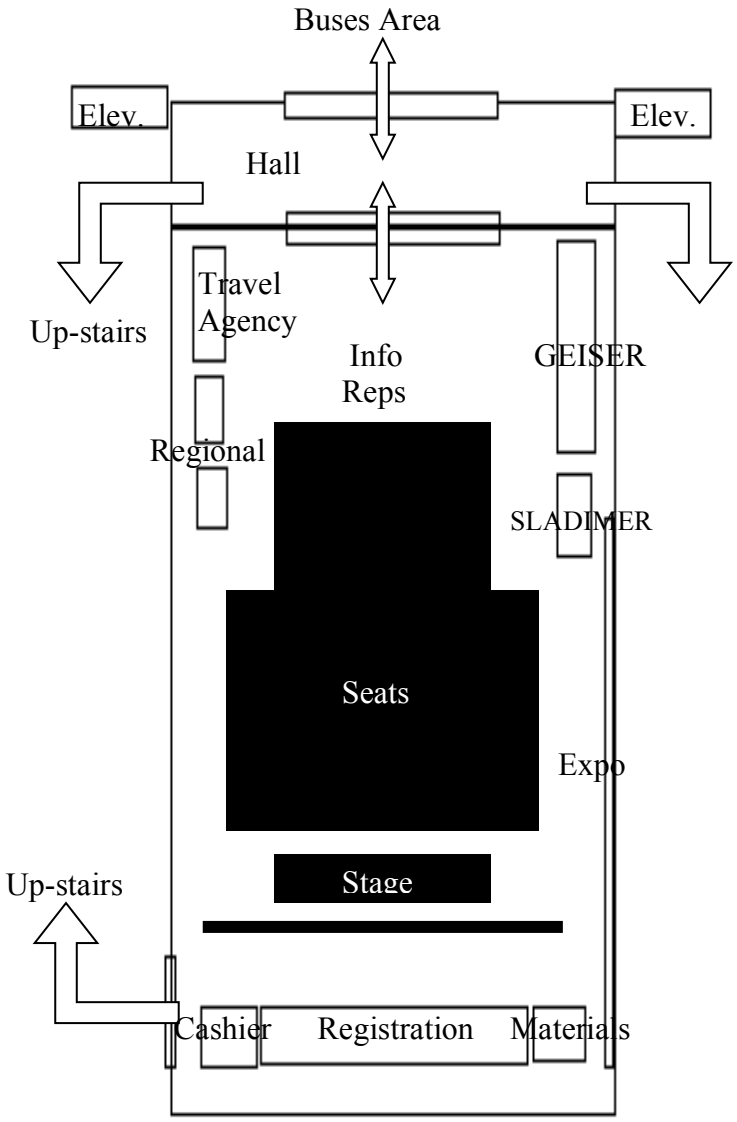
If you have special needs in terms of alimentation or drinks, please tell to the Congress Secretary.

SALGUERO STREET

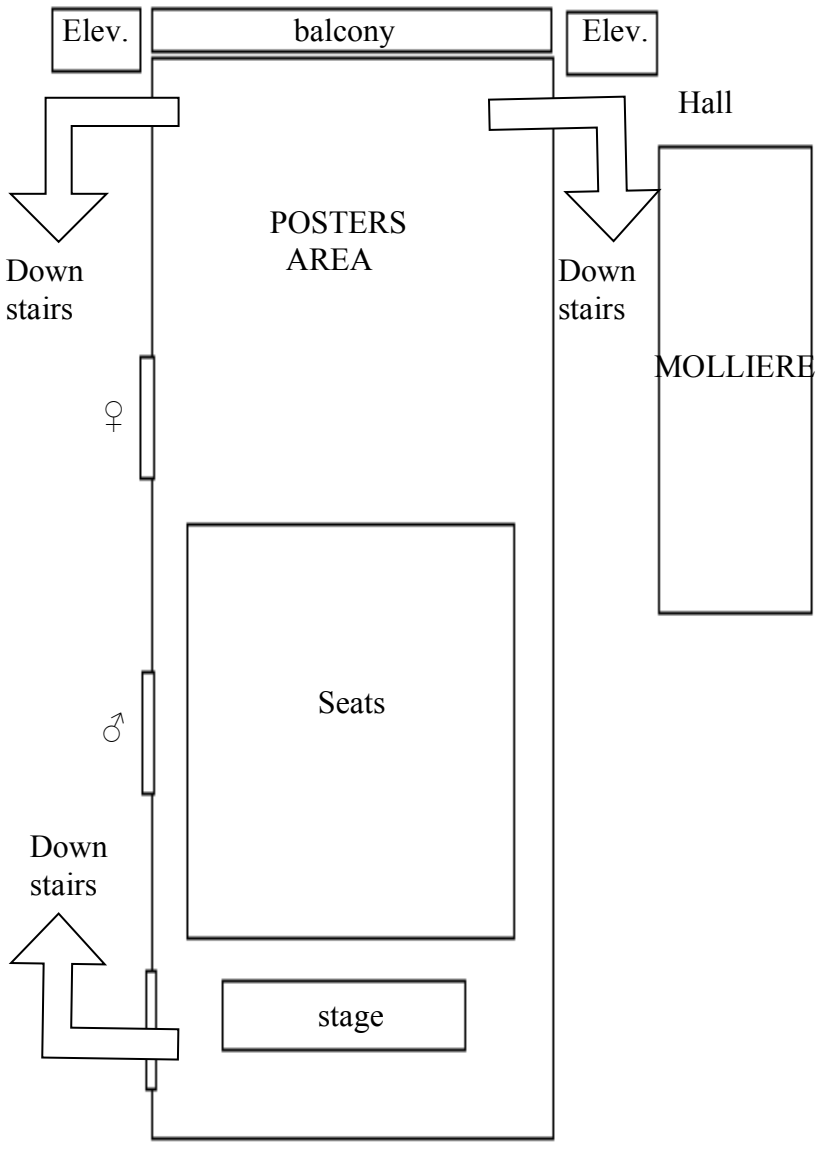


MATISSE BALLROOM
1st floor

SALGUERO STREET



MATISSE BALLROOM
1st floor
During ER2010LA – March 18th



DORE BALLROOM
2nd floor

Acknowledgments

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